The effect of cohorting of patients and health care workers on the dynamics of an infectious disease in an intensive care unit

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Co-workers

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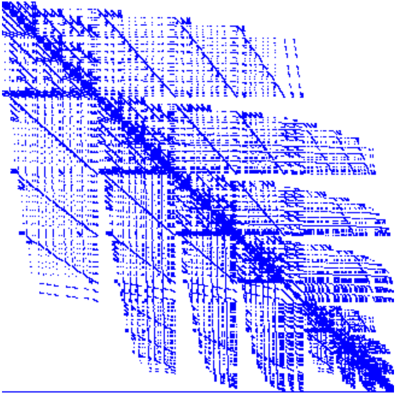


Introduction

- Why this topic?
- Hospital setting
- Health care workers vectors of nosocomial pathogens (MRSA/VRE)
- Distinction between site of colonization (hands vs nose/gut)

Ross-Macdonald model†

Uncolonized patients

Colonized patients

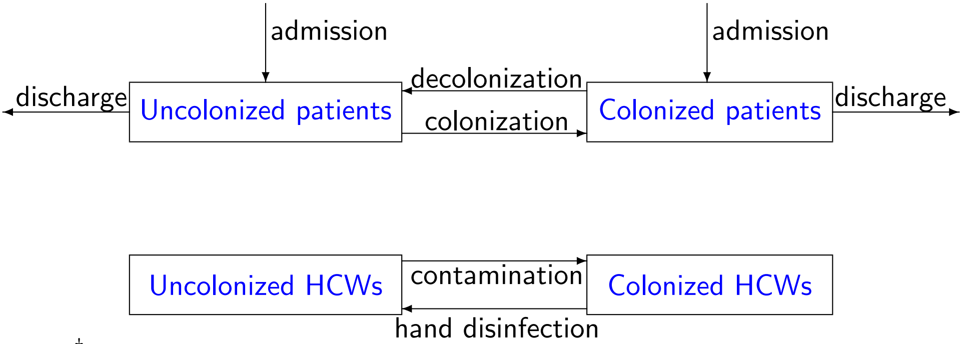
Uncolonized HCWs

Colonized HCWs

† Austin et al. (1999) PNAS **96**

† MacDonald (1957) The epidemiology and control of malaria. Oxford University Press.

Ross-Macdonald model†



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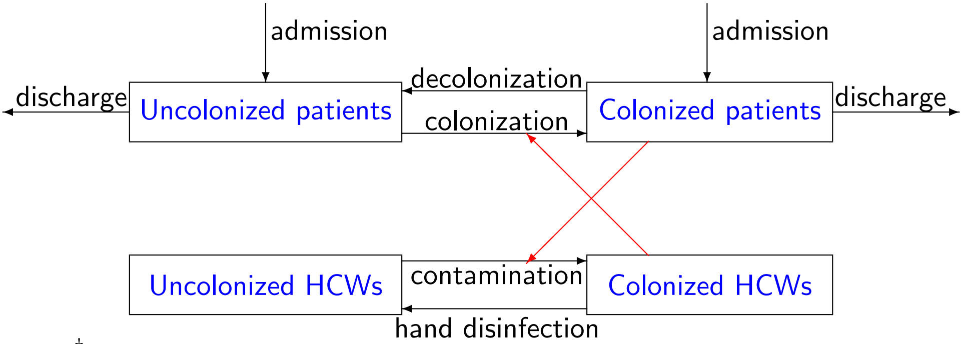

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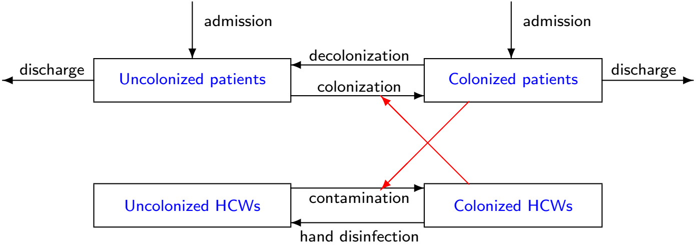
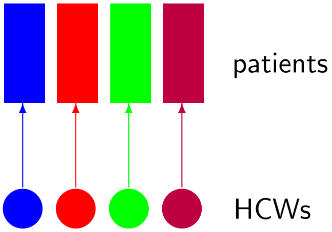
Possible Interventions

Generic (horizontal) Interventions:

- Prevention hand contamination, e.g., gloves, gowns
- Removing hand contamination: hand hygiene
- Patient decolonization: e.g., chlorhexidin body washings
- Cohorting of patients and HCWs

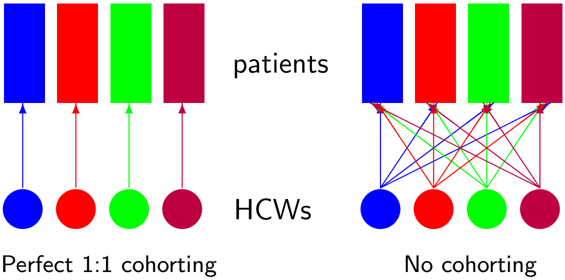


Cohorting

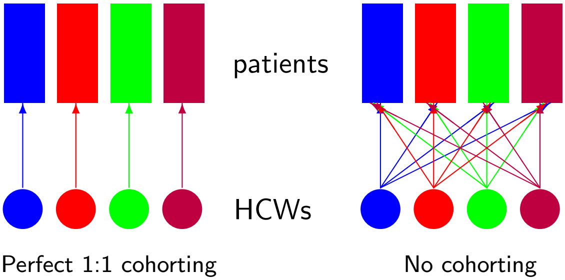


Perfect 1:1 cohorting

Cohorting



Cohorting



- Cohorting prevents spread
  - More wasted contacts
  - More local contacts
- In practice never 100%, e.g., due to physicians

