Clostridium difficile: Transmission and Future Prevention Strategies

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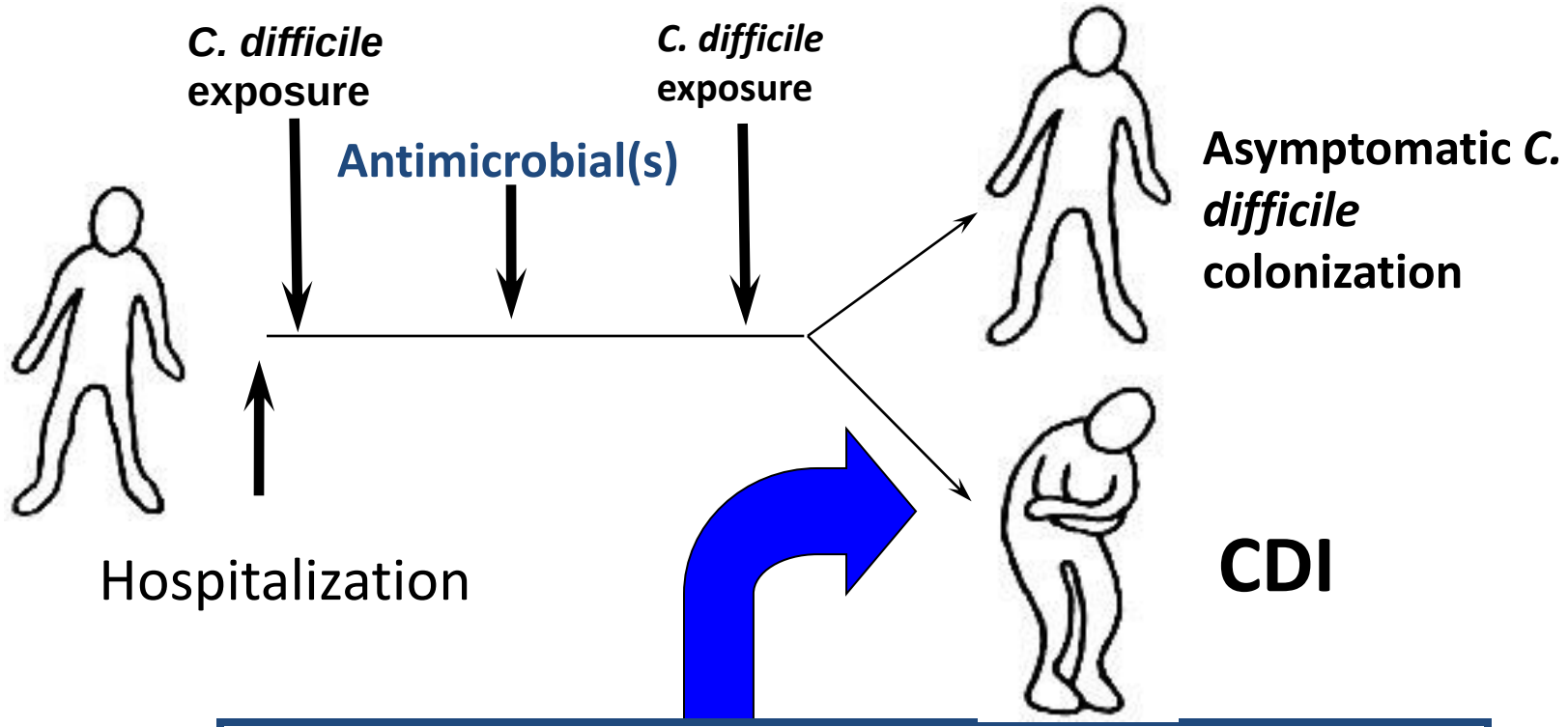
Disclosures

- Research: Rebiotix, Sanofi-Pasteur, Merck, Microdermis
- Consulting: Rebiotix, Sanofi-Pasteur, Merck, Pfizer, Astellas

Current Pathogenesis Model for CDI



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Kyne L, et al. *N Engl J Med*. 2000;342:390-397.

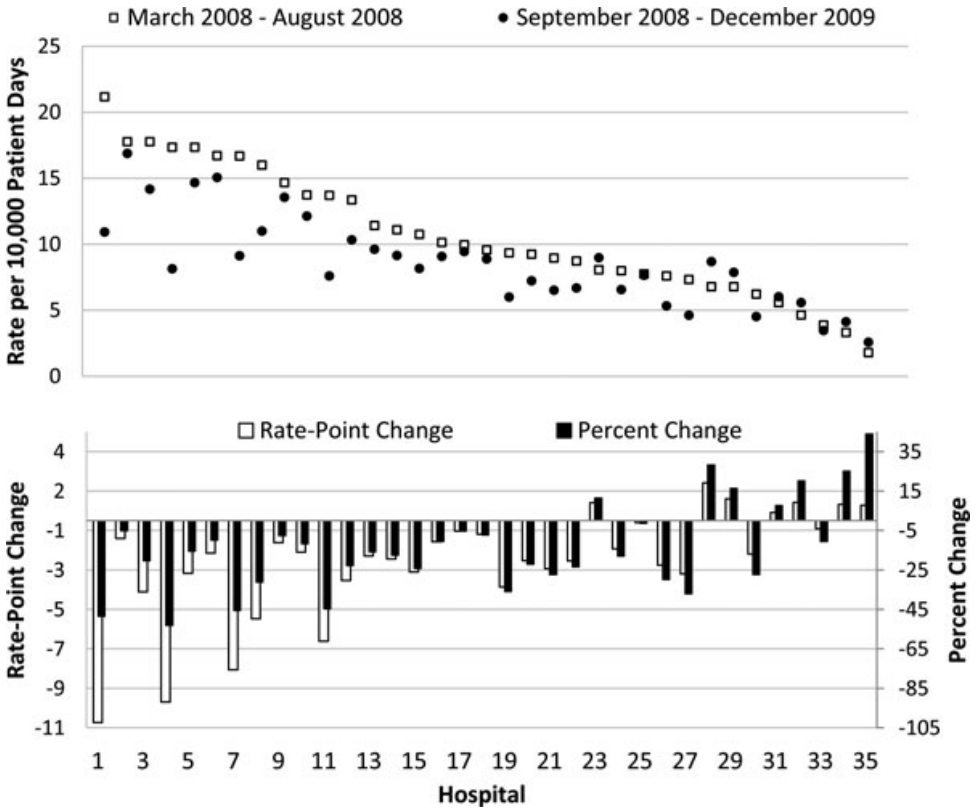
Status of CDI Prevention Today

- Decrease risk of transmission
  - Contact precautions
    - Gloves/gowns
    - Dedicated patient equipment
  - Environment decontamination
- Decrease risk of CDI if transmission occurs
  - Antimicrobial stewardship

