Efficacy of hand hygiene, cohorting of health care workers and patients and isolation

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Outline

Introduction

- Antimicrobial resistance problem
  - Size burden[1,2]
  - Addition/Replacement
- Nosocomial infections preventable
- Infection vs transmission prevention
- Horizontal vs vertical interventions

[1] **O'Neill**, **The Review on Antimicrobial Resistance 2014**.
[2] **Cassini**, **Lancet Infect Dis. 2019**.

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- Nosocomial infections preventable
- Infection vs transmission prevention
- Horizontal vs vertical interventions
  - Vertical: targeting single pathogen
    - screening & isolation
    - cohorting or decolonization of patients colonized with MRSA
  - Horizontal: targeting multiple pathogens
    - glove and gown use
    - improving hand hygiene adherence
    - universal chlorhexidin body washings
    - environmental cleaning
    - cohorting of patients and health care workers (HCWs)

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- Antimicrobial resistance problem
- Nosocomial infections preventable
- Infection vs transmission prevention
- Horizontal vs vertical interventions
  - Vertical: targeting single pathogen
    - screening & isolation
    - cohorting or decolonization of patients colonized with MRSA

AIM: Analyze interventions and their interaction in one framework

    - improving hand hygiene adherence
    - universal chlorhexidin body washings
    - environmental cleaning
    - cohorting of patients and health care workers (HCWs)

Cohorting of patients and HCWs

- Very often applied
- Horizontal vs vertical
- Mechanisms
  - Outbreaks restricted to cohorts
  - Frequency repeated contacts increased
- Imperfect
  - Physicians
  - Tasks requiring multiple HCWs
  - Breaks
- Many structures, not captured by single number

Hand hygiene and transmission

Assumptions:

- Only indirect transmission
- Hand hygiene may remove hand contamination
- Hand hygiene opportunities between patient contacts

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- Patients colonized/uncolonized
- HCWs hands contaminated/uncontaminated
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- For now: 1 type of HCW

Parameters:

- Probability hand decontamination successful: ξ.
- Probability acquisition by patient if hands HCW contaminated: π
- Probability acquisition hand contamination by HCW if patient is colonized: p
  - $p \approx 0.5 - 0.7$ for VRE[1]

[1] **Hayden et al. ICHE 2008: 29: 149-54**.

Acquisition colonization

Patient acquires colonization from previous contact of HCW

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- $P(t_{-j})$ is the probability that patient j contacts back was colonized
- Condition on most recent acquisition by HCW

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\begin{aligned}
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&P(t_{-3})p(1-\xi)(1-P(t_{-2})p)(1-\xi)(1-P(t_{-1})p)(1-\xi)\pi+\ldots=\\
&p(1-\xi)\pi\sum_{j=1}^{\infty}P(t_{-j})\prod_{k=1}^{j-1}(1-\xi)(1-P(t_{-k})p).
\end{aligned}
$$

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Acquisition colonization

$$p(1-\xi)\pi \sum_{j=1}^{\infty} P(t_{-j}) \prod_{k=1}^{j-1} (1-\xi)(1-P(t_{-k})p).$$

- Depends on cohorting structure
- Depends on changes in colonized patients over time

Approximation

- Assume $P(t_{-j})$ equals $P(t_0)$ for all $j > 0$.
- Multiple events rare during the typical duration of hand contamination.

$$p(1-\xi)\pi \sum_{j=1}^{\infty} P(t_{-j}) \prod_{k=1}^{j-1} (1-\xi)(1-P(t_{-k})p) = \frac{p(1-\xi)\pi P(t_0)}{1-(1-\xi)(1-P(t_0)p)}$$

- Assume mass action: $P(t_0) = \frac{i}{n}$
- Assume patient receives κ contacts per hour
- define $\beta = \kappa p \pi$
- rate acquisition: $\frac{\beta(1-\xi)\frac{i}{n}}{1-(1-\xi)(1-\frac{i}{n}p)}$.
- denominator due to persistence of hand contamination
- effect substantial if ξ in order of 0.5[1]

[1] **Nijssen et al., Archives of Internal Medicine. 2003;163:2785-6.**

General case

1. Each HCW may have a different level of hand hygiene.
2. Each patient may have a different susceptibility and infectivity.
3. Any cohorting scheme fits in the framework
4. The level of hand hygiene of a HCW may depend on the patients before and after the hand hygiene opportunity, e.g.,
   4.1 Hand hygiene higher between patients in different cohorts.
   4.2 Hand hygiene higher if HCW moves from a patient with known colonization to a patient without known colonization, i.e., isolation