Possible Interventions

Generic Interventions:

- Prevention hand contamination, e.g., gloves, gowns
- Removing hand contamination: hand hygiene
- Patient decolonization: e.g., chlorhexidin body washings
- Cohorting of patients and HCWs

Pathogen-specific interventions:

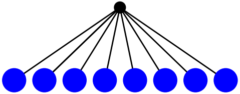
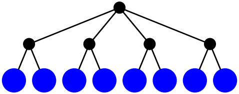
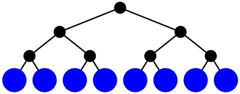
- Patient decolonization, e.g., mupirocin for MRSA
- Decolonization of persistently colonized HCW, e.g., for MRSA
- Screening → cohorting/patient isolation
  - admission/contact screening, regular surveillance, rapid diagnostic testing

Model for cohorting

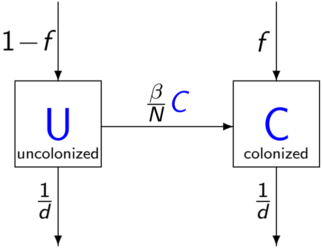
- Quasi steady state approximation
  - If decolonization rate HCW's high (hand hygiene efficient) $\longrightarrow$
  - Probability that a HCW is colonized after a hand hygiene opportunity proportional to P(last visited patient positive)
- Justified by data: Hands of HCW's typically not contaminated
- Model contact as if direct contact between patients

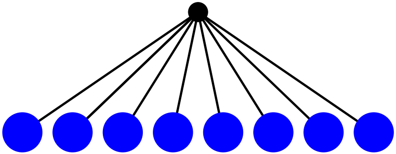
Three cohorting schemes

- Based on trees
- Patients with same distance in tree have the same transmission rate between them

1. No cohorting 
2. 1st order cohorting 
3. Hierarchical cohorting 

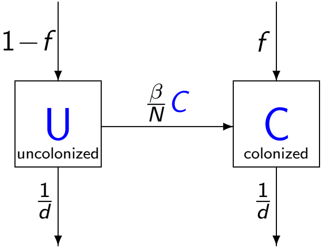
No cohorting: Stochastic SIS-model: Chapter 4.6

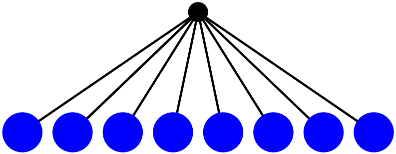




- Exponentially distributed length of stay. Scale time: $d = 1$
- Fraction f of patients colonized on admission
- \# colonized patients describes state of ward
- If n patients: $n + 1$ possible states (labeled 0, 1, ..., n). Assume all beds always occupied

No cohorting: Stochastic SIS-model: Chapter 4.6





- Exponentially distributed length of stay. Scale time: $d = 1$
- Fraction f of patients colonized on admission
- # colonized patients describes state of ward
- If n patients: $n+1$ possible states (labeled 0, 1, . . ., n). Assume all beds always occupied
- $p_i(t)$=Probability that ward is in state i at time t.
- $R_A := \frac{n-1}{n}\beta d = \frac{n-1}{n}\beta$

$$\frac{d}{dt}p_0(t) = -fnp_0(t) + (1-f)p_1(t)$$

$$\frac{d}{dt}p_i(t) = \begin{cases} +(\beta\frac{i-1}{n} + f)(n-i+1)p_{i-1}(t) \\ -\left((\beta\frac{i}{n} + f)(n-i) + (1-f)i\right)p_i(t) \\ +(1-f)(i+1)p_{i+1}(t) \end{cases} \quad \text{for } 0 < i < n$$

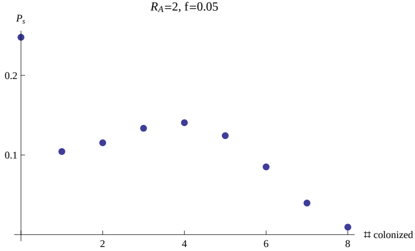
$$\frac{d}{dt}p_n(t) = +(\beta\frac{n-1}{n} + f)p_{n-1}(t) - (1-f)np_n(t)$$

Stable distribution p_s with components p_s^i given by:

$$p_s^i = \frac{\left(\frac{f}{1-f}\right)^i \prod_{j=1}^{i}\left(\frac{N-j+1}{j}\right)\left(\frac{\beta(j-1)}{Nf}+1\right)}{1+\sum_{k=1}^{N}\left(\frac{f}{1-f}\right)^k \prod_{j=1}^{k}\left(\frac{N-j+1}{j}\right)\left(\frac{\beta(j-1)}{Nf}+1\right)}.$$

