Competition, synergy or both: predicting the outcome of vaccination

Irene Man[1,2], **Hans Bogaards**[1], **Jacco Wallinga**[1,2], **Kari Auranen**[3]
[1] National Institute of Public Health and the Environment Netherlands
[2] Leiden University Medical Center
[3] The National Institute for Health and Welfare Finland

Where I work...

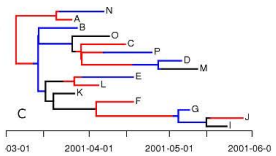
National Institute for Public Health and the Environment Netherlands

- Epidemiology and surveillance of infectious diseases
  - Gastroenteritis and zoonoses
  - Respiratory infections
  - Sexually transmitted diseases
  - Antimicrobial resistance and care related infections
  - National vaccination program surveillance and signaling
  - **Modelling of infectious diseases**

Topics at my department...

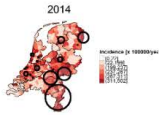
Simultaneous inference of phylogenetic and transmission trees in infectious disease outbreaks

Don Klinkenberg[1]*, Jantien A. Backer[1], Xavier Didelot[2], Caroline Colijn[3], Jacco Wallinga[1,4]



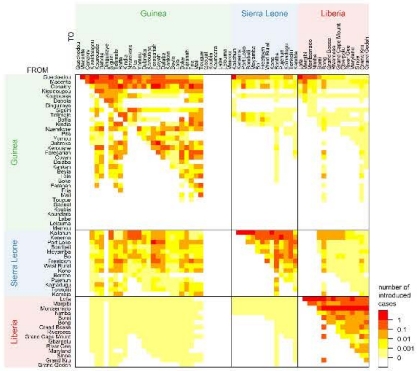
Space-time analysis of pneumonia hospitalisations in the Netherlands

Elisa Benincà[1,2]*, Michiel van Boven[1], Thomas Hagenaars[2], Wim van der Hoek[1]



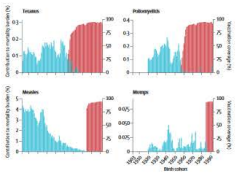
Spatiotemporal Analysis of the 2014 Ebola Epidemic in West Africa

Jantien A. Backer[1]*, Jacco Wallinga[1,2]



Effect of vaccination programmes on mortality burden among children and young adults in the Netherlands during the 20th century: a historical analysis

Maarten van Wijhe, Scott A McDonald, Hester E de Melker, Maarten J Postma, Jacco Wallinga

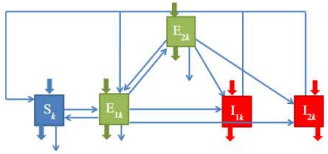


Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and meta-analysis of predictions from transmission-dynamic models

Marc Brisson*, Élodie Bénard, Mélanie Drolet, Johannes A Bogaards, Iacopo Baussano, Simopekka Vänskä, Mark Jit, Marie-Claude Boily, Megan A Smith, Johannes Berkhof, Karen Canfell, Harrell W Chesson, Emily A Burger, Yoon H Choi, Birgitte Freiesleben De Blasio, Sake J De Vlas, Giorgio Guzzetta, Jan A C Hontelez, Johannes Horn, Martin R Jepsen, Jane J Kim, Fulvia Lazzarato, Suzette M Matthijsse, Rafael Mikolajczyk, Andrew Pavelyev, Matthew Pillsbury, Leigh Anne Shafer, Stephen P Tully, Hugo C Turner, Cara Usher, Cathal Walsh

Latent tuberculosis infection in foreign-born communities: Import vs. transmission in The Netherlands derived through mathematical modelling

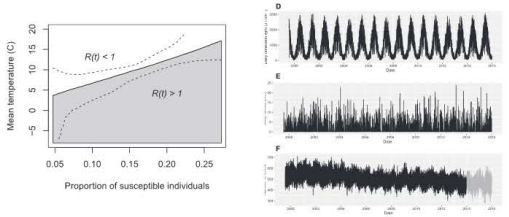
Hester Korthals Altes[1]*, Serieke Kloet[1], Frank Cobelens[2], Martin Bootsma[3,4]



Determinants of Rotavirus Transmission

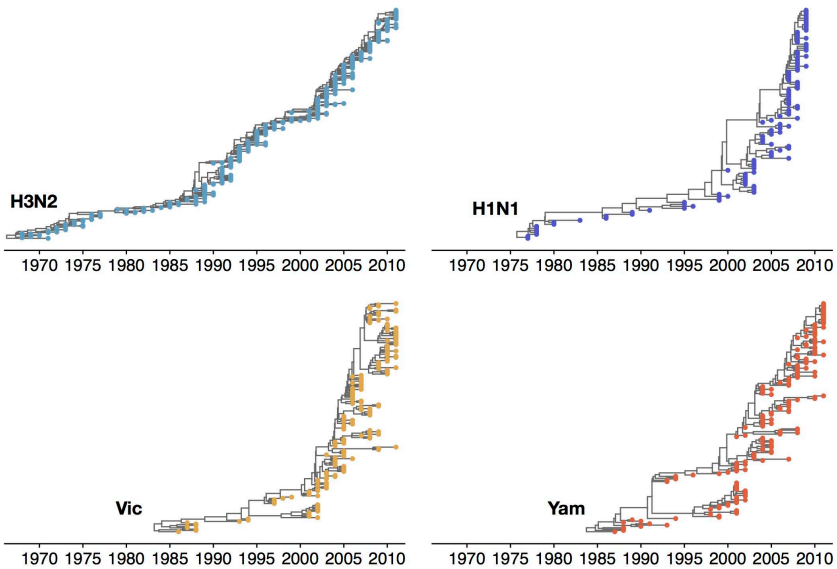
A Lag Nonlinear Time Series Analysis

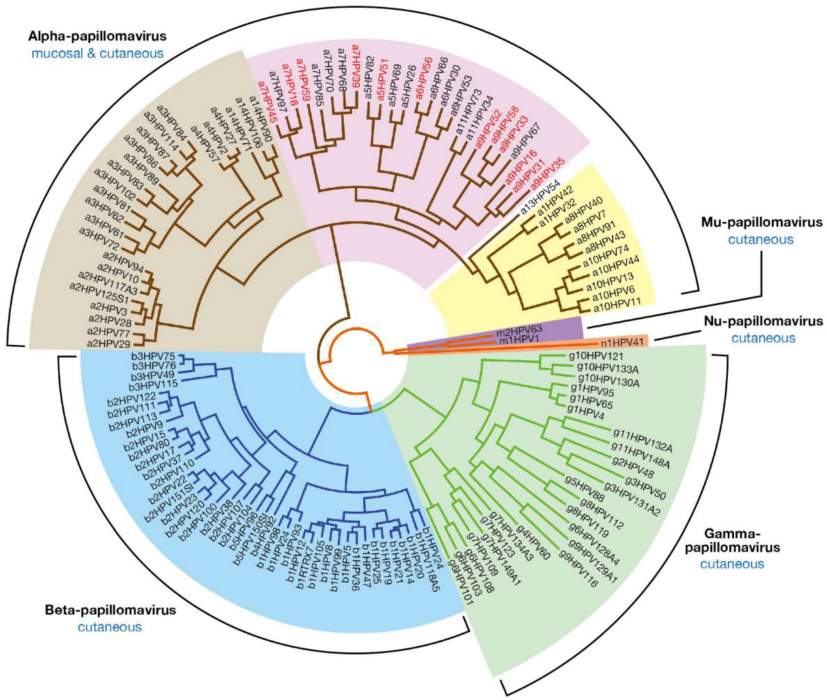
Rolina D. van Gaalen,[a] Jan van de Kassteele,[a] Susan J. M. Hahné,[a] Patricia Bruijning-Verhagen,[a,b] and Jacco Wallinga[a,c]



Competition, synergy or both: predicting the outcome of vaccination

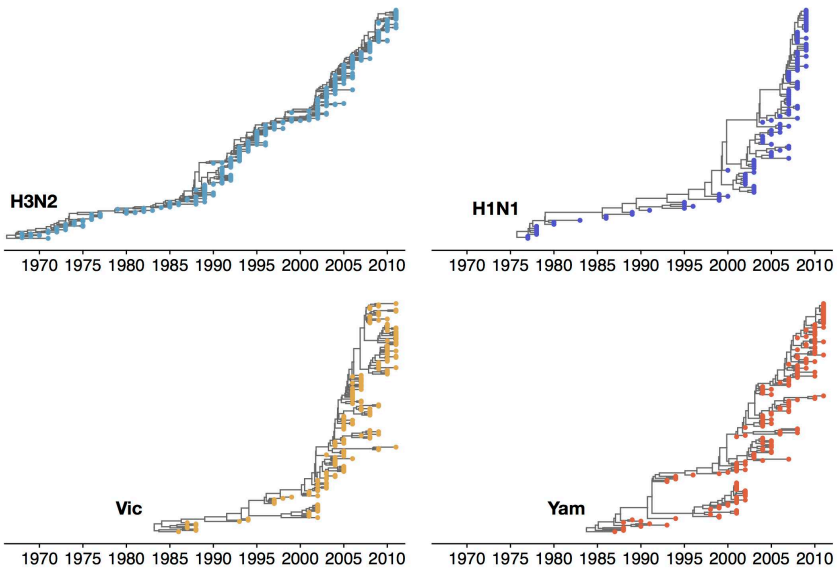
- Ecology of pathogens with many types
- What if the vaccine is only effective for a subset of types?
- Examples: influenza, pneumococcus, HPV, ...