Definitions

- ξ_{ij}^k: Probability hand hygiene is performed if HCW k moves from patient i to patient j.
- p_i^k: Probability that HCW k picks up hand contamination due to contact with patient i given that patient i is colonized.
- π_j^k: Probability that patient j acquires colonization during a contact with HCW k given that the hands of HCW k are contaminated.
- $\mathcal{I}_i$: $\mathcal{I}_i = 0$ if patient i is uncolonized and $\mathcal{I}_i = 1$ if patient i is colonized.
- m_{ij}^k: Probability that previous contact of HCW k was with patient i given current contact with patient j
- m_j^k: Probability that a random contact of HCW k is with patient j.

Acquisition rates: Assume a certain state

- Susceptible patient j at risk of acquisition if HCW contaminated.
- Contamination picked up by previous or earlier patient.
- Sum over most recent pick up of hand contamination.
- For patient j to be at risk, no successful hand decontamination could have occurred afterwards.

Define the $n \times n$-matrix $A(k)$ with elements

$$a_{ij}^{k} = m_{ij}^{k}(1 - \mathcal{I}_i p_i^{k})(1 - \xi_{ij}^{k}).$$

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$$a_{ij}^k = m_{ij}^k (1 - \mathcal{I}_i p_i^k)(1 - \xi_{ij}^k).$$

a_{ij}^k: $\mathcal{P}$(Previous contact of HCW k with patient i, no contamination picked up and no successful hand decontamination between contact with patient i and j| current contact of HCW k with patient j)

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Use $(1 - \mathcal{I}_i p_i^k)$ implies approximation multiple acquisitions are rare during the typical duration of hand contamination.

a

up and no successful hand decontamination between contact with patient i and j| current contact of HCW k with patient j)

Acquisition rates

If HCW k has c_k contacts per unit of time, the rate β_{ij}^k at which patient i infects patient j via HCW k is:

$$\beta_{ij}^k = c_k \mathcal{I}_i p_i^k ((1-\xi_{i1}^k) m_{i1}^k, (1-\xi_{i2}^k) m_{i2}^k, \ldots, (1-\xi_{in}^k) m_{in}^k) \left(\sum_{l=0}^{\infty} (A(k))^l e_j \right) \pi_j^k m_j^k (1-\mathcal{I}_j)$$

e_j:unit column vector of length n which is only non-zero at position j.

- Transmission rate β_{ij}^k depends on colonization status of other patients via the matrix $A(k)$.

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Acquisition rates

If $\xi_{ij}^k > 0$, the absolute value of all eigenvalues of the matrix $A(k)$ are less than one. Therefore, we can use the geometric series for matrices:

$$\beta_{ij}^k = c_k \mathcal{I}_i p_i^k \pi_j^k m_j^k (1-\mathcal{I}_j)((1-\xi_{i1}^k)m_{i1}^k, (1-\xi_{i2}^k)m_{i2}^k, \ldots, (1-\xi_{in}^k)m_{in}^k)(\mathbb{1}-A(k))^{-1}e_j$$

where $\mathbb{1}$ is the $n \times n$ identity matrix. The total rate β_{ij} at which patient i infects patients j is the sum of the rates via each HCW k. If there are N HCW, we obtain:

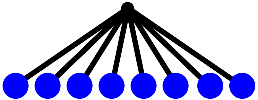
$$\beta_{ij} = \sum_{k=1}^{N} \beta_{ij}^k.$$

The overall rate β_j at which patient j becomes infected is:

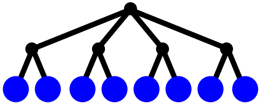
$$\beta_j = \sum_{i=1}^{n} \beta_{ij}.$$

Cohorting schemes

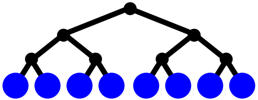
- A unit with $n = 8$ patients,
- 4 nurses who may be cohorted
- physicians who are not cohorted.
- Next contact HCW independent of previous one: $m_{ji}^k = m_i^k$.



A: No cohorting



B: 1^{st}−order



C: Higher−order

Higher-order cohorting

- Fraction x of contacts of a nurse are with his/her assigned patients
- Fraction $y \leq 1 - x$ of the contacts are with patients in the the same subunit he/she is not assigned
- Fraction $1 - x - y$ of the contacts are with one of the four patients in the other subunit.
- $x \geq y \geq \frac{1-x}{3}$.