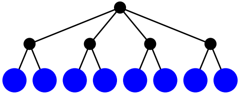
$$
\begin{aligned}
\frac{d}{dt}p_0(t) &= -fnp_0(t) + (1-f)p_1(t)\\
\frac{d}{dt}p_i(t) &= \begin{cases} +(\beta\frac{i-1}{n} + f)(n-i+1)p_{i-1}(t) \\ -\left((\beta\frac{i}{n} + f)(n-i) + (1-f)i\right)p_i(t) \\ +(1-f)(i+1)p_{i+1}(t)\end{cases} \quad \text{for } 0 < i < n\\
\frac{d}{dt}p_n(t) &= +(\beta\frac{n-1}{n} + f)p_{n-1}(t) - (1-f)np_n(t)
\end{aligned}
$$

example: n=8:



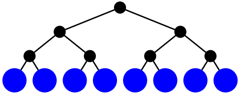
Calculate mean prevalence

1^{st}-order 2-1 cohorting



- Suppose even number of patients ($n = 2m$)
- Each pair can be in three states: (0,0), (0,1) or (1,1)
- # (0,0)=i, # (0,1)=j, # (1,1)=m-i-j,
- # states: $\sum_{i=0}^{m} \sum_{j=0}^{m-i} 1 = \frac{(m+1)(m+2)}{2}$
- Transmission rate between individuals in same cohort: β_1
- Transmission rate between individuals in other cohort: β_2
- $$\begin{aligned} \frac{d}{dt} p_{i,j} = \quad & -p_{i,j} && \{(2i+j)f+(2m-2i-j)(1-f)+(2m-2i-j)\beta_2 2i+j((2m-2i-j)-1)\beta_2+\beta_1)\} \\ & +p_{i,j+1} && \{(j+1)((2m-2i-j)\beta_2+\beta 1+f)\} \\ & +p_{i,j-1} && \{(2(m-i-j+1)(1-f)\} \\ & +p_{i-1,j+1} && \{(j+1)(1-f)\} \\ & +p_{i+1,j-1} && \{(2m-2i-j-1)\beta_2 2(i+1)+2(i+1)f\} \end{aligned}$$
- Determine stable distribution

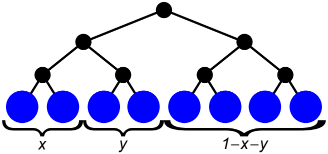
Hierarchical (2^{nd}-order) 2-1 cohorting



- Suppose number of patients power of 2 ($n = 2^k$)
- At k: $S(k)$ states; $S(1) = 3$,
  $S(k+1) = \sum_{i=1}^{S(k)} \sum_{j=i}^{S(k)} 1 = \frac{S(k)(S(k)+1)}{2}$
- Transmission rate between individuals in same cohort: β_1
- Transmission rate between individuals in 2^{nd}-order cohort: β_2
- Transmission rate between individuals in 3^{rd}-order cohort: β_3

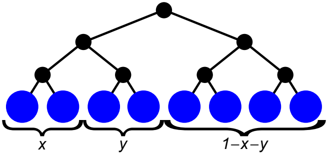
Number of states	$n = 2$	$n = 4$	$n = 8$	$n = 16$	$n = 32$
No cohorting	3	5	9	17	33
1st order cohorting	3	6	15	45	153
hierarchical cohorting	3	6	21	231	26796

Gauging the transmission parameters ($n = 8$)



- Fraction x of contacts within smallest cohort
- Fraction y of contacts in 2nd-order cohort
- Fraction $1-x-y$ of contacts in 3rd-order cohort
- Preferred patients indeed preferred: $x \geq y \geq \frac{1-x-y}{2}$
- No cohorting: $x = y = \frac{1}{4}$
- 1st-order cohorting: $y = \frac{1-x}{3}$

Gauging the transmission parameters ($n = 8$)