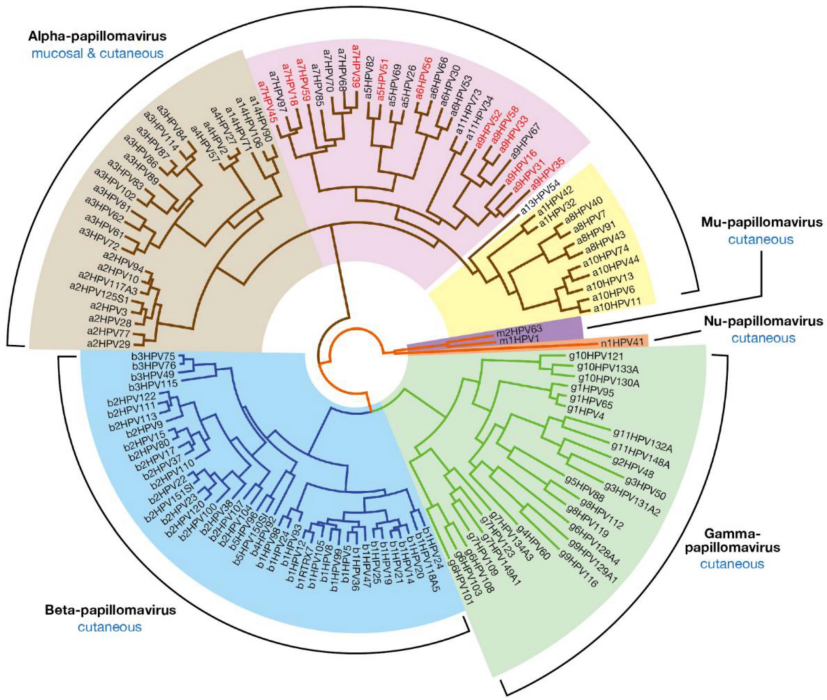




Competition, synergy or both: predicting the outcome of vaccination

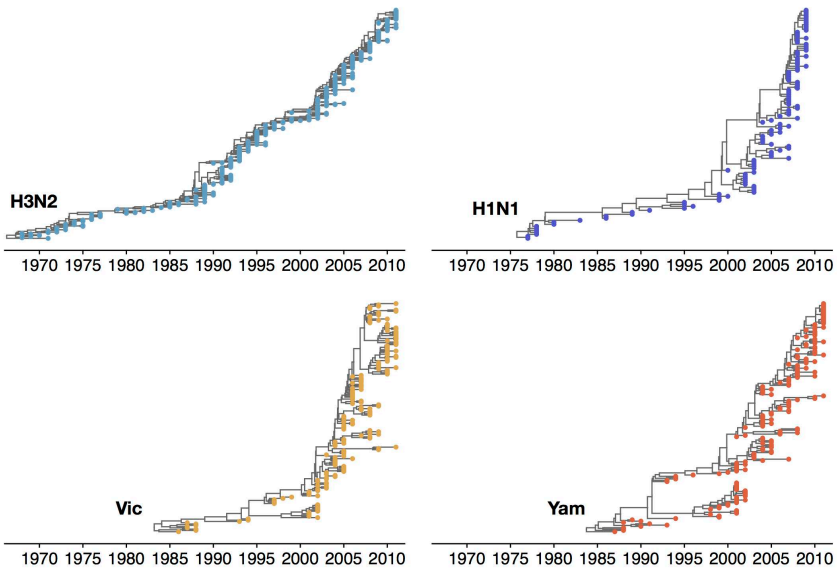
- Ecology of pathogens with many types
- What if the vaccine is only effective for a subset of types?
- Examples: influenza, pneumococcus, HPV, ...

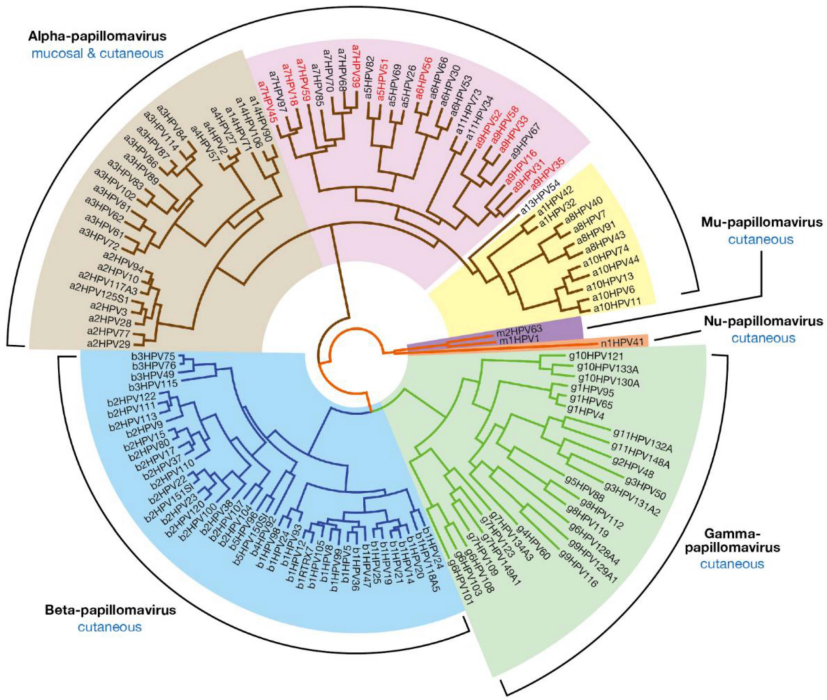




Competition, synergy or both: predicting the outcome of vaccination

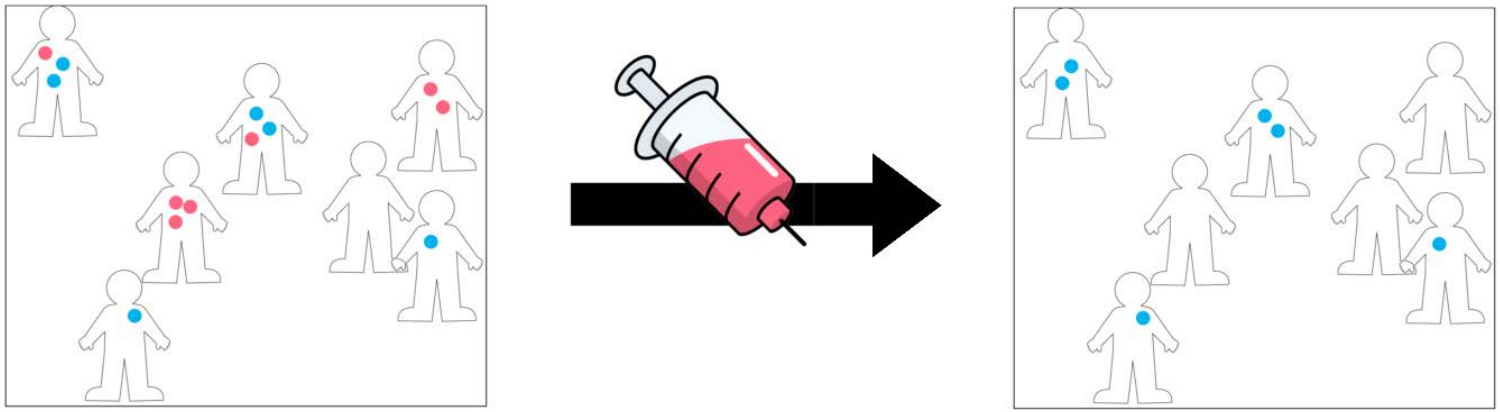
- Ecology of pathogens with many types
- What if the vaccine is only effective for a subset of types?
- Examples: influenza, pneumococcus, HPV, ...





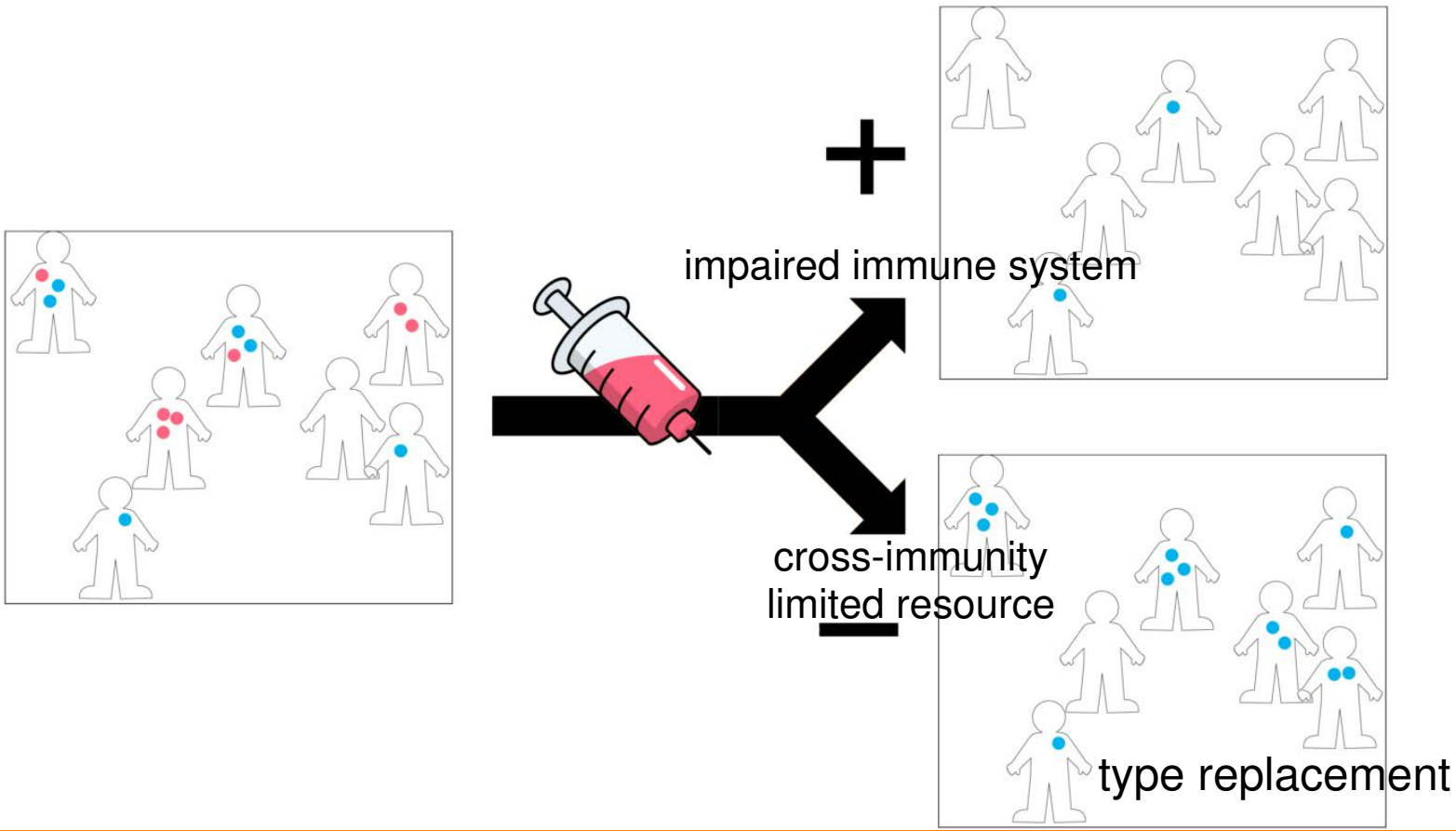
If types do not interact, what happen if we vaccinate?