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		Patient (i)							
HCW (k)		1	2	3	4	5	6	7	8
1	nurse A	$\frac{x}{2}$	$\frac{x}{2}$	$\frac{y}{2}$	$\frac{y}{2}$	$\frac{1-x-y}{4}$	$\frac{1-x-y}{4}$	$\frac{1-x-y}{4}$	$\frac{1-x-y}{4}$
2	nurse B	$\frac{y}{2}$	$\frac{y}{2}$	$\frac{x}{2}$	$\frac{x}{2}$	$\frac{1-x-y}{4}$	$\frac{1-x-y}{4}$	$\frac{1-x-y}{4}$	$\frac{1-x-y}{4}$
3	nurse C	$\frac{1-x-y}{4}$	$\frac{1-x-y}{4}$	$\frac{1-x-y}{4}$	$\frac{1-x-y}{4}$	$\frac{x}{2}$	$\frac{x}{2}$	$\frac{y}{2}$	$\frac{y}{2}$
4	nurse D	$\frac{1-x-y}{4}$	$\frac{1-x-y}{4}$	$\frac{1-x-y}{4}$	$\frac{1-x-y}{4}$	$\frac{y}{2}$	$\frac{y}{2}$	$\frac{x}{2}$	$\frac{x}{2}$
5	physicians	$\frac{1}{8}$	$\frac{1}{8}$	$\frac{1}{8}$	$\frac{1}{8}$	$\frac{1}{8}$	$\frac{1}{8}$	$\frac{1}{8}$	$\frac{1}{8}$

Cohorting

- 1^{st}-order cohorting: $y = \frac{1-x}{3}$
- No cohorting, i.e., mass action, $x = y = \frac{1}{4}$.

Dynamics

- Time scale is duration of stay (exponentially distributed)
- Fixed unit size
- Probability f to be colonized on admission
- Takes position in cohorting structure of previous patient
  - Vertical cohorting with admission screening needs adaptation

Kolmogorov forward equations

- define states

No cohorting:

number	state	# pos
0	{00000000}	0
1	{00000001}	1
2	{00000011}	2
3	{00000111}	3
4	{00001111}	4
5	{00011111}	5
6	{00111111}	6
7	{01111111}	7
8	{11111111}	8

Kolmogorov forward equations

$p_i(t)$: Probability that the ward is at time t in state i:

$$\frac{d}{dt}p_0(t) = -nfp_0 + (1-f)p_1(t)$$

$$\frac{d}{dt}p_i(t) = \begin{cases} +(f+\beta_{i-1})(n-i+1) & p_{i-1}(t) \\ -((f+\beta_i)(n-i)+(1-f)i) & p_i(t) \qquad \text{for } 1 \leq i < n \\ +(1-f)(i+1) & p_{i+1}(t) \end{cases}$$

$$\frac{d}{dt}p_n(t) = (f+\beta_{n-1})p_{n-1}(t) - (1-f)np_n(t)$$

β_i: acquisition rate if there are i colonized patients in the wards.

Suppose HCW k has on average c^k contacts per time unit, each patient receives on average receives c^k/n contacts per time unit from HCW k.

$$\beta_i = \sum_{k=1}^{N} \frac{c^k}{n} \frac{p^k(1-\xi^k)\pi^k \frac{i}{n}}{1-(1-\xi^k)(1-\frac{i}{n}p^k)}.$$

Steady state

- Long term effect interventions
- Solve $\frac{dp_i(t)}{dt} = 0$ for $0 \leq i \leq n$ with $\sum_{i=0}^{n} p_i = 1$

For mass action there is an explicit solution for $\mathbf{p}^s$:

$$p_i^s = \frac{\left(\frac{f}{1-f}\right)^i \prod_{j=1}^{i} \left(\frac{n-j+1}{j}\right)\left(\frac{\beta_{j-1}}{f} + 1\right)}{1 + \sum_{k=1}^{n} \left(\frac{f}{1-f}\right)^k \prod_{j=1}^{k} \left(\frac{n-j+1}{j}\right)\left(\frac{\beta_{j-1}}{f} + 1\right)}.$$

The mean prevalence, $\bar{p}$, in the unit equals:

$$\bar{p} := \frac{1}{n} \sum_{i=0}^{n} i p_i^s$$

Matrix representation

$$\frac{d}{dt}\mathbf{p}(t) = B\mathbf{p}(t)$$

where the matrix elements b_{ij} of the $(n+1)\times(n+1)$ matrix B satisfy

$$\begin{aligned}
b_{i,i} &= -((f+\beta_i)(n-i)+(1-f)i) && \text{if } 0 \leq i \leq n \\
b_{i,i+1} &= (1-f)(i+1) && \text{if } 0 \leq i < n \\
b_{i,i-1} &= (f+\beta_{i-1})(n-i+1) && \text{if } 1 \leq i \leq n \\
b_{i,j} &= 0 && \text{if } |i-j| > 1
\end{aligned}$$