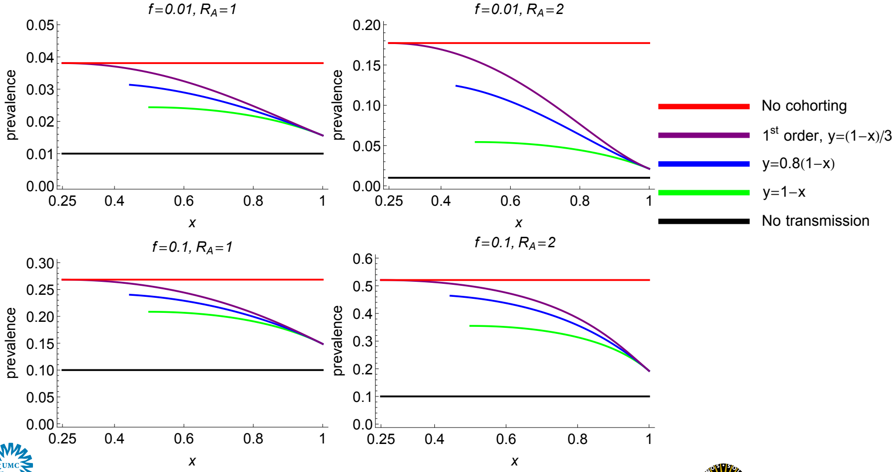


- Consider two subsequent contact of a HCW
- $P(1^{st}\text{patient } 1,\ 2^{nd}\text{patient } 2) = \frac{1}{4}\frac{x}{2}\frac{x}{2} + \frac{1}{4}\frac{y}{2}\frac{y}{2} + \frac{1}{2}\frac{1-x-y}{4}\frac{1-x-y}{4}$
- $P(1^{st}\text{patient } 1,\ 2^{nd}\text{patient } 3) = \frac{1}{4}\frac{x}{2}\frac{y}{2} + \frac{1}{4}\frac{x}{2}\frac{y}{2} + \frac{1}{2}\frac{1-x-y}{4}\frac{1-x-y}{4}$
- $P(1^{st}\text{: } 1,\ 2^{nd}\text{: } 5) = \frac{1}{4}\frac{x}{2}\frac{1-x-y}{4} + \frac{1}{4}\frac{y}{2}\frac{1-x-y}{4} + \frac{1}{4}\frac{1-x-y}{4}\frac{x}{2} + \frac{1}{4}\frac{1-x-y}{4}\frac{y}{2}$
- Assume same level of hand hygiene after each contact (in each order cohort)
- $\frac{\beta_1}{\beta_2} = \frac{P(1^{st}\text{patient } 1,\ 2^{nd}\text{patient } 2)}{P(1^{st}\text{patient } 1,\ 2^{nd}\text{patient } 3)},\ \frac{\beta_1}{\beta_3} = \frac{P(1^{st}\text{patient } 1,\ 2^{nd}\text{patient } 2)}{P(1^{st}\text{patient } 1,\ 2^{nd}\text{patient } 5)}$

Gauging the transmission parameters ($n = 8$)

- Choose transmissibility of disease
- $\beta_1 = CP(1^{\text{st}}\text{patient 1, } 2^{\text{nd}}\text{patient 2})$
- $\beta_2 = CP(1^{\text{st}}\text{patient 1, } 2^{\text{nd}}\text{patient 3})$
- $\beta_3 = CP(1^{\text{st}}\text{patient 1, } 2^{\text{nd}}\text{patient 2})$
- No cohorting: $\beta_1 = \beta_2 = \beta_3$.
- 1 colonized patient: Rate of transmission: $7\beta_1$.
- $R_A := 7\beta_1 \Rightarrow C = \frac{R_A}{7P(1^{\text{st}}\text{patient 1, } 2^{\text{nd}}\text{patient 2})}$

Results ($n = 8$)


f=0.01, R_A=1
f=0.01, R_A=2
f=0.1, R_A=1
f=0.1, R_A=2
prevalence
x
0.25
0.4
0.6
0.8
1
0.00
0.01
0.02
0.03
0.04
0.05
0.05
0.10
0.15
0.20
0.25
0.30
0.1
0.2
0.3
0.4
0.5
0.6
No cohorting
1st order, y=(1−x)/3
y=0.8(1−x)
y=1−x
No transmission

Conclusion

- Cohorting can prevent a substantial amount of the acquisitions
- Can keep subpopulation in pathogen-free state
- Hierarchical cohorting can add substantially to first oder cohorting.
- Level of cohorting should be sufficiently high

Vertical cohorting

- Patients with known colonization placed in same cohort
- No other infection prevention
- Movements of patients not associated with risk of transmission
- Should reduce spread: but how much?

Detection

- Admission screening
  - Sensitivity: ξ
  - Specificity: 100%
  - Results immediately available
- Clinical cultures
  - At rate ϕ
  - Specificity: 100%
  - Results immediately available
- Known colonized patients are cohorted as much as possible
- If due to detection/admission imperfect cohorting, switch 2 patients.

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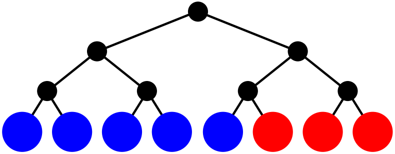

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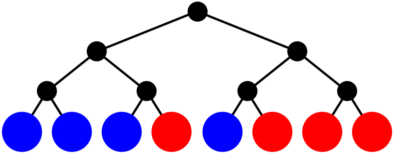

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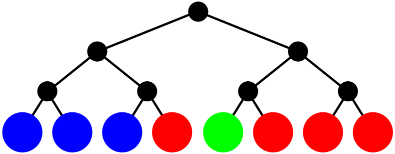

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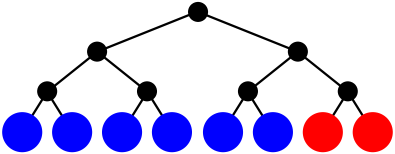
- Known colonized patients are cohorted as much as possible
- If due to detection/admission imperfect cohorting, switch 2 patients.
- More switches possible: each equally likely



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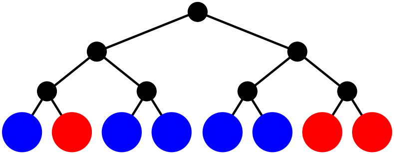