Dubberke. ICHE. 2014

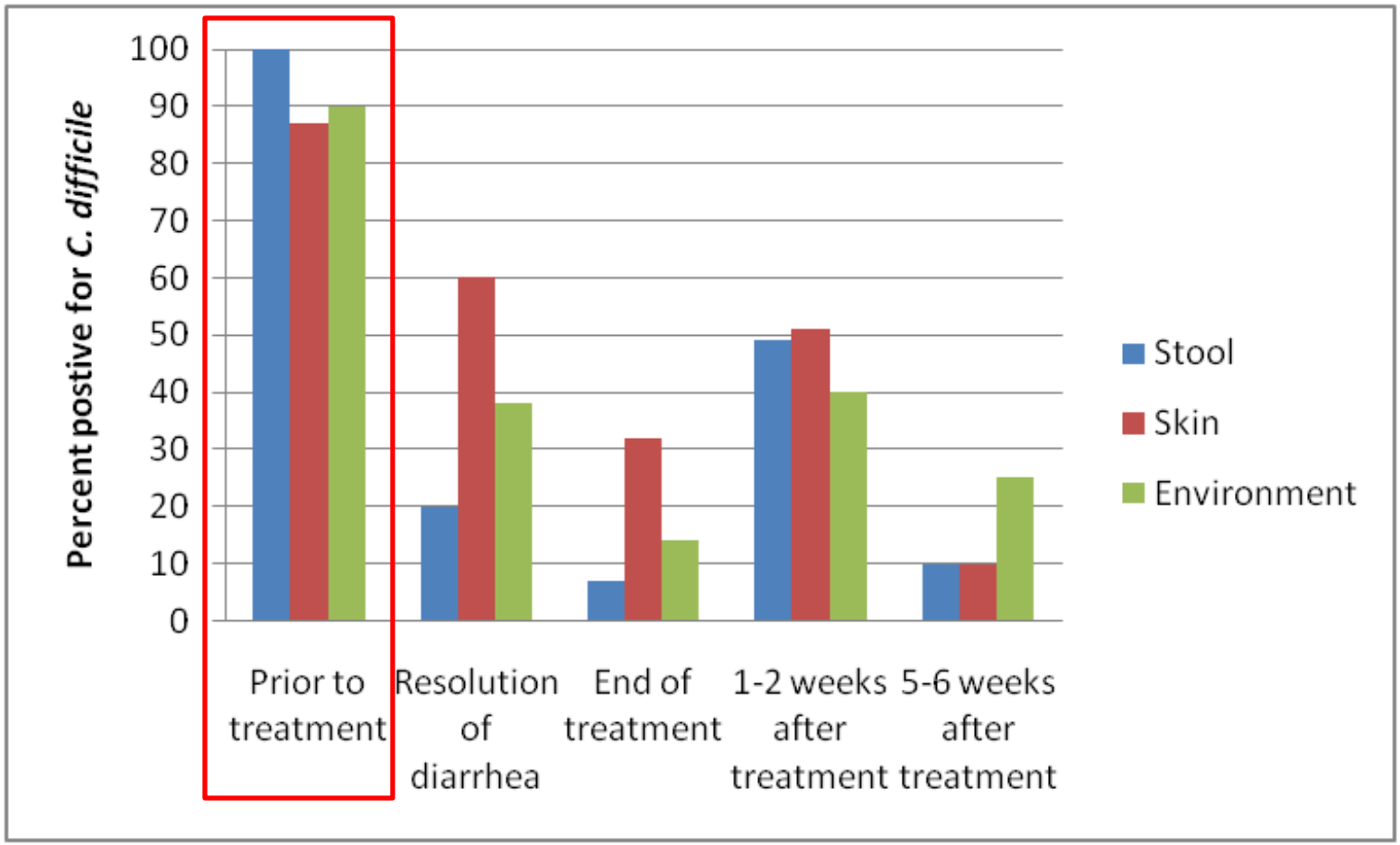
Limitations of Current Approaches

- Feasible only in hospital / hospital-like setting
- Floor effect
- Preventing transmission
  - Secondary prophylaxis



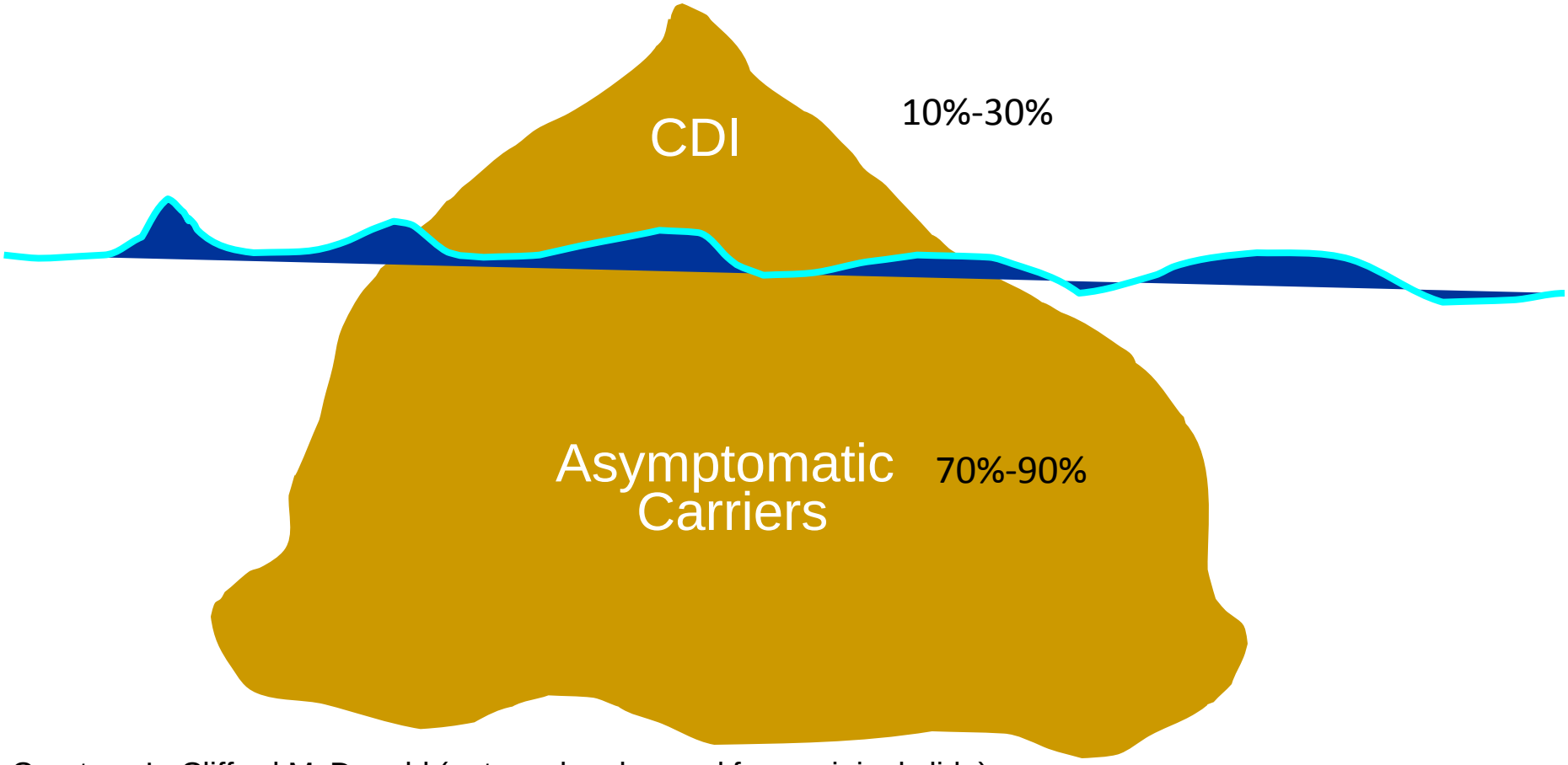
Koll. J Healthc Qual. 2013

Period of Greatest Risk for Transmission



Sethi AJ, ICHE 2010;31:21-7

The *C. difficile* "Iceberg"



Courtesy L. Clifford McDonald (note: color changed from original slide)