- With a vaccine that targets only the vaccine types (VTs)
- The non-vaccine types (NVTs) are not affected



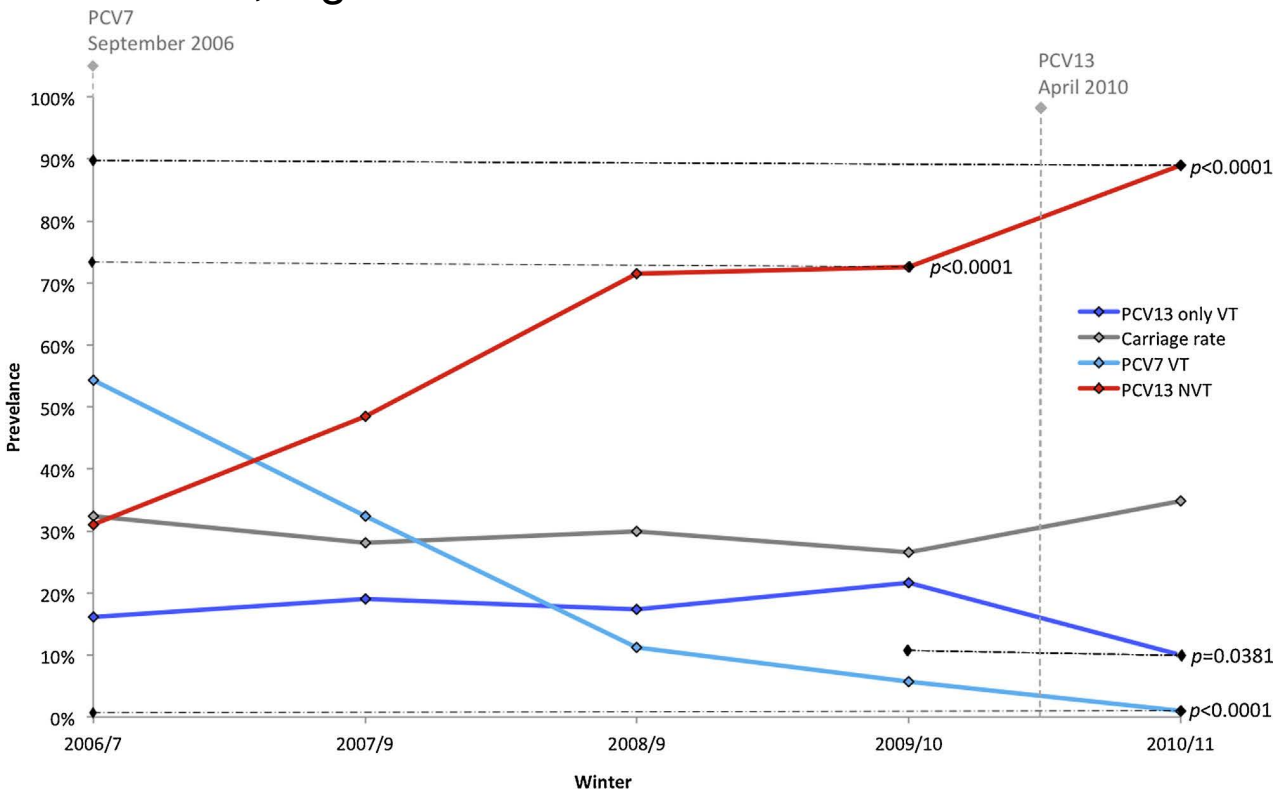
If types do interact, what happen if we vaccinate?

- With a vaccine that targets only the VTs
- The NVTs are also affected



A real-world example

- Pneumococcus: type replacement in many countries after introduction of vaccination, e.g. in the UK:

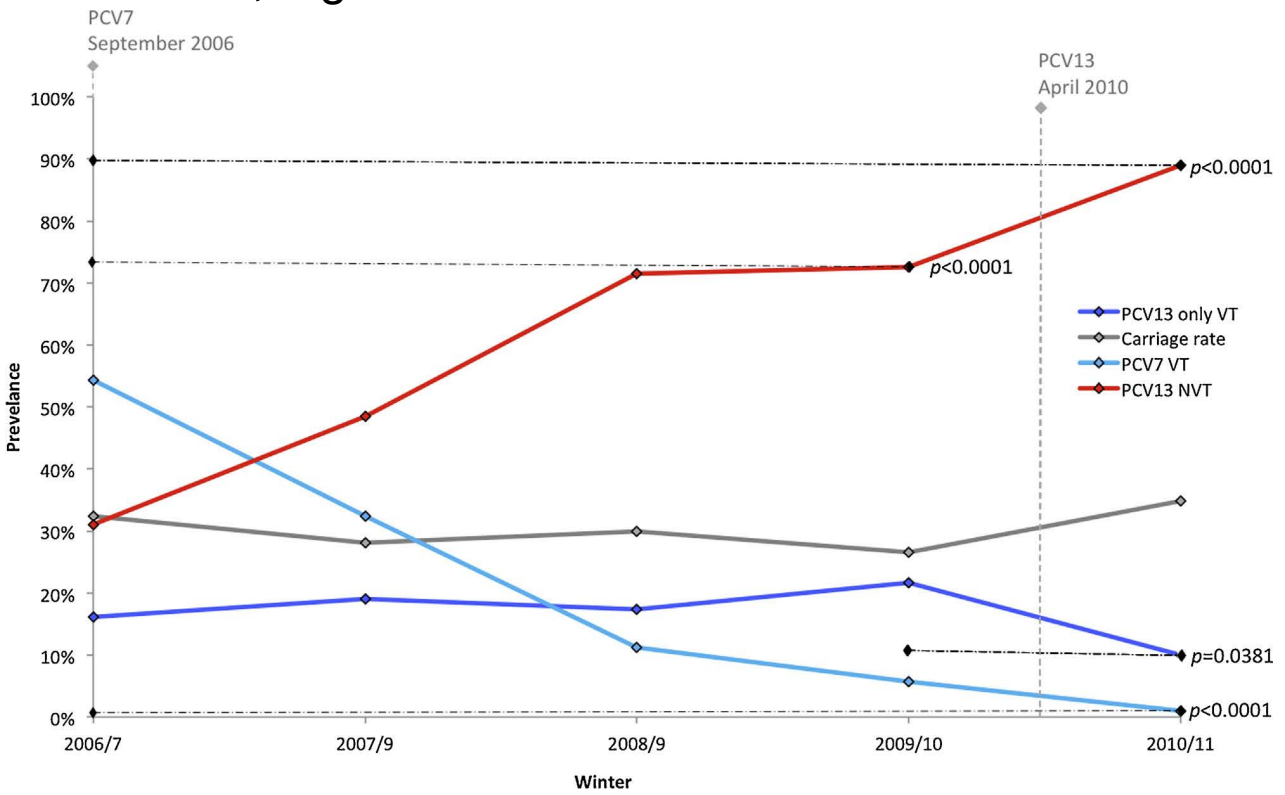


Gladstone et al. Vaccine 2015

- Fortunately, carriages by NVT increases, but diseases not so much.

A real-world example

- Pneumococcus: type replacement in many countries after introduction of vaccination, e.g. in the UK:



Gladstone et al. Vaccine 2015

- Fortunately, carriages by NVT increases, but diseases not so much.

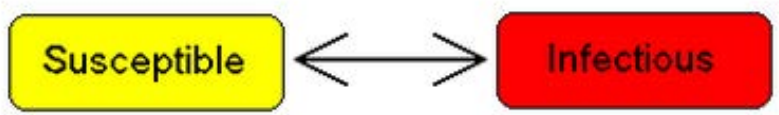
Competition, synergy or both: predicting the outcome of vaccination

- For some pathogens, we don't know whether types compete or help each other and whether type replacement will occur.
- Can we predict the outcome before vaccination?

What I am going to talk about now...

- Formulate the system that describes the dynamics of the type distribution
- Formulate the event we want to predict
- Formulate what data we have to predict
- A predictor we propose, why and how well does it work?