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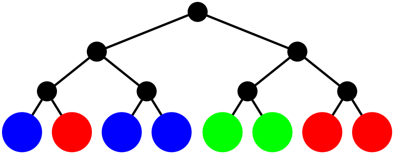
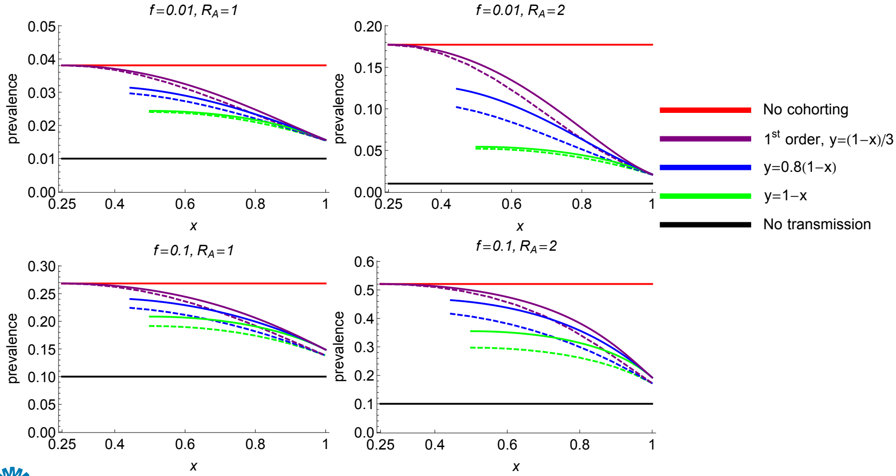


Vertical cohorting

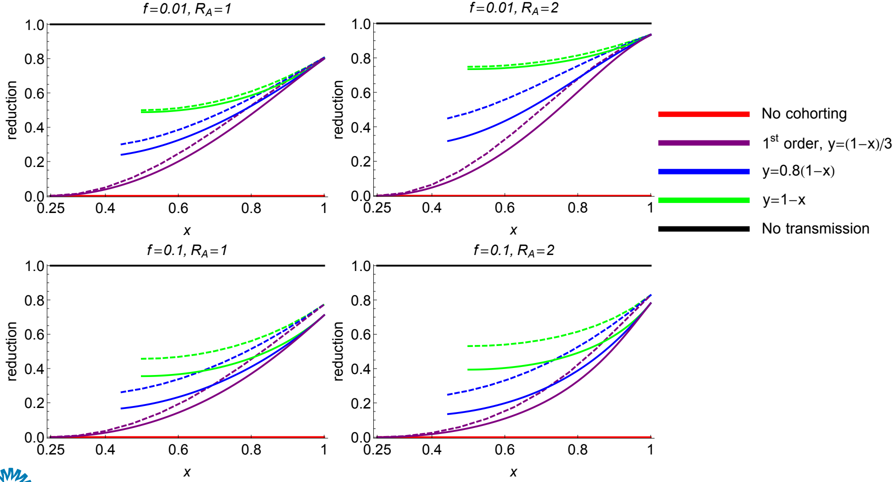
- Analysis similar

Number of states	$n = 1$	$n = 2$	$n = 4$	$n = 8$	$n = 16$	$n = 32$
No cohorting	2	3	5	9	17	33
	Horizontal cohorting					
1st order cohorting	2	3	6	15	45	153
hierarchical cohorting	2	3	6	21	231	26,796
	Vertical cohorting					
1st order cohorting	3	6	18	75	405	2,601
hierarchical cohorting	3	6	18	105	2,079	455,532

Results ($n = 8$)


f=0.01, R_A=1
f=0.01, R_A=2
f=0.1, R_A=1
f=0.1, R_A=2
prevalence
x
No cohorting
1st order, y=(1−x)/3
y=0.8(1−x)
y=1−x
No transmission

Results ($n = 8$): Fraction transmissions prevented



Conclusion

- Vertical cohorting lowers prevalence compared to horizontal cohorting
  - Largest effect if room for improvement (efficient cohorting scheme, disease prevalent)

2 pathogens: for 1 vertical cohorting

- Vertical cohorting introduces additional movement of patients
  - Never negative for pathogen of interest
  - Possible negative effect for other pathogens

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	Horizontal cohorting					
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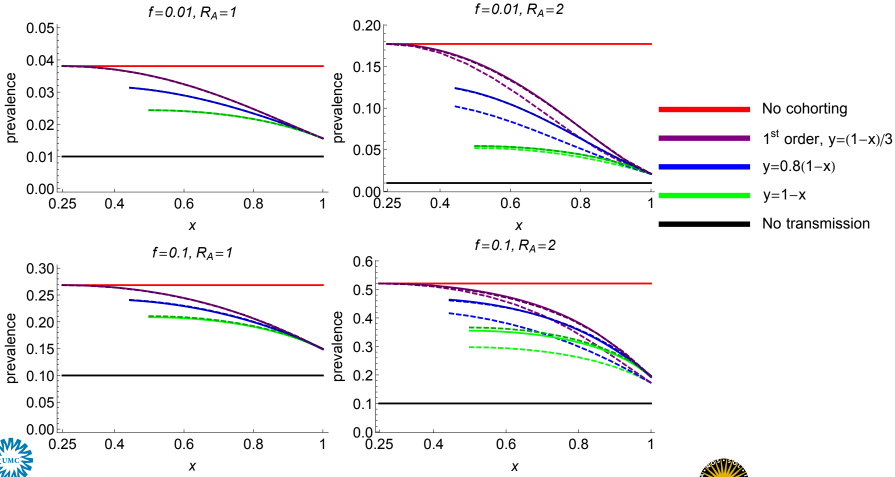
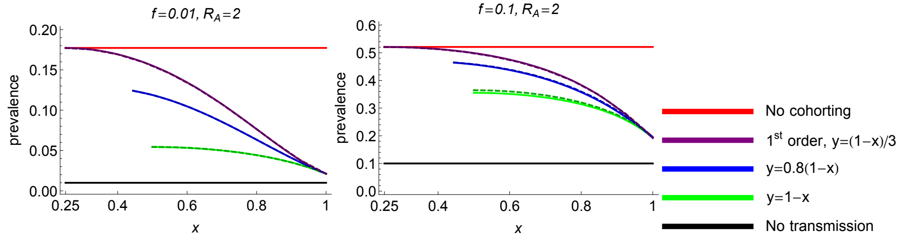
	Vertical cohorting					
1st order cohorting	3	6	18	75	405	2,601
hierarchical cohorting	3	6	18	105	2,079	455,532
	Vertical cohorting and 2nd pathogen					
1st order cohorting	6	21	195	5,460	529,074	169,492,635
hierarchical cohorting	6	21	195	10,065	13, 978, 755	15,885,752,699,355