Asymptomatic Carriers Contribute to New *C. difficile* Acquisitions and CDI

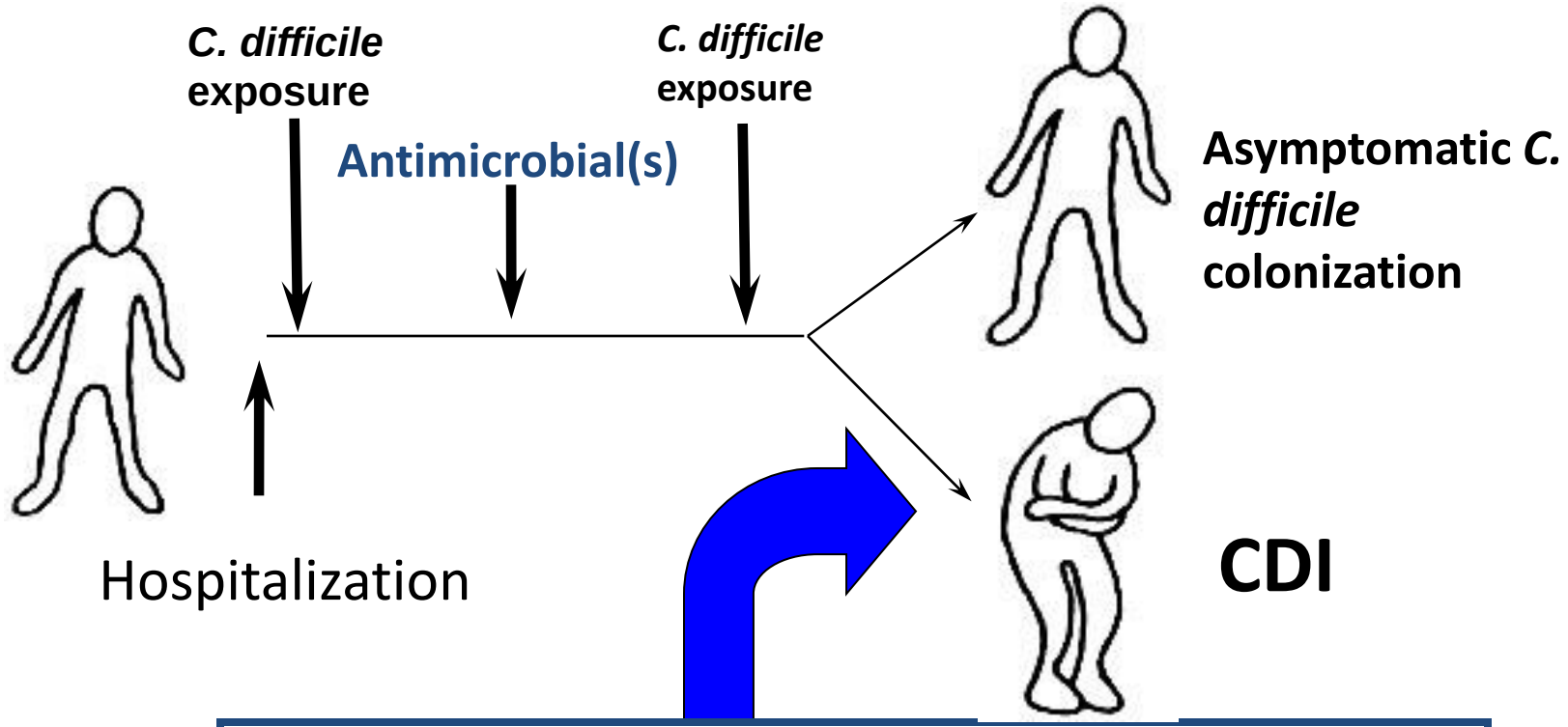
- Clabots: 84% of new acquisitions came from an asymptomatic carrier
- Lanzas: at least 50% of hospital-onset CDI cases come from asymptomatic carriers
- Eyre: transmission from as few as 1% of asymptomatic carriers can account for 50% of CDI cases
  - Prevalence on admission 5%
- Curry: new hospital-onset CDI
  - 30% from other CDI cases
  - 29% from known asymptomatic carriers
  - Other 41%: only 25% of patients were screened for *C. difficile* carriage

Clabots. JID. 1992; Lanzas. ICHE. 2011; Eyre PLoS One. 2013; Curry. CID. 2013; McDonald. CID. 2013

Antimicrobial Stewardship

- ~25% of patients on antimicrobials do not have an infection requiring antimicrobials
  - Therefore 75% DO require antimicrobials
- Fluoroquinolones were considered “low” CDI risk
  - Until they weren’t
- Antimicrobial stewardship essential to CDI prevention, but durability may be an issue

Current Pathogenesis Model for CDI



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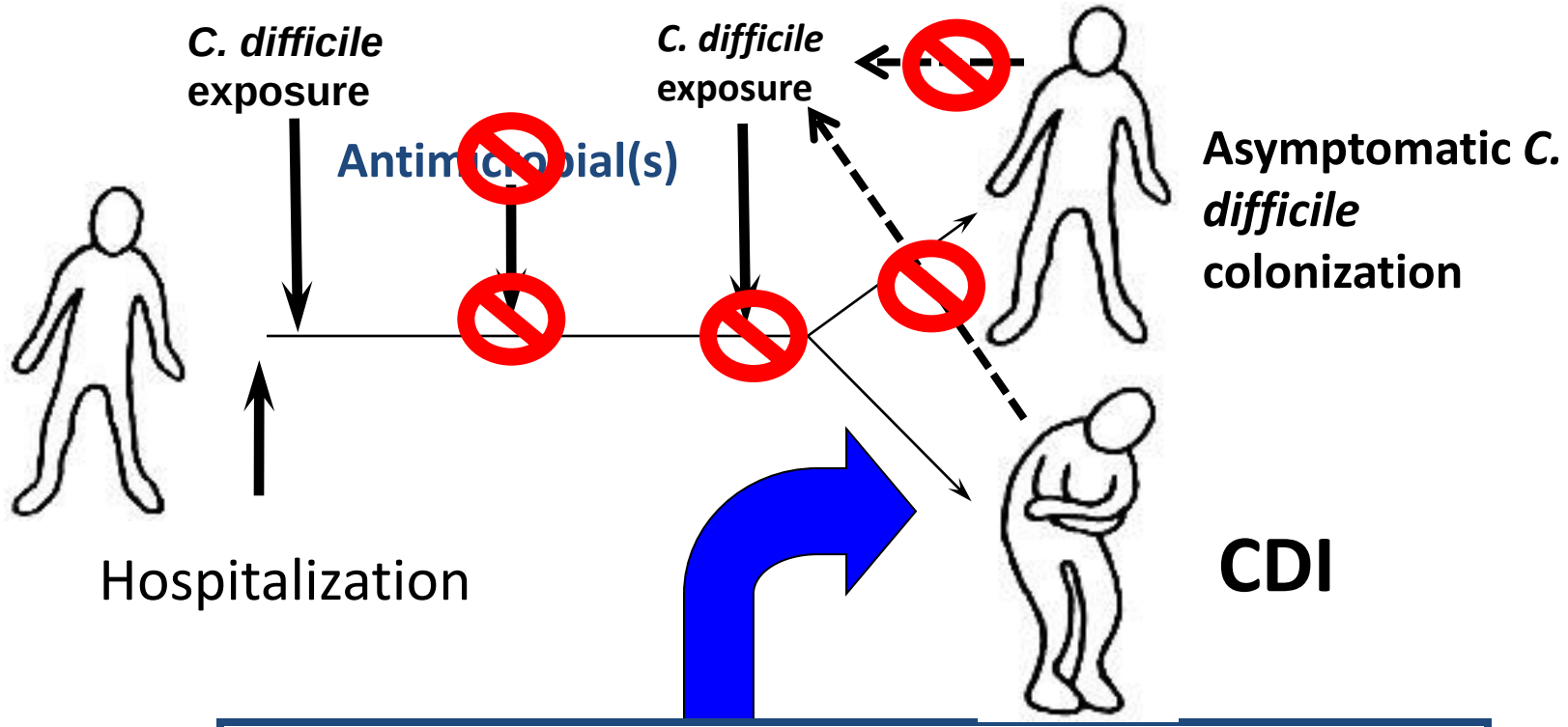
Targets for CDI Prevention