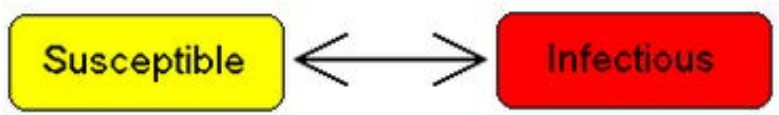
Formulate the system



A SIS model for more than one type

- n: number of types
- $S = \{1, \cdots, n\}$: index set of types
- $X \in \mathcal{P}(S)$: infection state, i.e. sets of types a host is infected with
- I_X: proportion of the population in infection state X
- $\{I_X\}_{X \in \mathcal{P}(S)}$: type distribution
- $q_{X \to Y}$: transition rate from state X to Y

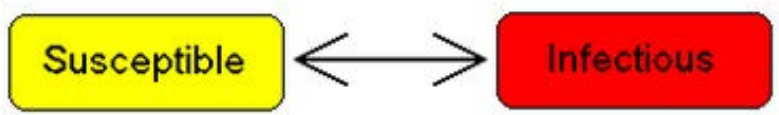
Formulate the system



A SIS model for more than one type

- n: number of types
- $S = \{1, \cdots, n\}$: index set of types
- $X \in \mathcal{P}(S)$: infection state, i.e. sets of types a host is infected with
- I_X: proportion of the population in infection state X
- $\{I_X\}_{X \in \mathcal{P}(S)}$: type distribution
- $q_{X \to Y}$: transition rate from state X to Y

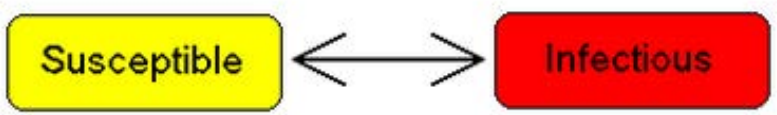
Formulate the system



A SIS model for more than one type

- n: number of types
- $S = \{1, \cdots, n\}$: index set of types
- $X \in \mathcal{P}(S)$: infection state, i.e. sets of types a host is infected with
- I_X: proportion of the population in infection state X
- $\{I_X\}_{X \in \mathcal{P}(S)}$: type distribution
- $q_{X \to Y}$: transition rate from state X to Y

Formulate the system



A SIS model for more than one type

- n: number of types
- $S = \{1, \cdots, n\}$: index set of types
- $X \in \mathcal{P}(S)$: infection state, i.e. sets of types a host is infected with
- I_X: proportion of the population in infection state X
- $\{I_X\}_{X \in \mathcal{P}(S)}$: type distribution
- $q_{X \to Y}$: transition rate from state X to Y

Formulate the system

Possible transitions involving I_X:

- from and to $I_{X\setminus\{i\}}$, $i \in X$;
- from and to $I_{X\cup\{i\}}$, $i \notin X$.

The term for I_X in the ODE system

$$\frac{dI_X}{dt} = \sum_{i\in X} I_{X\setminus\{i\}} q_{X\setminus\{i\}\to X} - \sum_{i\in X} I_X q_{X\to X\setminus\{i\}} + \sum_{i\notin X} I_{X\cup\{i\}} q_{X\cup\{i\}\to X} - \sum_{i\notin X} I_X q_{X\to X\cup\{i\}}$$

Formulate the system

Transition without type interactions

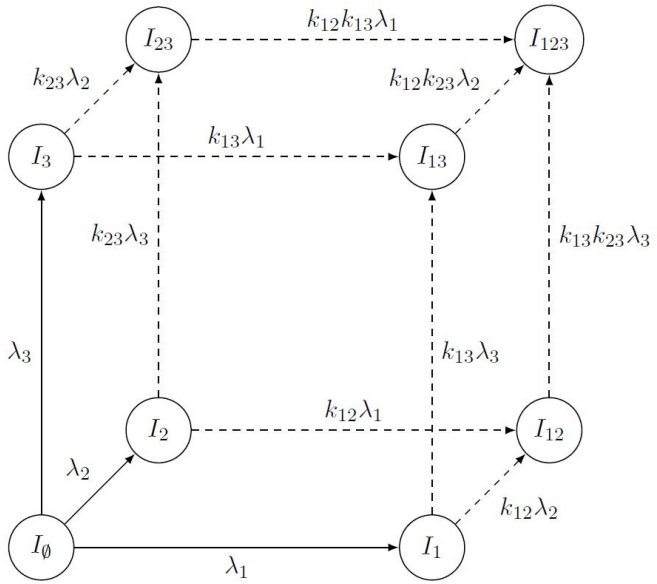
- c: contact rates
- β_i: transmission probability
- $q_{\emptyset \to \{i\}} = c\beta_i \sum_{i \in X} I_X$: baseline acquisition rate of type i
- $q_{X \cup \{i\} \to X} = \mu_i$: clearance rate of i at any state with type i

Formulate the system

Type interactions

- Infections with one type interfere with the acquisition of infections with another type.
- Each resident type contributes a factor to the interactions with the incoming type.
- Pairwise symmetric interactions, i.e. $k_{ij} = k_{ji}$.
synergy	neutrality	competition
$k_{ij} > 1$	$k_{ij} = 1$	$k_{ij} < 1$
- For example, $I_{12} \to I_{123}$ at rate $k_{13}k_{23}\lambda_3$.

$(n = 3)$

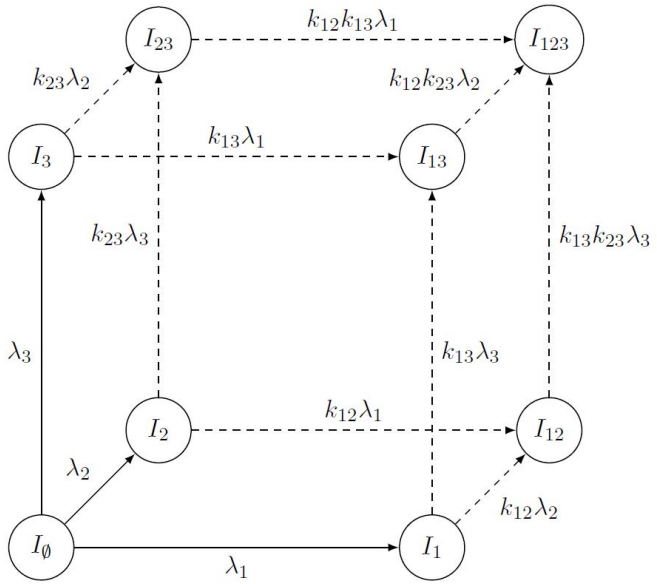


Formulate the system

Type interactions

- Infections with one type interfere with the acquisition of infections with another type.
- Each resident type contributes a factor to the interactions with the incoming type.
- Pairwise symmetric interactions, i.e. $k_{ij} = k_{ji}$.
synergy	neutrality	competition
$k_{ij} > 1$	$k_{ij} = 1$	$k_{ij} < 1$
- For example, $I_{12} \to I_{123}$ at rate $k_{13}k_{23}\lambda_3$.

$(n = 3)$

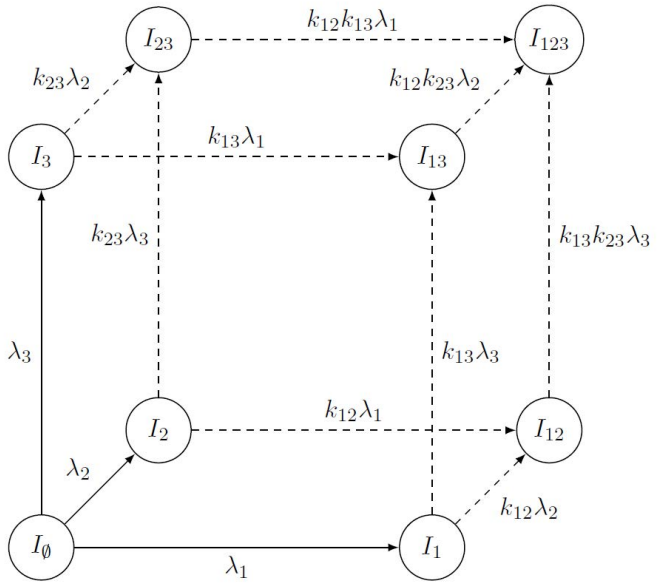


Formulate the system

Type interactions

- Infections with one type interfere with the acquisition of infections with another type.
- Each resident type contributes a factor to the interactions with the incoming type.
- Pairwise symmetric interactions, i.e. $k_{ij} = k_{ji}$.
synergy	neutrality	competition
$k_{ij} > 1$	$k_{ij} = 1$	$k_{ij} < 1$
- For example, $I_{12} \to I_{123}$ at rate $k_{13}k_{23}\lambda_3$.

$(n = 3)$

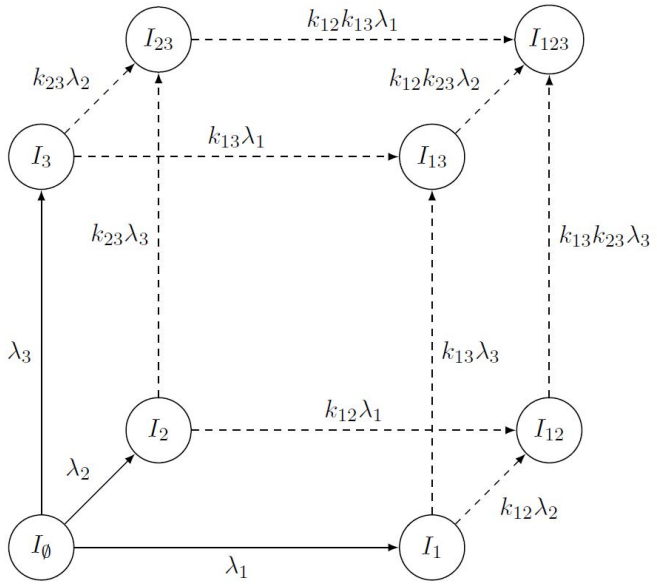


Formulate the system

Type interactions

- Infections with one type interfere with the acquisition of infections with another type.
- Each resident type contributes a factor to the interactions with the incoming type.
- Pairwise symmetric interactions, i.e. $k_{ij} = k_{ji}$.
synergy	neutrality	competition
$k_{ij} > 1$	$k_{ij} = 1$	$k_{ij} < 1$
- For example, $I_{12} \to I_{123}$ at rate $k_{13}k_{23}\lambda_3$.

$(n = 3)$



Formulate the system

Vaccination

- VT: set of vaccine types
- NVT: set of non-vaccine types
- For $i \in VT$, change $\beta_i \rightarrow \theta\beta_i$, with $\theta < 1$.