Results: 2 identical pathogens. No admission screening, twice per <LOS> screening



Results: $R_A^2 = 2,\ R_A^1 = 1.$ No admission screening, twice per <LOS> screening



Conclusion

- Vertical cohorting increases prevalence other pathogens
  - Effect small
  - But, many other pathogens

Conclusions & Discussion

- Cohorting can be very efficient.
- Vertical cohorting even more effective
- Vertical cohorting small negative impact on other pathogens
  - Cohorting efficient
  - High transmission rate
  - Both pathogens high prevalence
- Movements of patients not associated with risk of transmission
- Other than 2-1 cohorting schemes?
- Generic interventions to be preferred over pathogen-specific measures?

Thank you for your attention

- Questions?
- Suggestions?

Effect isolation

Isolation $\sim$ additional generic interventions for some patients

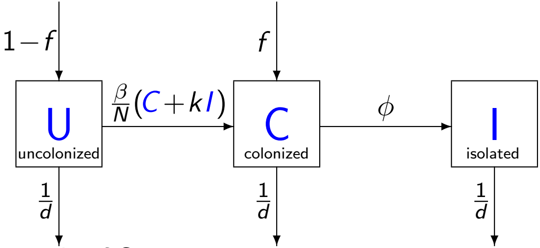
- Theoretically should be effective
- Mixed effects clinical studies†
- Expensive
  - materials (gowns, gloves)
  - additional nursing time.
  - changes in hospital procedures and/or constructional modifications.
- Deleterious for some patients
  - health care workers visit patients in isolation less often

† Cepeda (2005) Lancet **365**. Harbarth (2008) JAMA **299**. Robicsek (2008) Ann Intern Med **148**. Huskins (2011) N Engl J Med **364**. Jain (2011) N Engl J Med **364**.

Hypothesis

- Isolation increases (perception of) workload
- Cohorting less strict with increased workload
- High workload associated with more adverse events (including transmission and infection)
- Intrinsic positive effect isolation outweighted by negative effects due to increased workload

Model



d: Mean Length of Stay

f: Admission prevalence

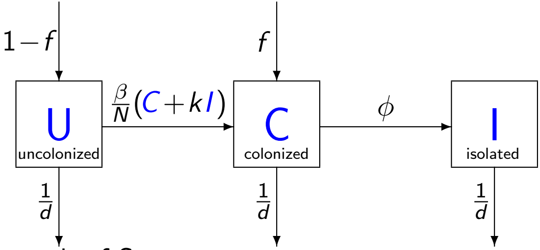
N: # patients$=U+C+I$

β: Transmission parameter

k: Effect isolation ($k=0$: 100% effective, $k=1$: no effect)

ϕ: isolation/detection rate

Model



d: Mean Length of Stay
f: Admission prevalence
N: # patients$=U+C+I$
β: Transmission parameter
k: Effect isolation
ϕ: isolation/detection rate

- No admission screening
- No patient heterogeneity
- Exponentially distributed LOS
- Constant bed occupancy

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Efficacy isolation $(1-k)$ constant

- 1 stable equilibrium

$$C + I = \frac{\xi - 1 + \sqrt{(\xi - 1)^2 + 4f\xi}}{2\xi}$$

with $\xi = \beta d \left(1 - \frac{(1-k)\phi}{1+\phi}\right)$

- Equilibrium global attractor
- $\phi \uparrow \implies C + I \downarrow$:
  Isolation always useful

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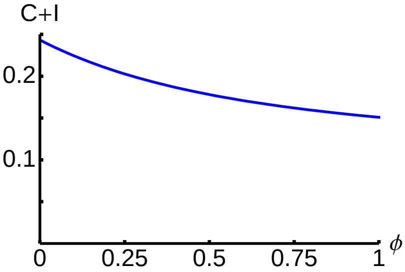
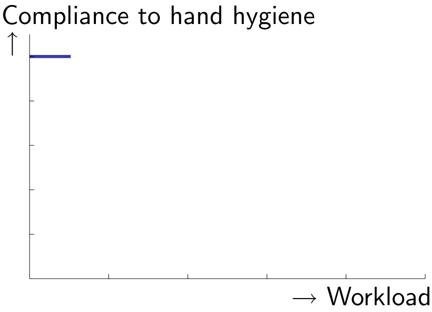