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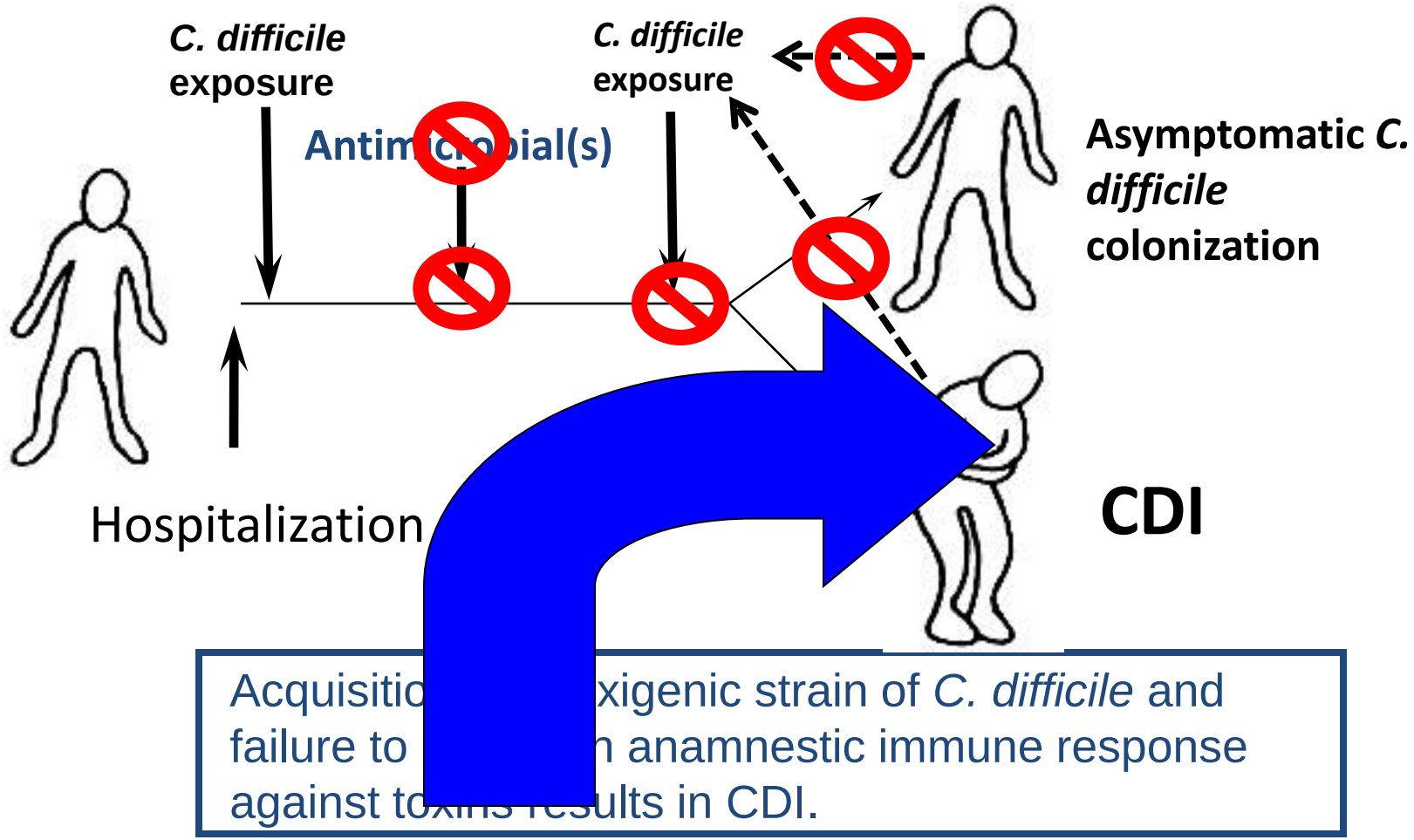

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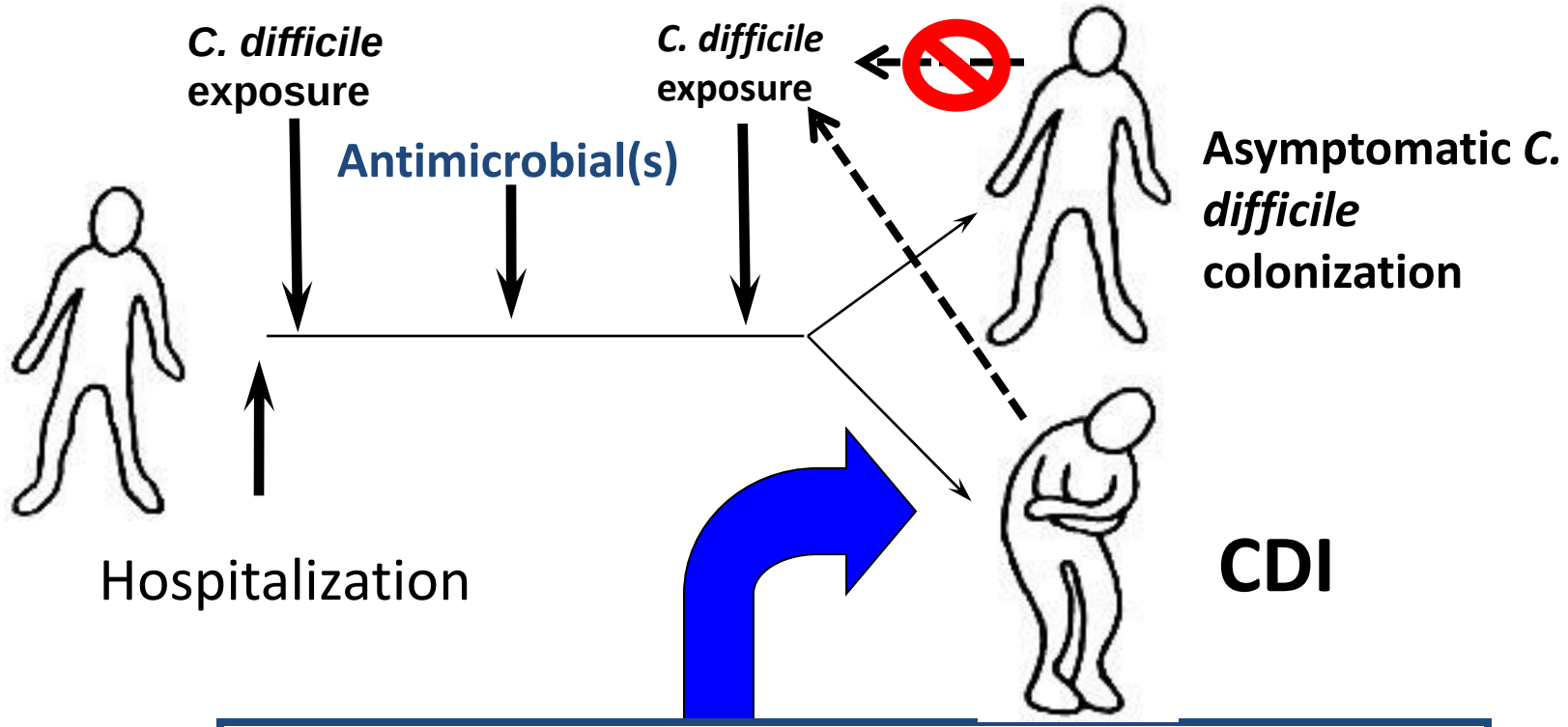