- Last row of the matrix B is linearly dependent of other rows
- define matrix $\tilde{B}$ by its elements:

$$\begin{aligned}
\tilde{b}_{i,j} &= b_{ij} && \text{if } i < n \\
\tilde{b}_{i,j} &= 1 && \text{if } i = n
\end{aligned}$$

The stable distribution $\mathbf{p^s}$ is the solution of the equation:

$$\tilde{B}\mathbf{p^s} = \mathbf{e_n},$$

First-order cohorting schemes

- define states

number (s)	state	g	h	$m-g-h$	# pos
0	{{0, 0}, {0, 0}, {0, 0}, {0, 0}}	4	0	0	0
1	{{0, 0}, {0, 0}, {0, 0}, {0, 1}}	3	1	0	1
2	{{0, 0}, {0, 0}, {0, 0}, {1, 1}}	3	0	0	2
3	{{0, 0}, {0, 0}, {0, 1}, {0, 1}}	2	2	0	2
4	{{0, 0}, {0, 0}, {0, 1}, {1, 1}}	2	1	1	3
5	{{0, 0}, {0, 0}, {1, 1}, {1, 1}}	2	0	2	4
6	{{0, 0}, {0, 1}, {0, 1}, {0, 1}}	1	3	0	3
7	{{0, 0}, {0, 1}, {0, 1}, {1, 1}}	1	2	1	4
8	{{0, 0}, {0, 1}, {1, 1}, {1, 1}}	1	1	2	5
9	{{0, 0}, {1, 1}, {1, 1}, {1, 1}}	1	0	3	6
10	{{0, 1}, {0, 1}, {0, 1}, {0, 1}}	0	4	0	4
11	{{0, 1}, {0, 1}, {0, 1}, {1, 1}}	0	3	1	5
12	{{0, 1}, {0, 1}, {1, 1}, {1, 1}}	0	2	2	6
13	{{0, 1}, {1, 1}, {1, 1}, {1, 1}}	0	1	3	7
14	{{1, 1}, {1, 1}, {1, 1}, {1, 1}}	0	0	4	8

First-order cohorting schemes

- Kolmogorov equations can be defined
- For each state, determine $\beta_j = \sum_{i=1}^{n} \beta_{ij} = \sum_{i=1}^{n} \sum_{k=1}^{N} \beta_{ij}^k$
- Involves matrix-inversion of 8×8 matrix
- Still explicit expression:

$$\beta_{ij} = \sum_{k=1}^{5} c_k m_i^k \mathcal{I}_i p \pi m_j^k (1 - \mathcal{I}_j) \frac{1-\xi^k}{1-\sum_{l=1}^{8} m_l^k (1-I_l p)(1-\xi^k)}$$

Extensions

Extension	Number of states
Horizontal 2^{nd}-order	21
Vertical 1^{st}order	75
Vertical 2^{nd}-order	105
Vertical, 2 pathogens, 1^{st}-order	5460
Vertical, 2 pathogens, 2^{nd}-order	10065

Parameters

- Hand hygiene adherence nurses: 0.59[1]
- Hand hygiene adherence physicians: 0.43[1]

[1] **Nijssen et al.**, **Archives of Internal Medicine. 2003;163:2785-6.**

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- Hand hygiene adherence nurses: 0.59[1]
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- 69% contact by nurses, 31% by physicians[1]
- Patient has 97 contacts per day

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- Choose $\pi^k = \pi$ such $R_A \in \{0.5, 1, 2\}$, check assumption