Influence workload on transmission and isolation

Assumptions

- Workload of HCWs (w) has 3 components:
  - Activities directly related to patient care (w_b)
  - Basic hygienic measures (w_h)
  - Additional measures per patient in isolation ($w_i I$)
  - $w = w_b + w_h + w_i I$
- Workload that all available HCWs can perform: n
- HCW can deliver basic care ($n \geq w_b$)
- If $n \geq w$, efficacy of isolation and hand hygiene is optimal

What if HCW's cannot adhere to both protocols? ($w_b < n < w$)



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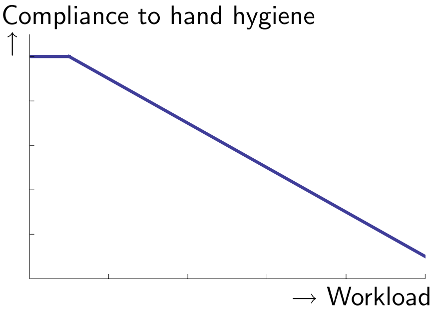

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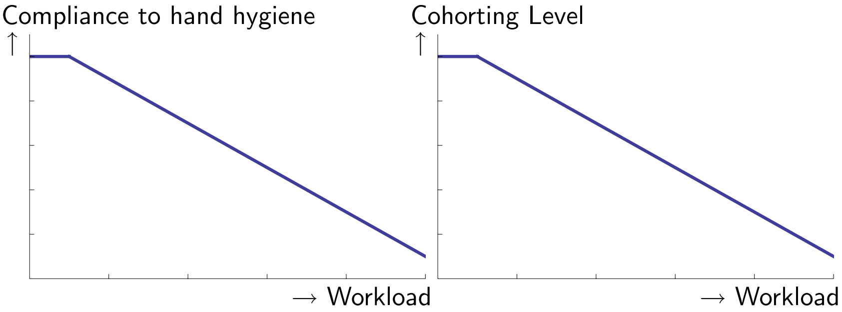

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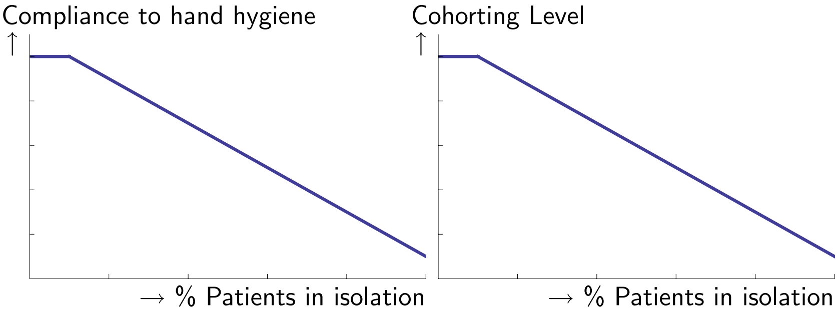

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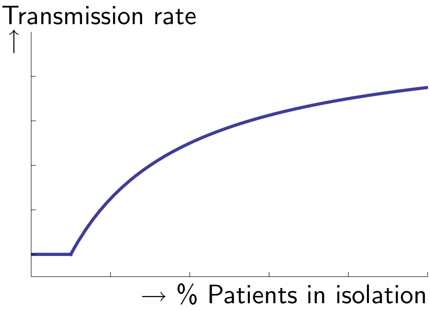

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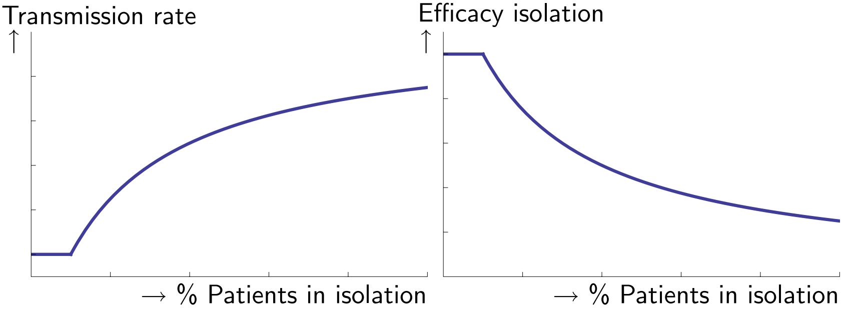