Formulate the events

- $\{I_X\}_{X \in \mathcal{P}(S)}$: equilibrium before vaccination
- $\{I'_X\}_{X \in \mathcal{P}(S)}$: equilibrium after vaccination

Type-specific replacement

- $\sum_{i \in X} I_X < \sum_{i \in X} I'_X$, for $i \in NVT$

All NVTs replacement

- $\sum_{X \cap NVT \neq \emptyset} I_X < \sum_{X \cap NVT \neq \emptyset} I'_X$

Formulate the data

- $\{I_X\}_{X \in \mathcal{P}(S)}$: equilibrium before vaccination

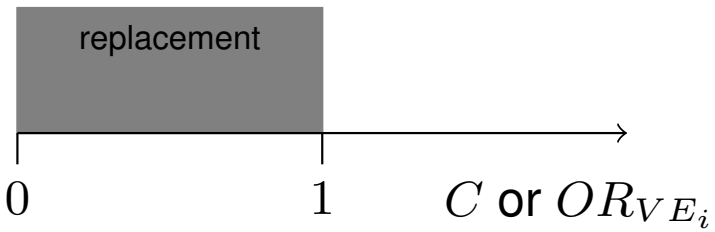
A predictor based on the odds ratio of co-infections

Type-specific predictor

- $$OR_{VT,i} = \left(\frac{\sum_{X \cap VT \neq \emptyset, i \notin X} I_{X \cup \{i\}}}{\sum_{X \cap VT \neq \emptyset, i \notin X} I_X} \right) / \left(\frac{\sum_{X \cap VT = \emptyset, i \notin X} I_{X \cup \{i\}}}{\sum_{X \cap VT = \emptyset, i \notin X} I_X} \right)$$

All NVTs predictor

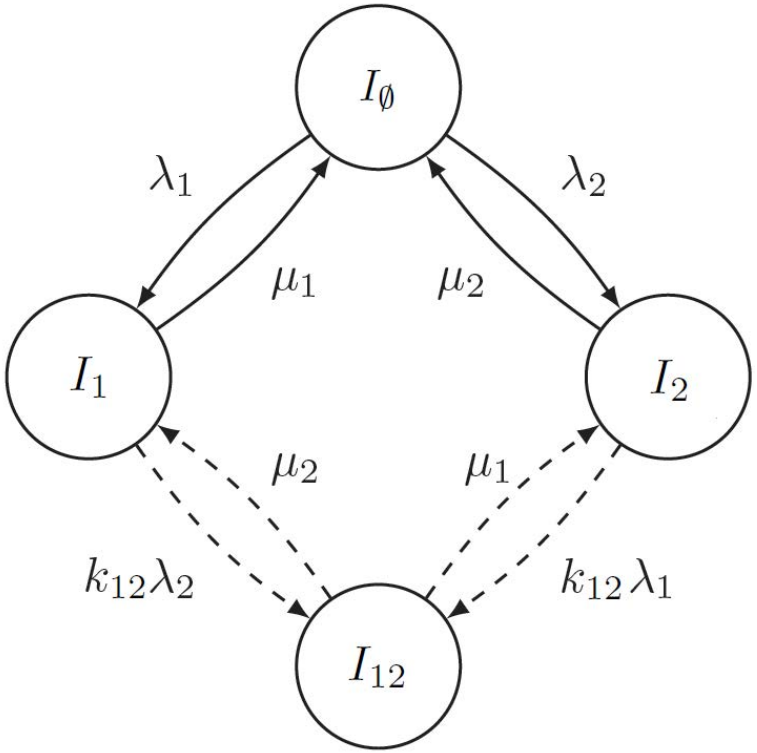
- $$C = \prod_{i \in NVT} OR_{VT,i}$$



An exact predictor for $n = 2$

$P = OR_{1,2}$

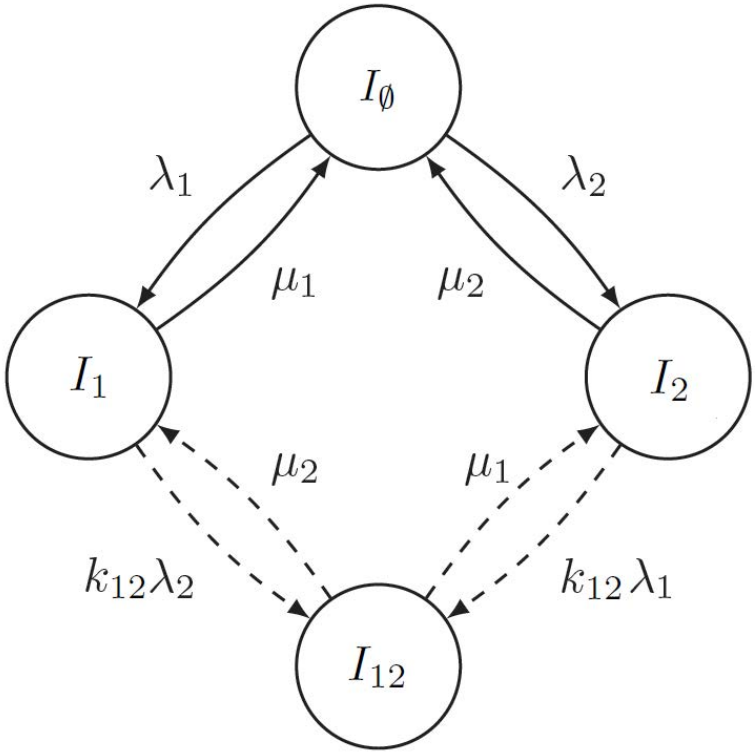
- $VT = \{1\}$
- $NVT = \{2\}$



An exact predictor for $n = 2$

$\{I_X\}_{X \in \mathcal{P}(S)}$ satisfies:

- $$\begin{cases} I_\emptyset = \mu_1 \mu_2 / C \\ I_1 = \lambda_1 \mu_2 / C \\ I_2 = \mu_1 \lambda_2 / C \\ I_{12} = k_{12} \lambda_1 \lambda_2 / C \end{cases}$$



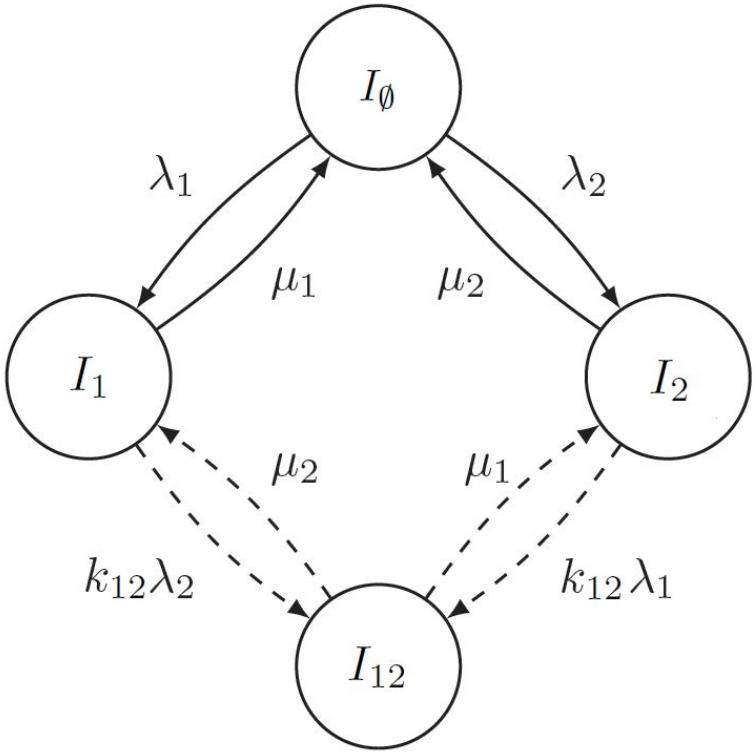
An exact predictor for $n = 2$

Detailed balance equations:

- For any I_X and I_Y:

$$\frac{I_X}{I_Y} = \frac{q_{Y \to X}}{q_{X \to Y}}$$

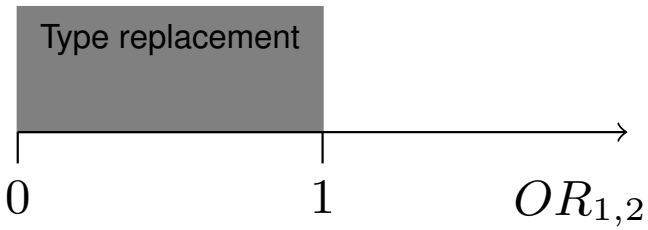
- (reversibility)

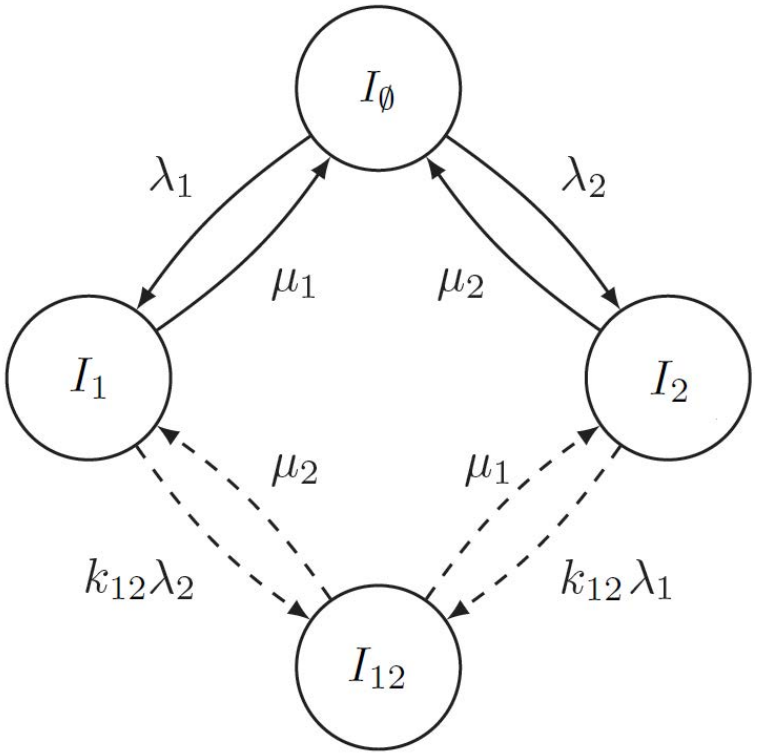


An exact predictor for $n = 2$

An estimator of k

$$
\begin{aligned}
OR_{1,2} &= \left(\frac{I_{12}}{I_2}\right) / \left(\frac{I_1}{I_\emptyset}\right) \\
&= \left(\frac{q_{2\to 12}}{q_{12\to 2}}\right) / \left(\frac{q_{\emptyset\to 1}}{q_{1\to\emptyset}}\right) \\
&= \left(\frac{k\lambda_1}{\mu_1}\right) / \left(\frac{\lambda_1}{\mu_1}\right) \\
&= k
\end{aligned}
$$