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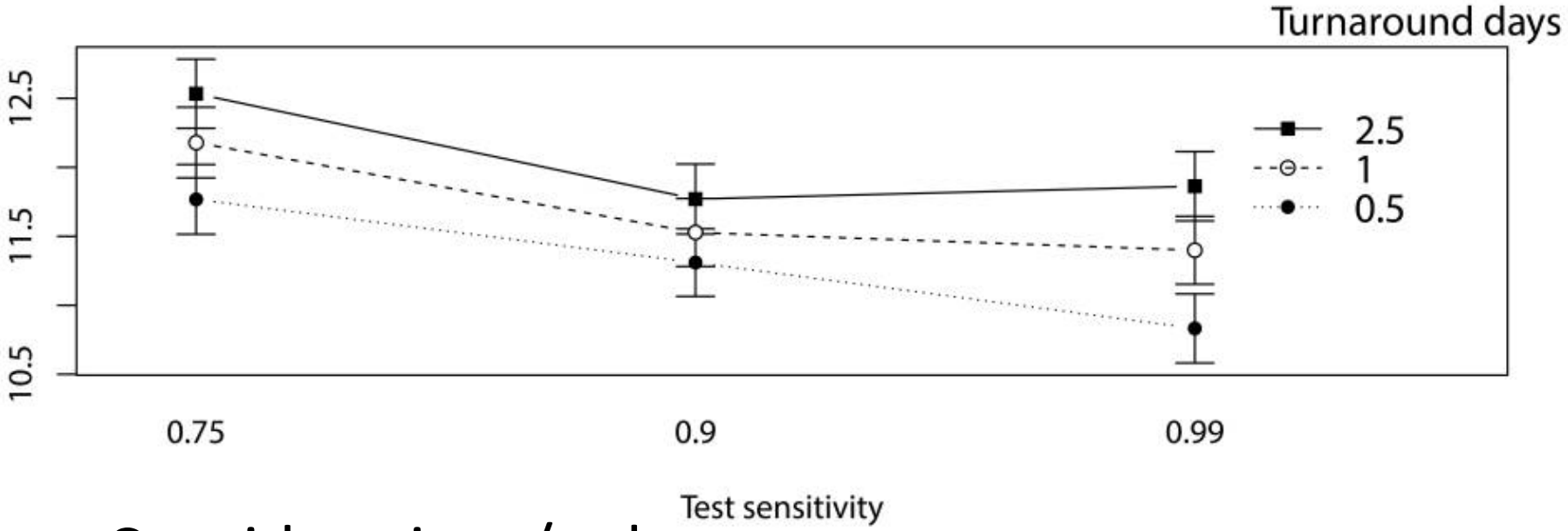
Prevent Transmission from Asymptomatic Carriers



- Considerations/unknowns
  - Test sensitivity / turnaround time
  - *C. difficile* colonization prevalence / strains
  - Proportion of carriers who to convert to CDI
  - Feasibility: time / expense / beds

Lanzas. ICHE. 2014

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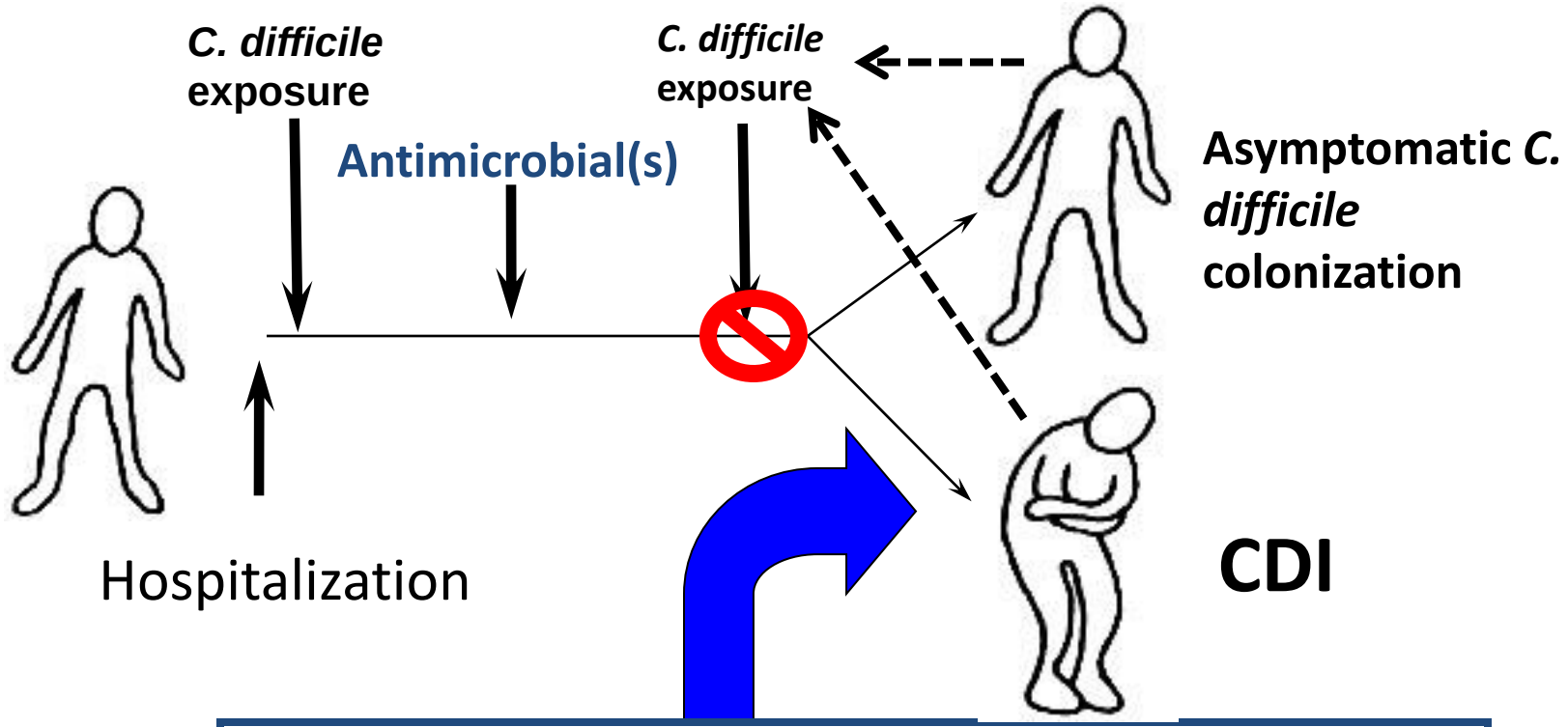

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Prevent *C. difficile* Acquisition / Proliferation

- *C. difficile* targeted chemoprophylaxis
- Probiotics
- Non-toxigenic *C. difficile*
- Bacteriocins