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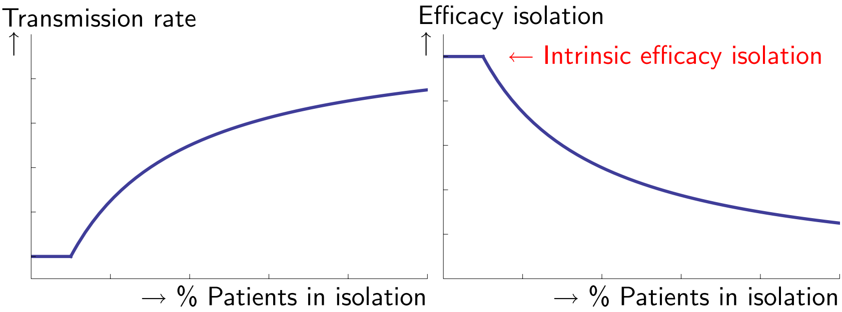
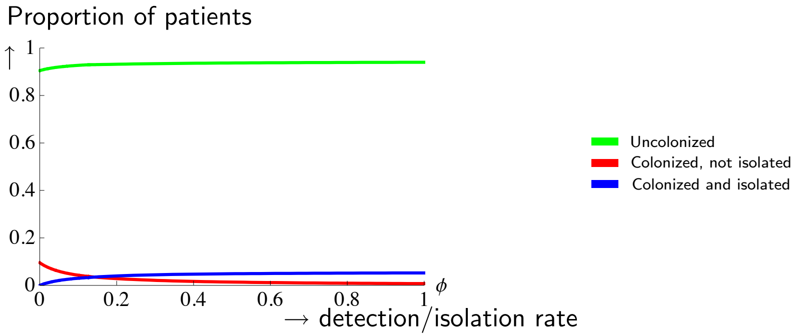


Isolation intrinisic effective, not time consuming



- Detection/isolation rate ↑ $\Longrightarrow$ More Uncolonized patients
- Isolation always useful

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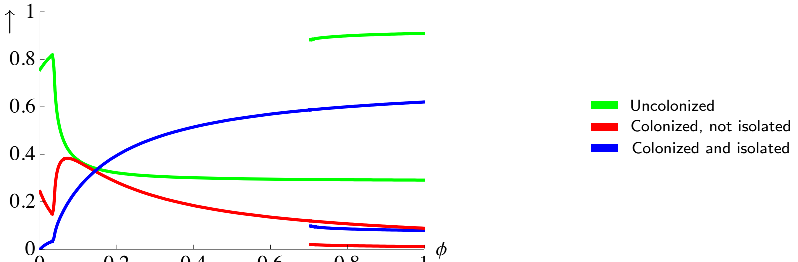
Isolation intrinsic effective but time consuming

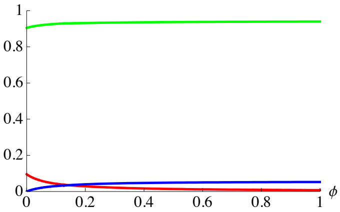
Proportion of patients



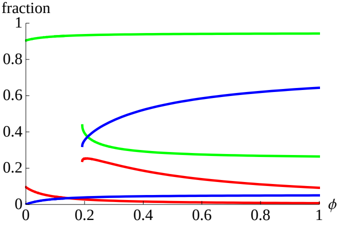
→ detection/isolation rate

- Efficacy isolation may depend on number of patients in isolation

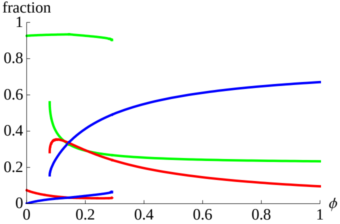
Possible behaviour (qualitatively)



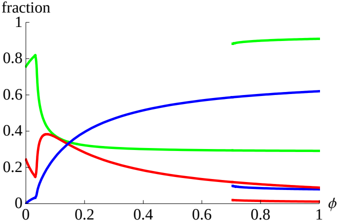
Isolation intrinsic effective, not time-consuming



Isolation neither very effective nor time-consuming



Isolation not very effective & time-consuming



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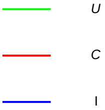

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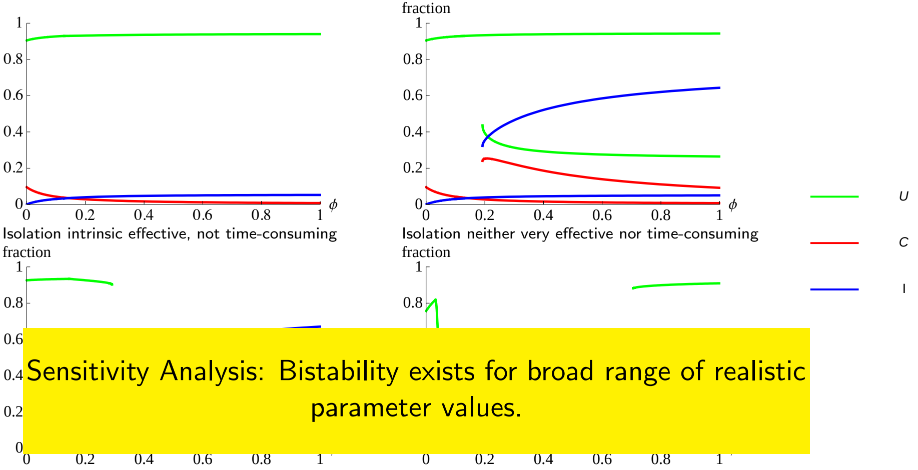

Isolation intrinsic effective, not time-consuming

Isolation neither very effective nor time-consuming

Isolation not very effective & time-consuming

Isolation intrinsic effective but time-consuming

Sensitivity Analysis: Bistability exists for broad range of realistic parameter values.

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To prove

- Only Fold/Saddle-Node bifurcation can occur, no Pitchfork-bifurcation
- Use conditions on $f(\mathbf{x})$ in $\mathbf{x}' = f(\mathbf{x})$ to limit # bifurcations
- Find Parameter regions for every case