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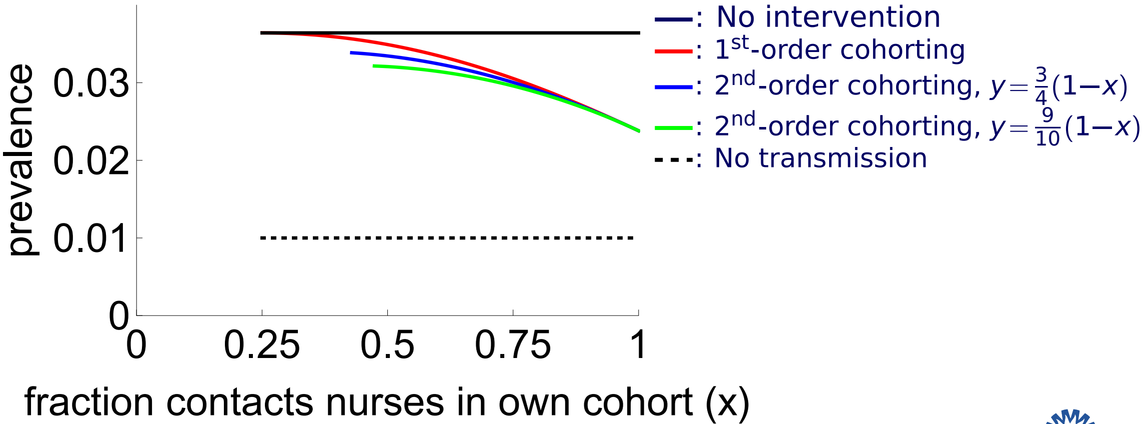
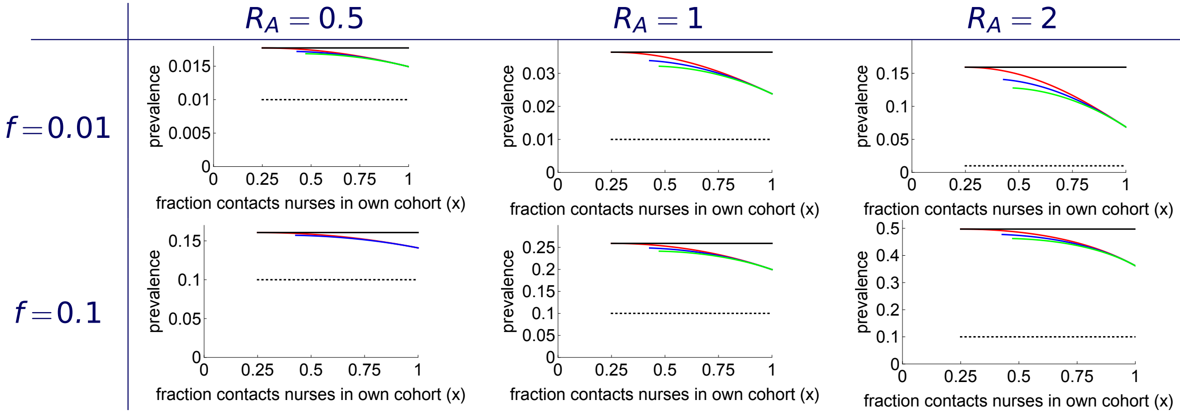
Results

Effect horizontal cohorting, $R_A = 1$, $f = 0.01$



Dependence on R_A and f

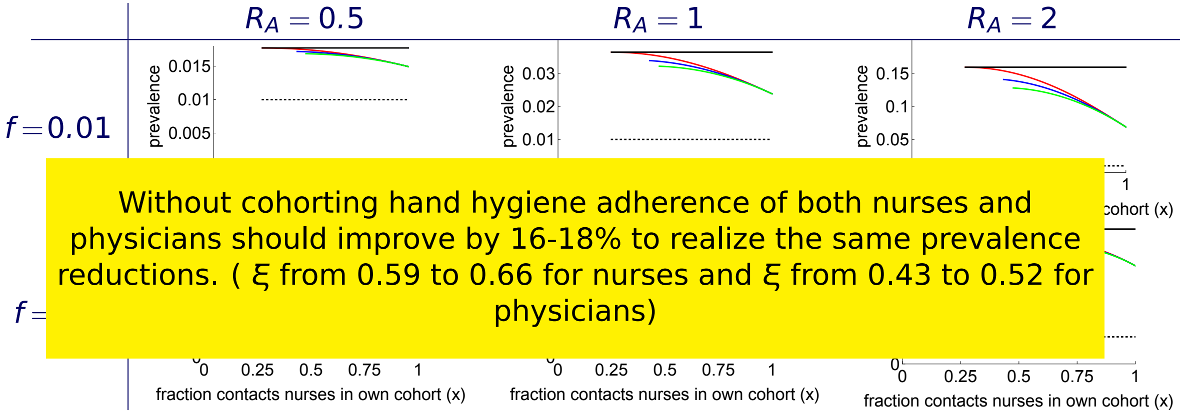


—: No intervention; —: 1^{st}-order cohorting

—: 2^{nd}-order cohorting, $y = \frac{3}{4}(1-x)$; —: 2^{nd}-order cohorting, $y = \frac{9}{10}(1-x)$