Targeted Chemoprophylaxis

- Secondary prophylaxis not uncommon clinical practice for patients with history of CDI
- Studies have inconsistently found metronidazole to be protective against CDI
- Ongoing study with fidaxomicin
- Risks
  - Resistance
  - May increase risk for CDI once discontinued

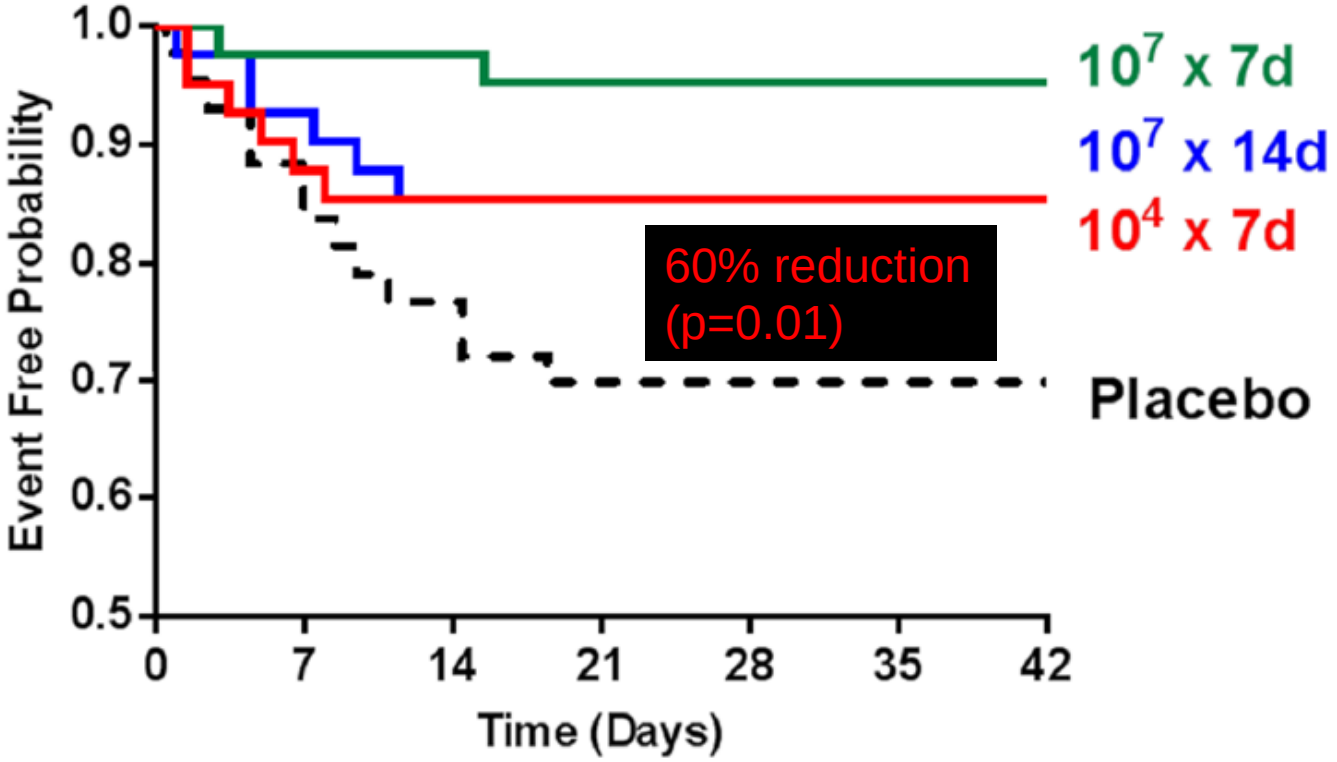
Dubberke. AAC. Accepted; clinicaltrials.gov; Johnson. Ann Intern Med. 1992

Probiotics

- Not effective for recurrent CDI in any RCT
- Primary prophylaxis meta-analysis:
  - Concern: high CDI incidence in placebo arm
  - Placebo incidence 5.8% (versus 2.0% for probiotic)
    - Three studies (out of 20) account for 48% of the study weight
    - The CDI incidence in placebo arms were 7%, 24%, and 40%
  - Highest risk population (elderly hospitalized patient on antibiotics): typical incidence <1% to 3%
  - Methodological concerns: study population, CDI definition, follow-up, numerous preparations

Johnston. Annals. 2012

Non-toxigenic *C. difficile* (NTCD)



- Recurrence rate if became colonized with NTCD: 2%
- Recurrence rate is not colonized with NTCD: 31%