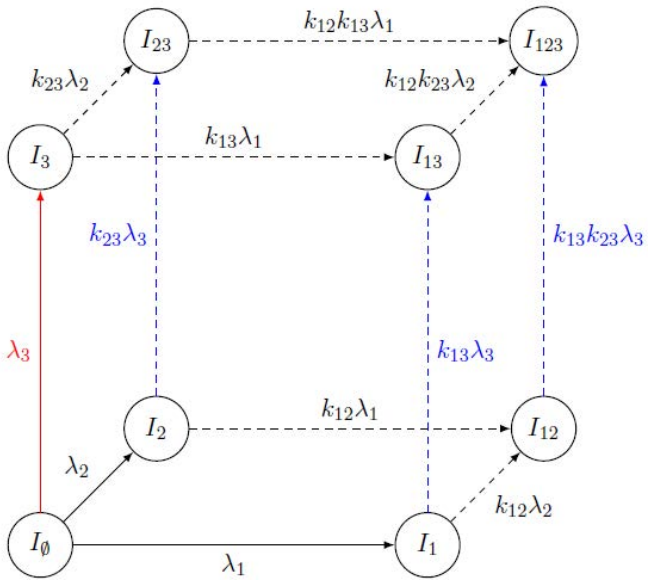




When $n > 2$

- Why is this a good predictor?
  - $\{I_X\}_{X \in \mathcal{P}(S)}$ satisfies: $I_X = \left(\prod_{i \in X} \lambda_i \right) \left(\prod_{i \notin X} \mu_i \right) \left(\prod_{i,j \in X} k_{ij} \right) / C$
  - Still reversible!
- How well does it work? Zooming into 2 settings:
  - VT $= \{1, 2\}$, NVTs $= \{3\}$
  - VT $= \{1\}$, NVTs $= \{2, 3\}$

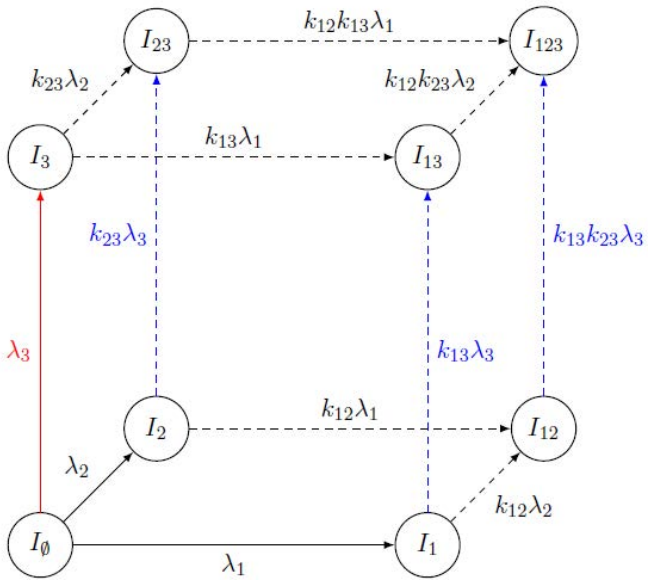
VT $= \{1, 2\}$ and NVTs $= \{3\}$



- A weighted average of k_{13}, k_{23} and $k_{12}k_{23}$ as a predictor for type replacement.
- I_1, I_2 and I_{12} are the appropriate weights.
- Due to reversibility:

$$
\begin{aligned}
C &= OR_{VT,3} \\
&= \left(\frac{I_{13} + I_{23} + I_{123}}{I_1 + I_2 + I_{12}}\right) / \left(\frac{I_3}{I_\emptyset}\right) \\
&= \frac{k_{13}I_1 + k_{23}I_2 + k_{13}k_{23}I_{12}}{I_1 + I_2 + I_{12}}
\end{aligned}
$$

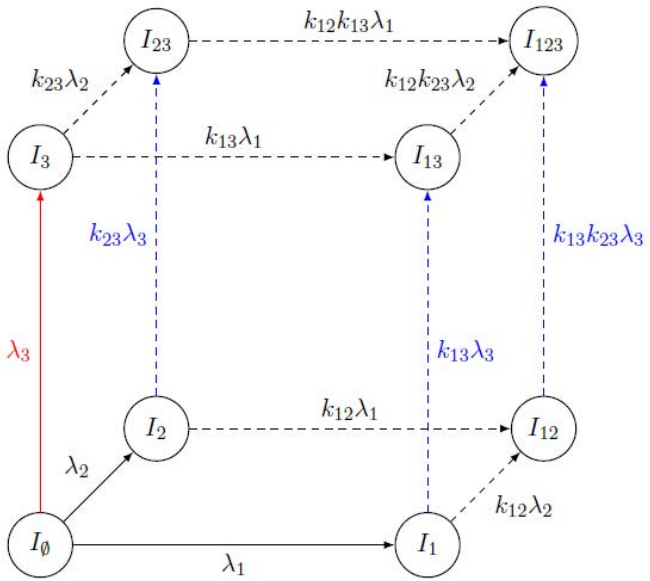
VT $= \{1, 2\}$ and NVTs $= \{3\}$



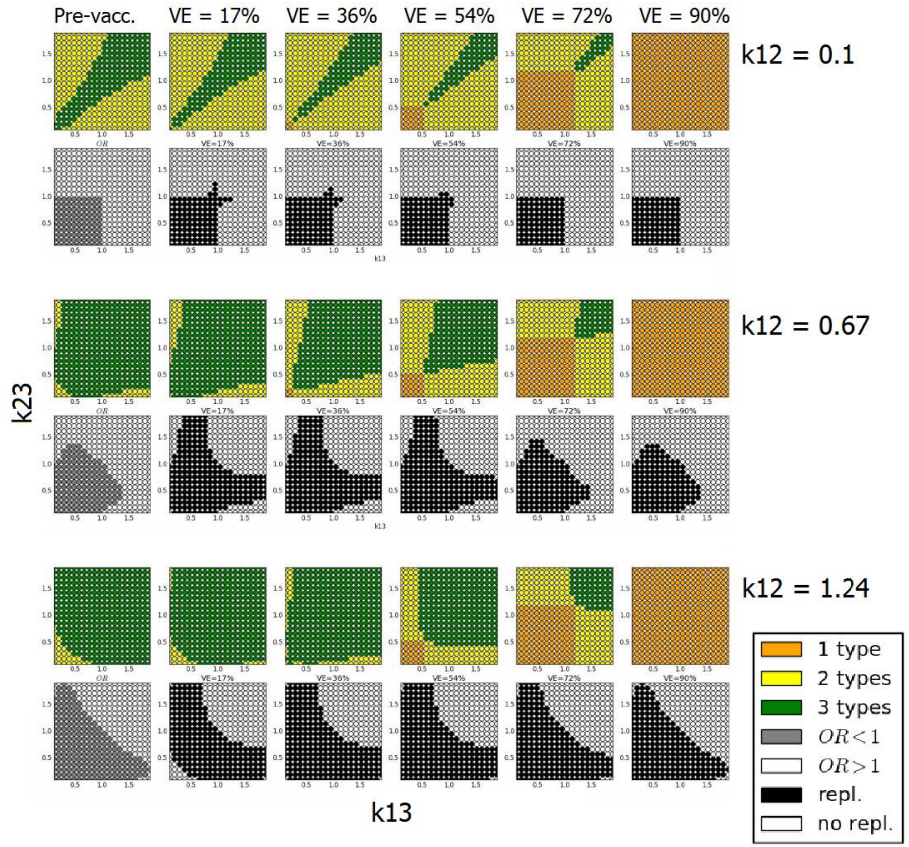
- A weighted average of k_{13}, k_{23} and $k_{12}k_{23}$ as a predictor for type replacement.
- I_1, I_2 and I_{12} are the appropriate weights.
- Due to reversibility:

$$
\begin{aligned}
C &= OR_{VT,3} \\
&= \left(\frac{I_{13} + I_{23} + I_{123}}{I_1 + I_2 + I_{12}}\right) / \left(\frac{I_3}{I_\emptyset}\right) \\
&= \frac{k_{13}I_1 + k_{23}I_2 + k_{13}k_{23}I_{12}}{I_1 + I_2 + I_{12}}
\end{aligned}
$$