- - -: No transmission

Dependence on R_A and f



Without cohorting hand hygiene adherence of both nurses and physicians should improve by 16-18% to realize the same prevalence reductions. (ξ from 0.59 to 0.66 for nurses and ξ from 0.43 to 0.52 for physicians)

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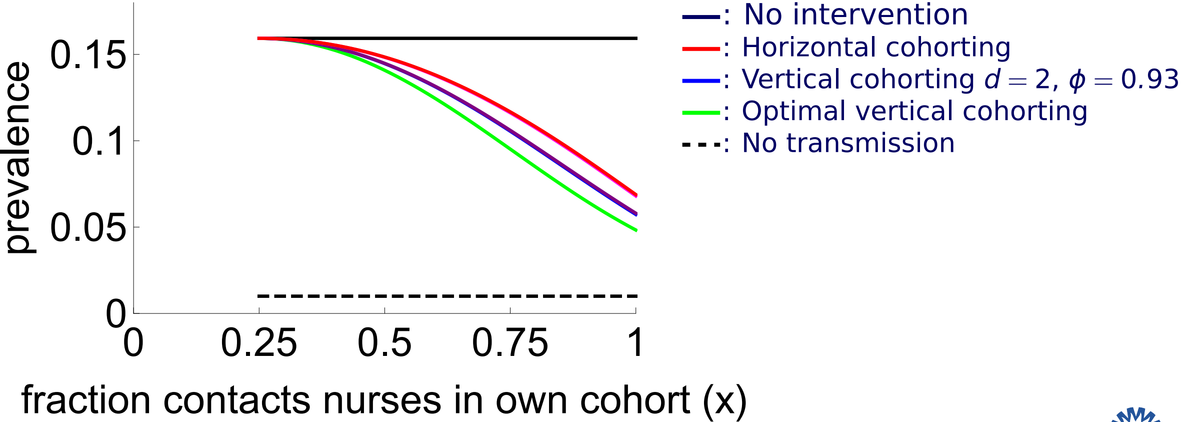
1^{st}-order vertical cohorting, $R_A = 2$, $f = 0.01$



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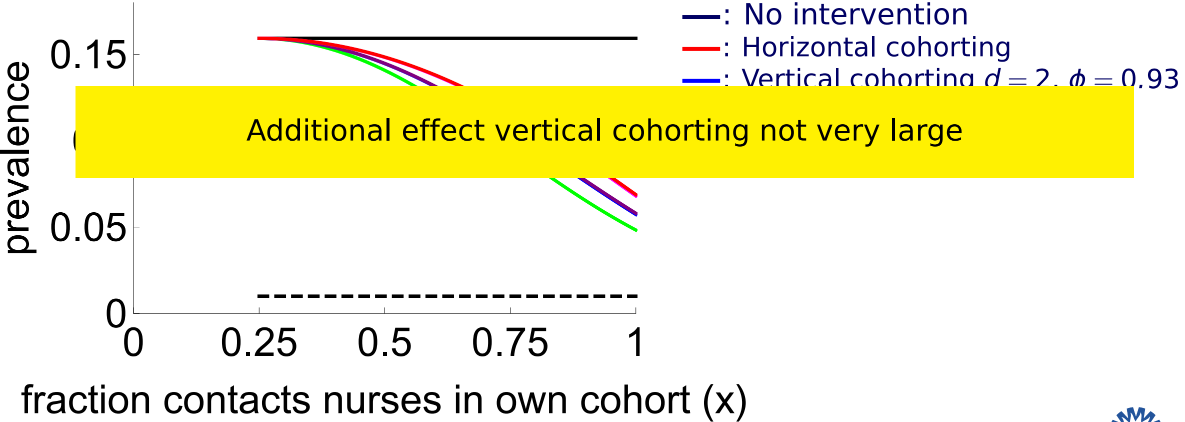