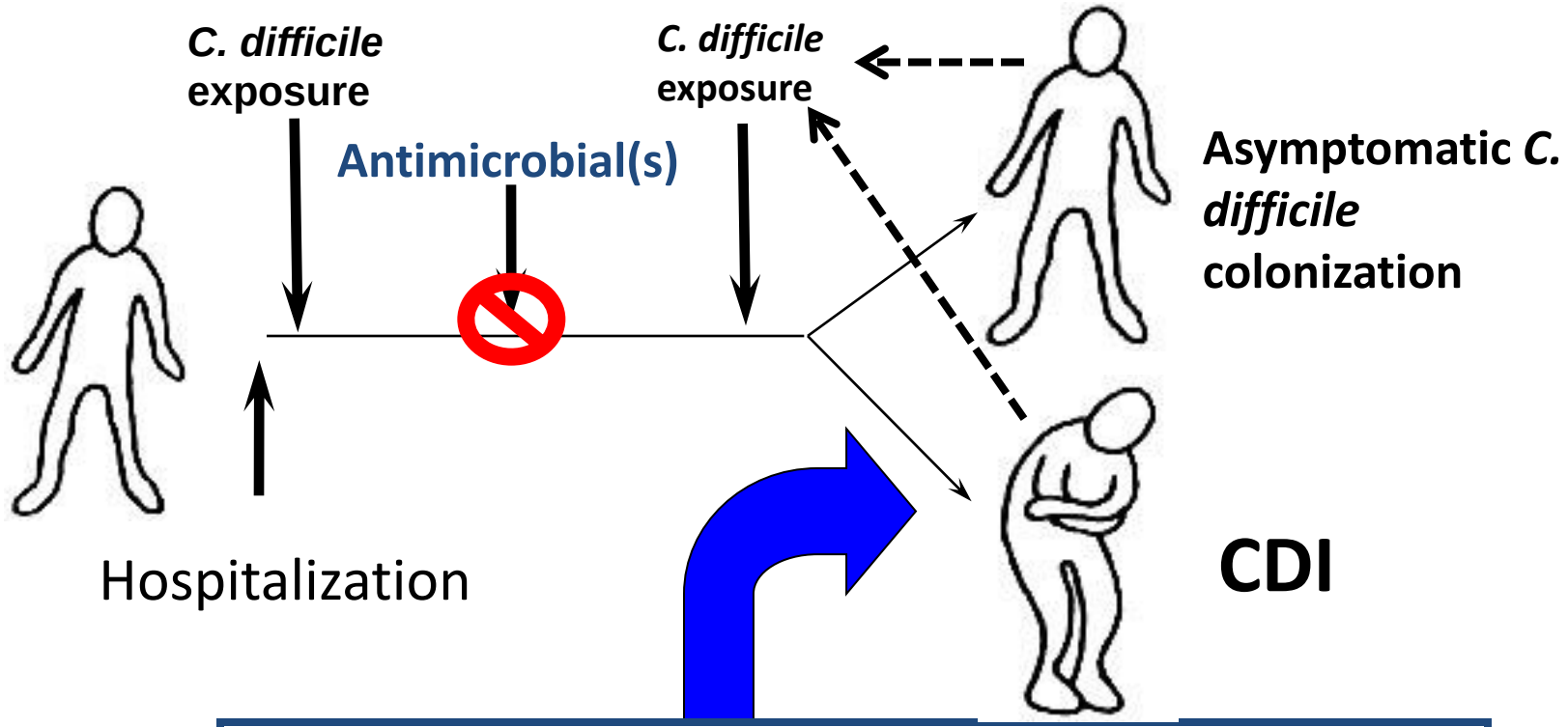
Gerding. JAMA. 2015

Bacteriocins

	Results for[a]:					
	Day 4			Day 7[b]		
Cohort	Infected (*n*)	Total (*n*)	%	Infected (*n*)	Total (*n*)	%
Placebo						
Female	8	10	80	10	10	100
Male	10	10	100	10	10	100
Total	**18**	**20**	**90**	**20**	**20**	**100**
Av-CD291.2						
Female	0*	10	0*	9	10	90
Male	0**	10	0**	10	10	100
Total	**0****	**20**	**0****	**19**	**20**	**95**

Gebhart. mBio 6(2):e02368-14. doi:10.1128/mBio.02368-14.

Targets for CDI Prevention



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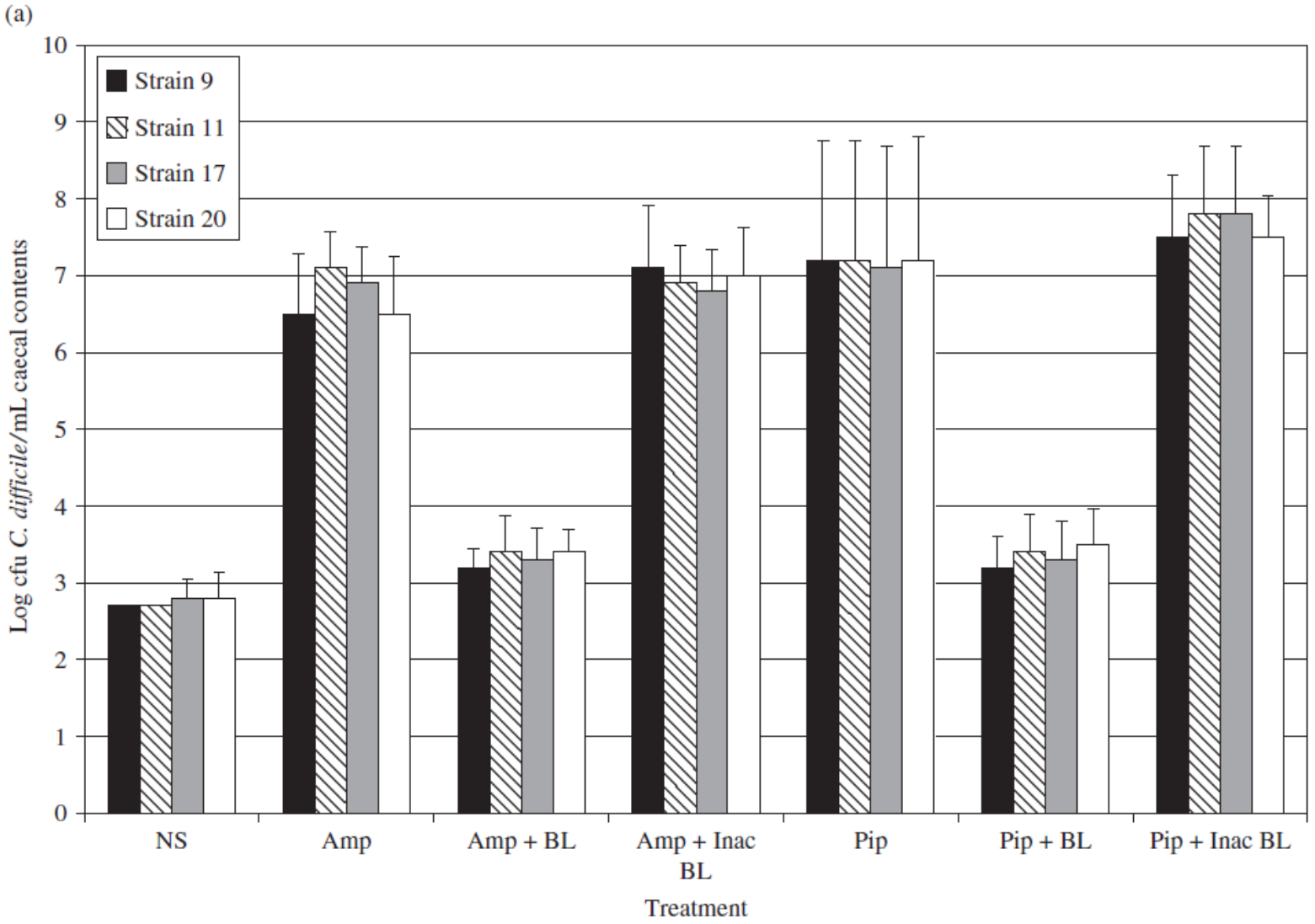
Prevent / Restore Antimicrobial-Induced Microbiota Alteration

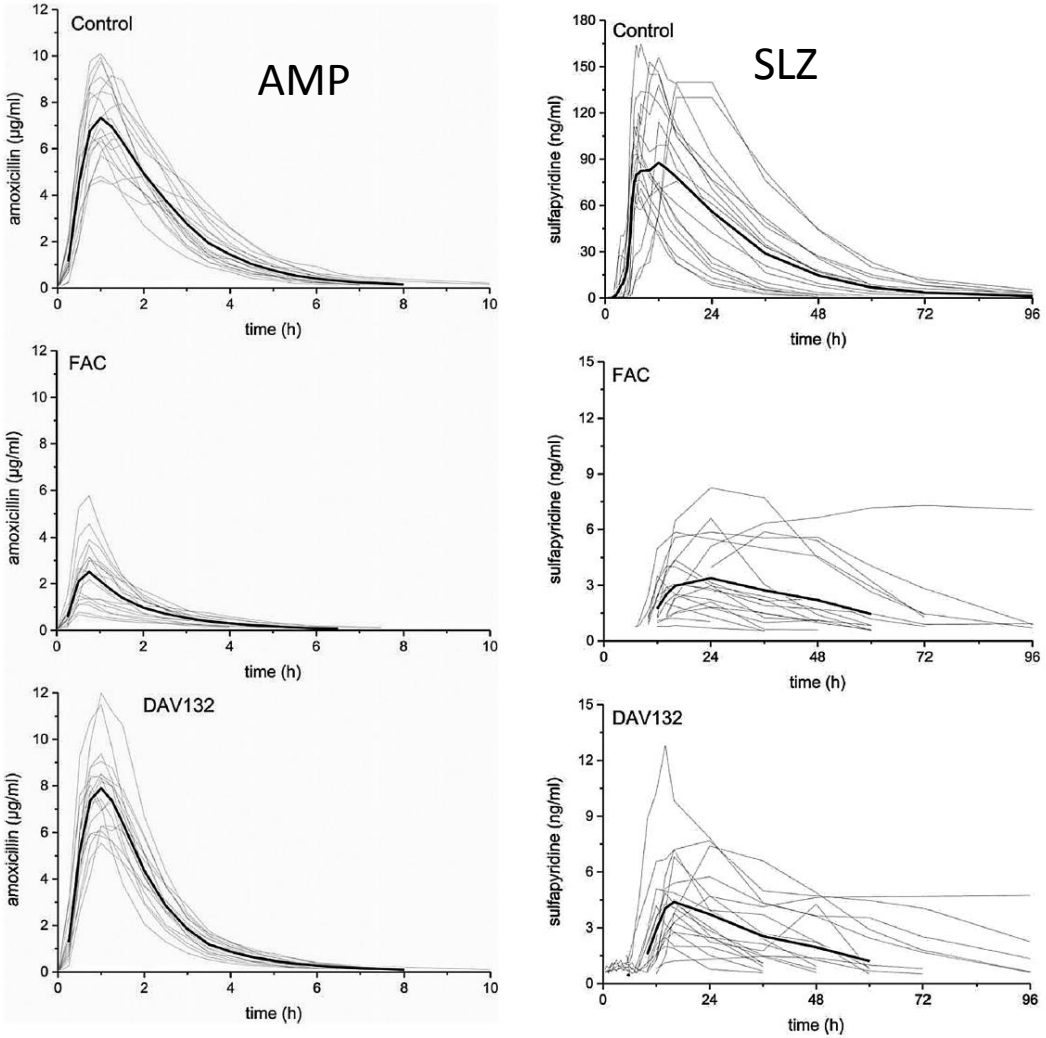
- Selective antimicrobial inhibition
- Non-selective antimicrobial inhibition
- Restoration of microbiome