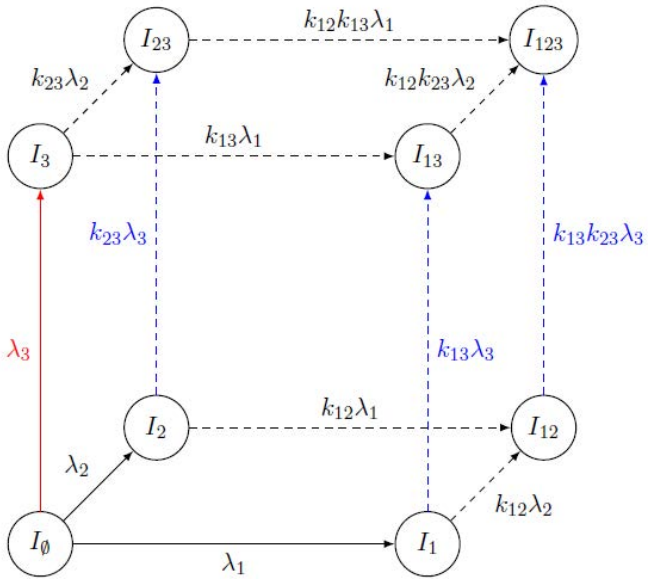
VT $= \{1, 2\}$ and NVTs $= \{3\}$



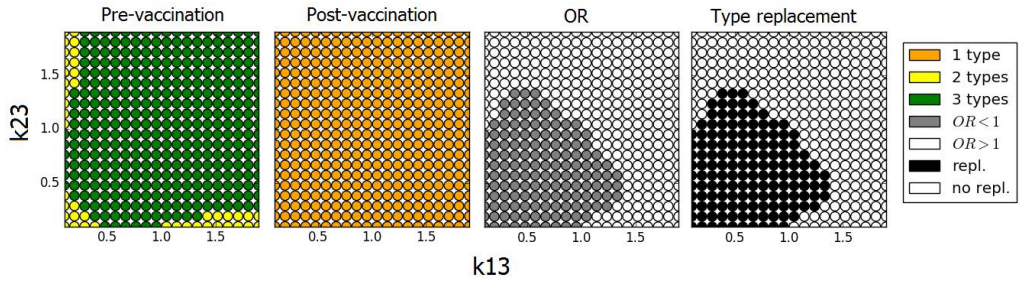
- It works when all VTs are eradicated:



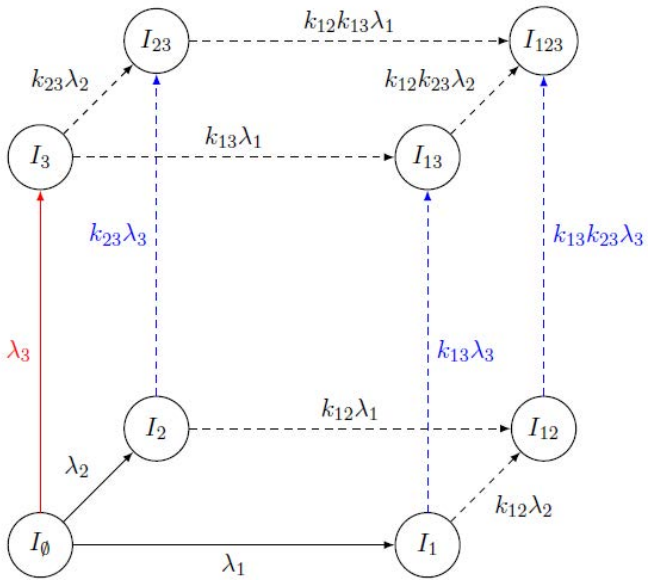
VT $= \{1, 2\}$ and NVTs $= \{3\}$



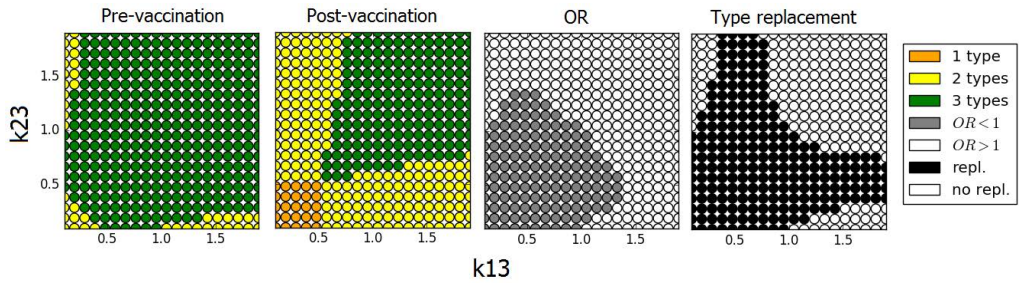
- $VE = 90\%, k_{12} = 0.67$:



VT $= \{1, 2\}$ and NVTs $= \{3\}$

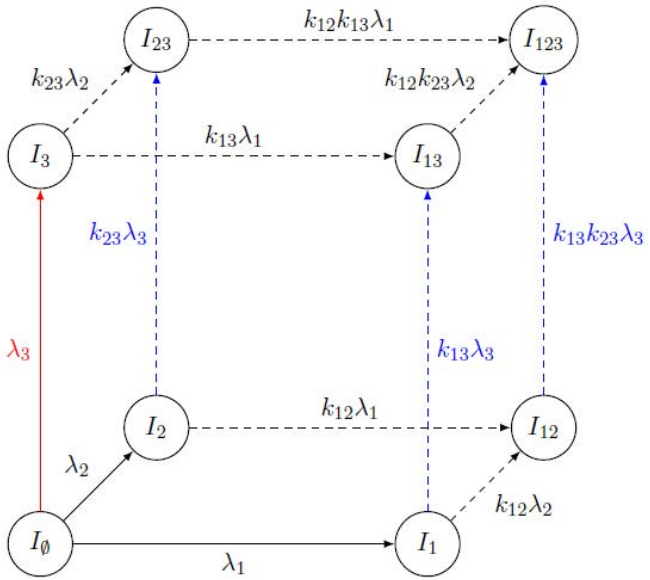


- For example, $VE = 50\%, k_{12} = 0.67$:

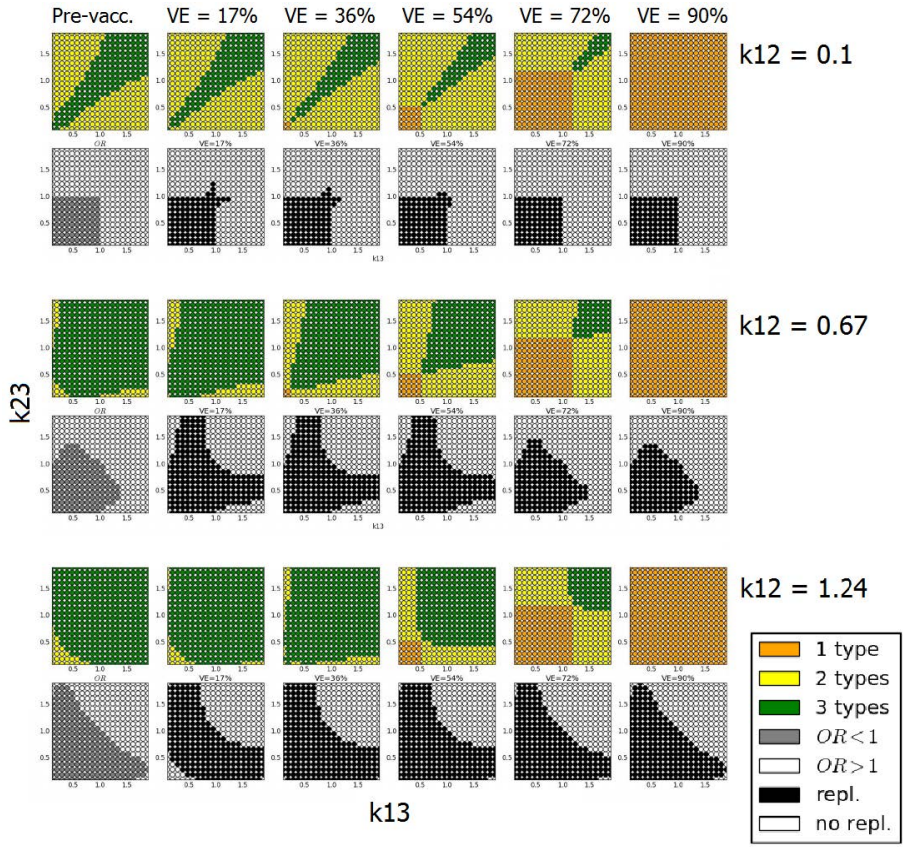


- Incorrect prediction if:
  - no total eradication
  - k_{13}, k_{23} not both > 1 or < 1.

VT $= \{1, 2\}$ and NVTs $= \{3\}$

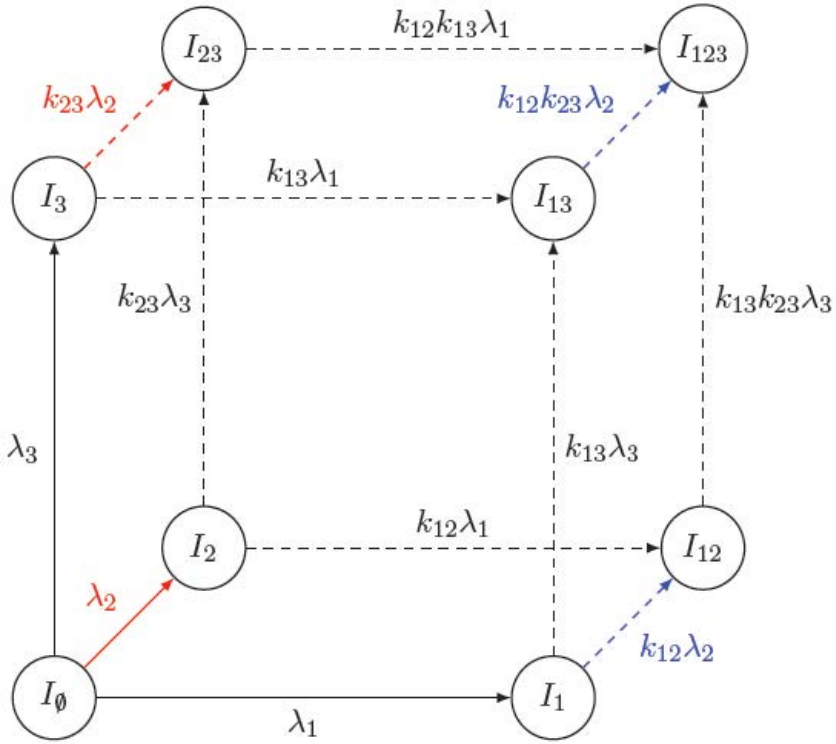


- Other values of VE and k_{12}:

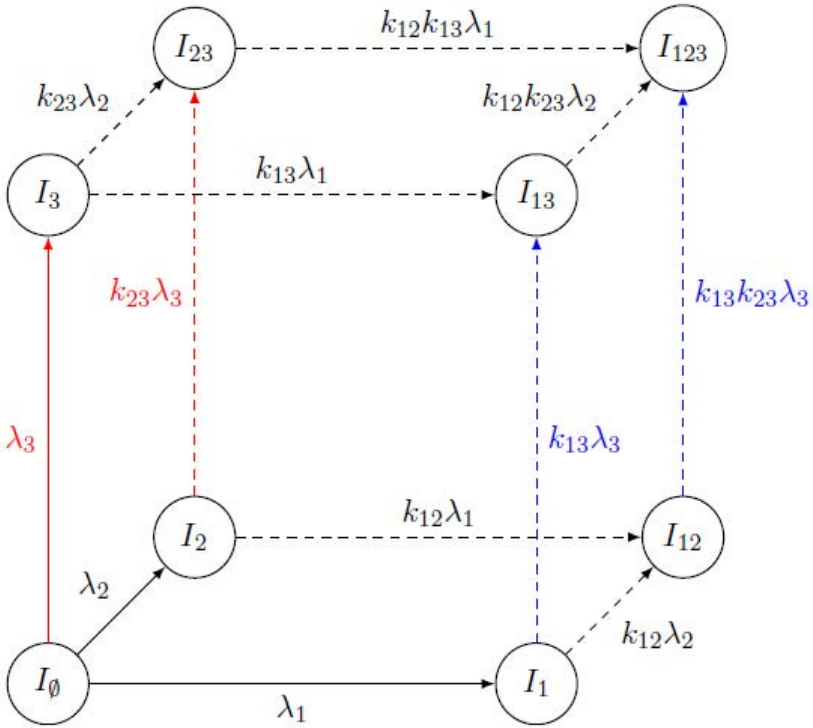


VT $= \{1\}$ and NVTs $= \{2, 3\}$

type 2



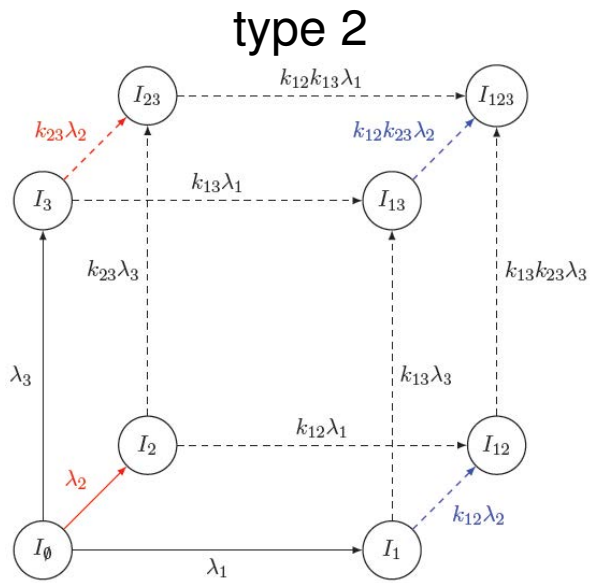
type 3



$$C = OR_{1,2}OR_{1,3}$$

$$= \left[\left(\frac{I_{12} + I_{123}}{I_1 + I_{13}}\right)/\left(\frac{I_2 + I_{23}}{I_\emptyset + I_3}\right)\right] \cdot \left[\left(\frac{I_{13} + I_{123}}{I_1 + I_{12}}\right)/\left(\frac{I_3 + I_{23}}{I_\emptyset + I_3}\right)\right]$$

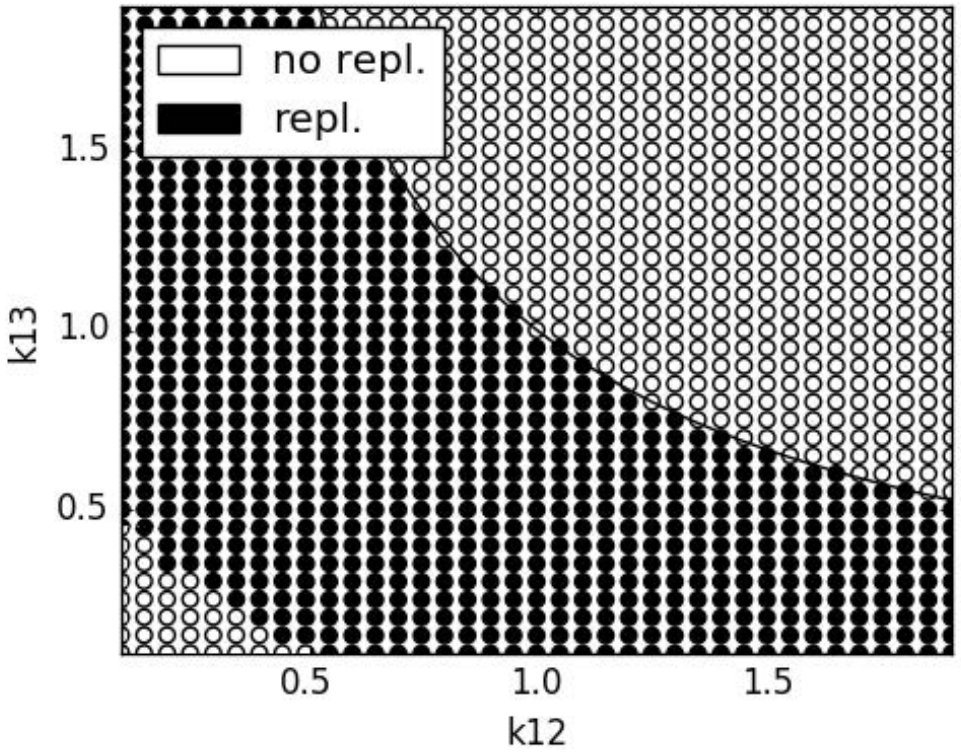
VT $= \{1\}$ and NVTs $= \{2, 3\}$



$$
\begin{aligned}
OR_{1,2} &= \left(\frac{I_{12} + I_{123}}{I_1 + I_{13}}\right) / \left(\frac{I_2 + I_{23}}{I_\emptyset + I_3}\right) \\
&= \left(\frac{k_{12} I_1 + k_{12} k_{23} I_{13}}{I_1 + I_{13}}\right) / \left(\frac{1 I_\emptyset + k_{23} I_3}{I_\emptyset + I_3}\right) \\
&= k_{12} \cdot \left[\left(\frac{I_\emptyset + k_{23} k_{13} I_3}{I_\emptyset + k_{13} I_3}\right) / \left(\frac{I_\emptyset + k_{23} I_3}{I_\emptyset + I_3}\right)\right]
\end{aligned}
$$

VT $= \{1\}$ and NVTs $= \{2, 3\}$

- C predicts correctly in most cases.
- For example, with $k_{23} = 1$:



VT $= \{1\}$ and NVTs $= \{2, 3\}$

- If $k_{23} \neq 1$, prediction sometimes fails.
- When:
  - $C \approx 1$ (small increase),
  - some NVTs also disappear (small increase),
  - some previously extinct NVTs reappear (big increase).
- Prediction becomes harder with more types.

VT $= \{1\}$ and NVTs $= \{2, 3\}$

- If $k_{23} \neq 1$, prediction sometimes fails.
- When:
  - $C \approx 1$ (small increase),
  - some NVTs also disappear (small increase),
  - some previously extinct NVTs reappear (big increase).
- Prediction becomes harder with more types.

VT $= \{1\}$ and NVTs $= \{2, 3\}$

- If $k_{23} \neq 1$, prediction sometimes fails.
- When:
  - $C \approx 1$ (small increase),
  - some NVTs also disappear (small increase),
  - some previously extinct NVTs reappear (big increase).
- Prediction becomes harder with more types.

VT $= \{1\}$ and NVTs $= \{2, 3\}$

- If $k_{23} \neq 1$, prediction sometimes fails.
- When:
  - $C \approx 1$ (small increase),
  - some NVTs also disappear (small increase),
  - some previously extinct NVTs reappear (big increase).
- Prediction becomes harder with more types.

1 VTs and >1 NVTs

Performance of C, provided that

- all VTs eradicated by vaccination,
- all NVTs present before vaccination.

		Sensitivity	Specificity
$VT = \{1\}$	$NVT = \{2, 3\}$	99.98%	99.56%
$VT = \{1\}$	$NVT = \{2, 3, 4\}$	96.36%	98.57%
$VT = \{1\}$	$NVT = \{2, 3, 4, 5\}$	95.80%	97.67%

		True condition	
		occurrence type repl.	non-occurrence type repl.
Predicted condition	$C < 1$	P_o =Predicted occurrence	U_n =Unpredicted non-occurrence
	$C > 1$	U_o =Unpredicted occurrence	P_n =Predicted non-occurrence
		Sensitivity$= \frac{P_o}{P_o + U_o}$	**Specificity**$= \frac{P_n}{P_n + U_n}$

>1 VTs and >1 NVTs

Performance of C, provided that

- all VTs eradicated by vaccination,
- all NVTs present before vaccination.

		Sensitivity	Specificity
$VT = \{1, 2\}$	$NVT = \{3, 4\}$	96.03%	99.22%
$VT = \{1, 2\}$	$NVT = \{3, 4, 5\}$	92.97%	98.78%
$VT = \{1, 2, 3\}$	$NVT = \{4, 5\}$	89.40%	98.63%

Conclusions and discussions

- An easy to calculate predictor with a clear interpretation that works quite well.
- Would our predictor still work if some model assumptions are violated?
  - SIS infection dynamics (not reversible otherwise)
  - Symmetric pairwise interactions (not reversible otherwise)
  - Multiplicative interactions (not reversible otherwise)
  - No unobserved heterogeneity (need adjustment otherwise)

Conclusions and discussions

- An easy to calculate predictor with a clear interpretation that works quite well.
- Would our predictor still work if some model assumptions are violated?
  - SIS infection dynamics (not reversible otherwise)
  - Symmetric pairwise interactions (not reversible otherwise)
  - Multiplicative interactions (not reversible otherwise)
  - No unobserved heterogeneity (need adjustment otherwise)