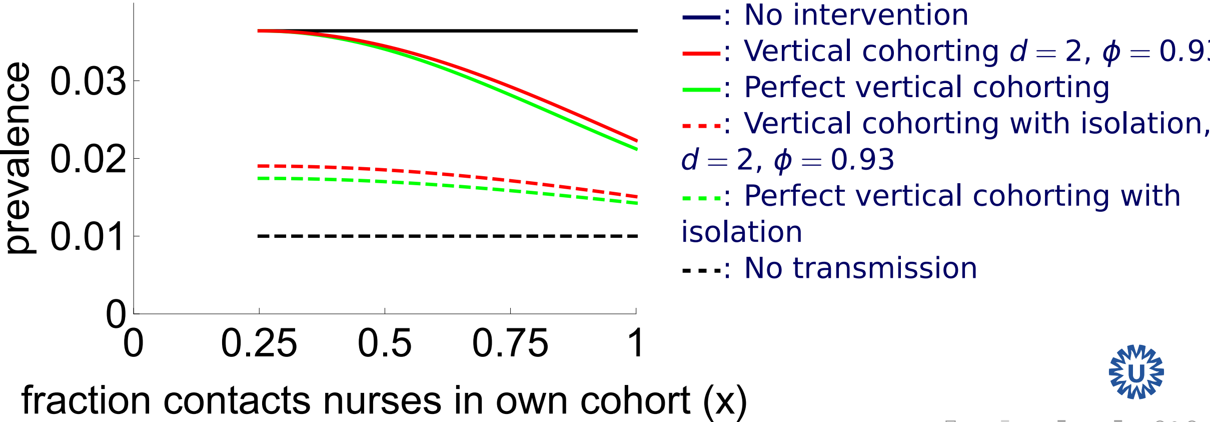
Additional effect vertical cohorting not very large

Effect vertical cohorting on other pathogen

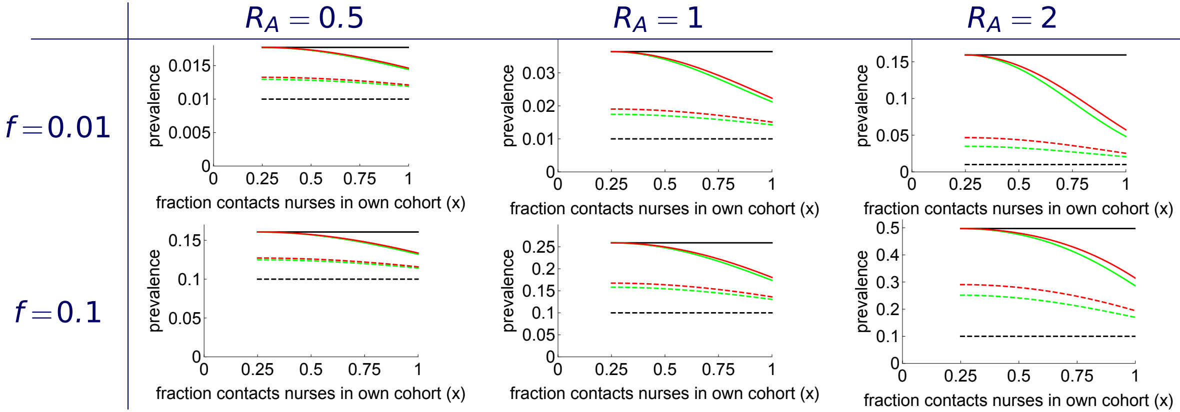
- Effect minimal
- No need for large state space

Isolation (50% effective), $R_A = 1$, $f = 0.01$

- Higher hand hygiene after contact with known colonized patients
- Detection of colonized individuals vital



Isolation (50% effective)

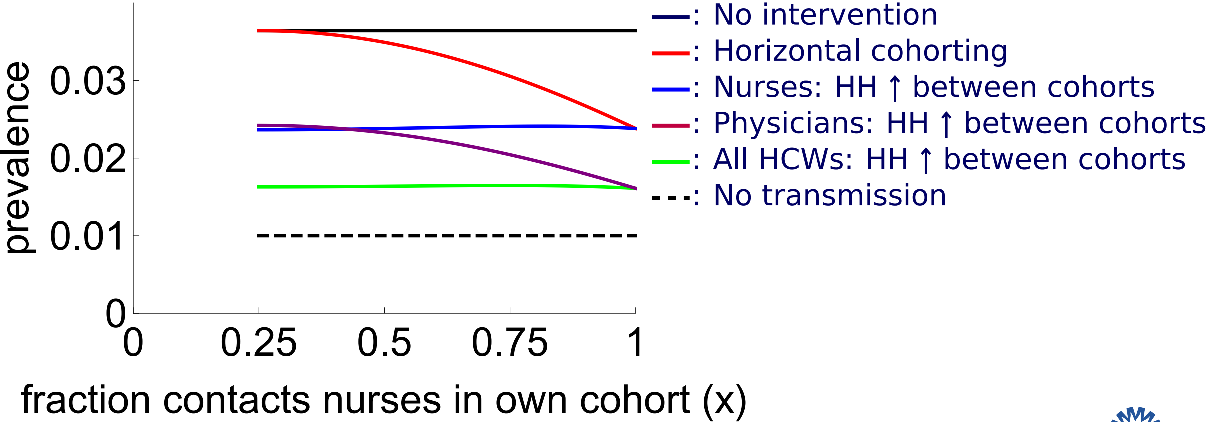


—: No intervention, —: Vertical cohorting $d = 2$, $\phi = 0.93$

—: Perfect vertical cohorting, - - -: Vertical with isolation $d = 2$, $\phi = 0.93$

- - -: Perfect vertical cohorting with isolation, - - -: No transmission

Hand hygiene 50% higher between cohorts



Discussion

- Hand Hygiene the most efficient intervention
- Important to model hand hygiene not as constant rate
- Higher-order cohorting not very useful due to physicians
- Fits (almost) into the unified stochastic modelling framework
- Choice 8 beds convenient, ideas remain valid
- Understaffing associated with lower compliance and lower cohorting
- Works for quite large unit sizes.

Dimension state space

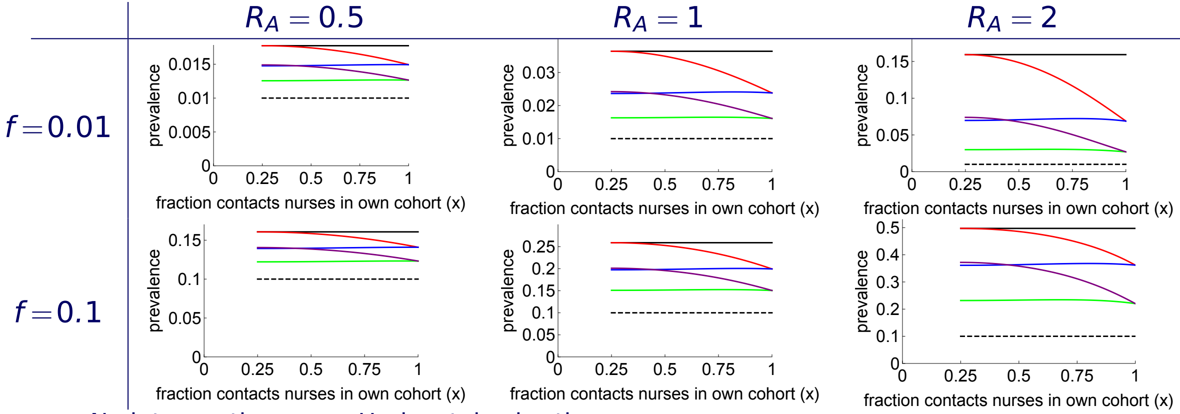
Number of states (S)	formula	$n=1$	$n=2$	$n=4$	$n=8$	$n=16$	$n=32$
No cohorting	$n+1$	2	3	5	9	17	33
		Horizontal cohorting					
1st-order cohorting	$\frac{(m+1)(m+2)}{2}$	2	3	6	15	45	153
2nd-order cohorting	$\binom{v+5}{v}$	2	3	6	21	126	1287
hierarchical cohorting	$\frac{S(k)(S(k)+1)}{2}$	2	3	6	21	231	26,796
		Vertical cohorting					
1st-order cohorting	$\frac{(m+1)^2(m+2)}{2}$	3	6	18	75	405	2,601
2nd-order cohorting	$\frac{1+2v}{120}\prod_{i=1}^{5}(i+v)$	3	6	18	105	1134	21,879
hierarchical cohorting	∅	3	6	18	105	2,079	455,532
		Vertical cohorting and 2nd pathogen					
1st-order cohorting	$\frac{(4+3m)}{4}\binom{m+11}{m}$	6	21	195	5,460	529,074	169,492,635
2nd-order cohorting	∅	6	21	195	10,065	5,956,650	123,924,869,640
hierarchical cohorting	∅	6	21	195	10,065	13,978,755	15,885,752,699,355

Number of states for the several variants of the model. The number of patients is $n = 2m = 4v = 2^k$.

The symbol ∅ indicates that we could not obtain a closed form expression.

Thank You!

Hand hygiene 50% higher between cohorts



—: No intervention ; —: Horizontal cohorting

—: Nurses: higher HH between cohorts ; —: Physicians: higher HH between cohorts

—: All HCWs: higher HH between cohorts; - - -: No transmission