Selective Antimicrobial Inhibition



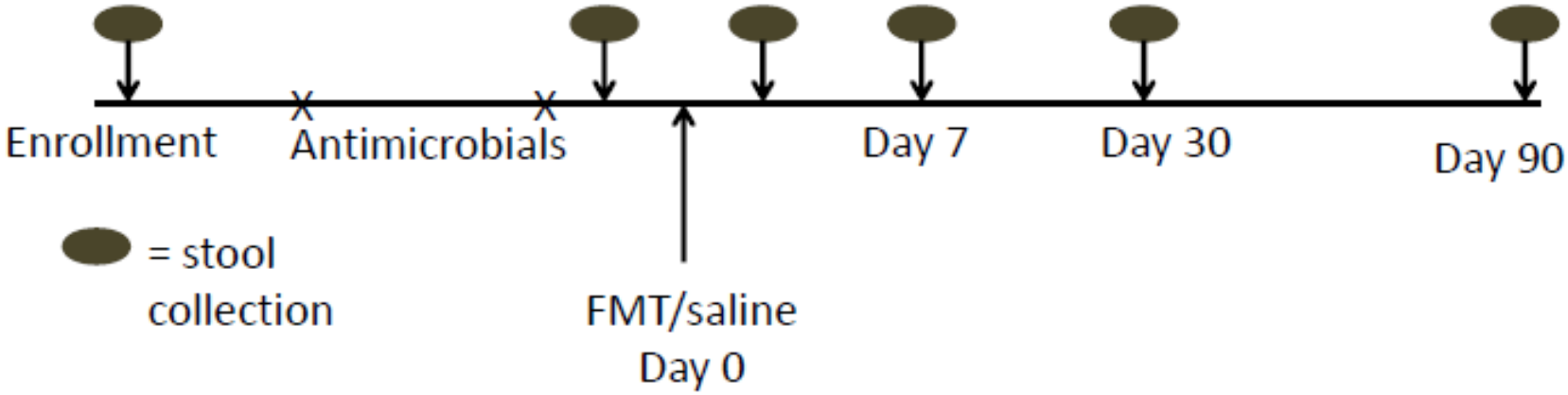
Stiefel. JAC. 2008;

Non-Selective Antimicrobial Inhibition



Gunzburg. J Clin Pharm. 2015

Restoration of Microbiome



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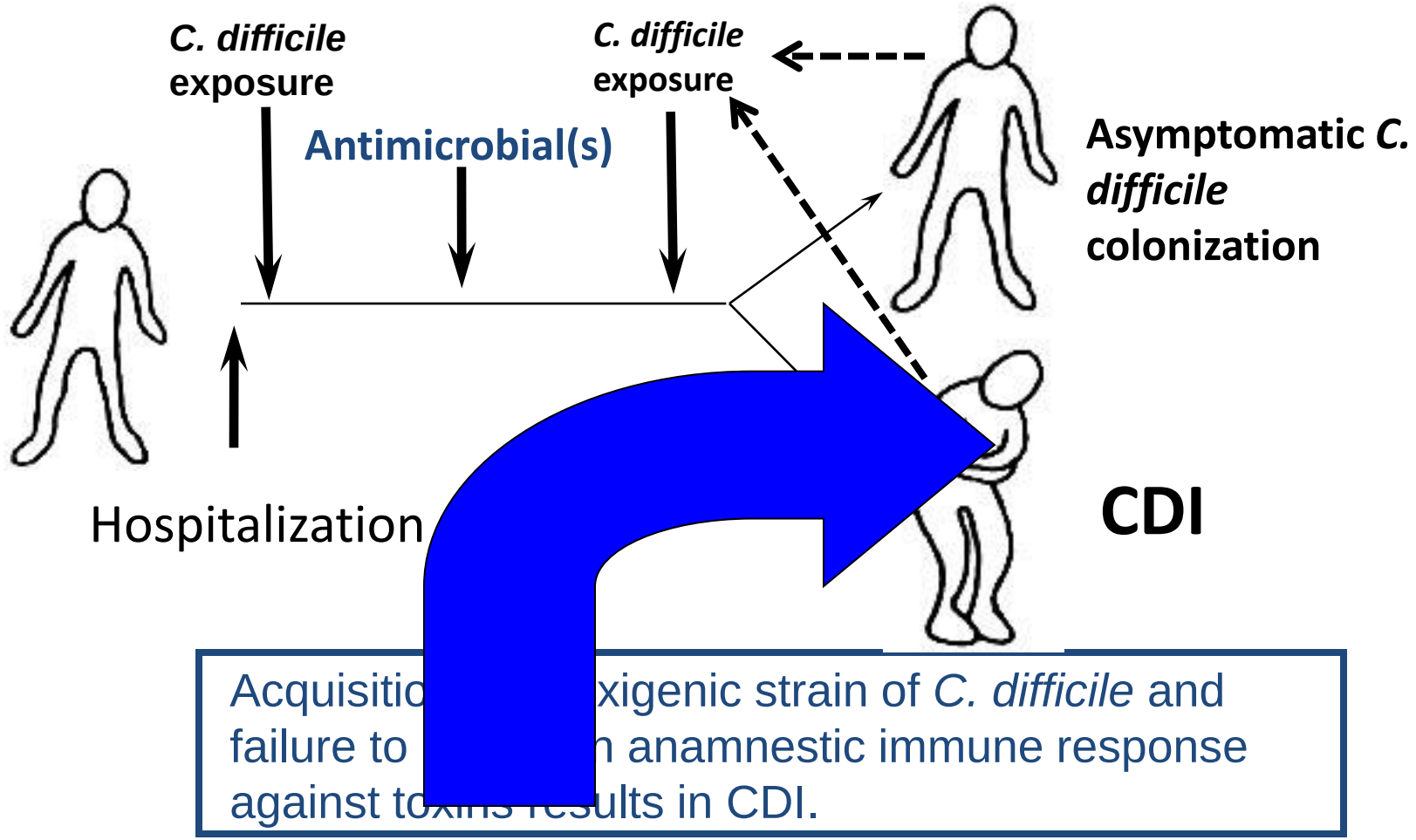

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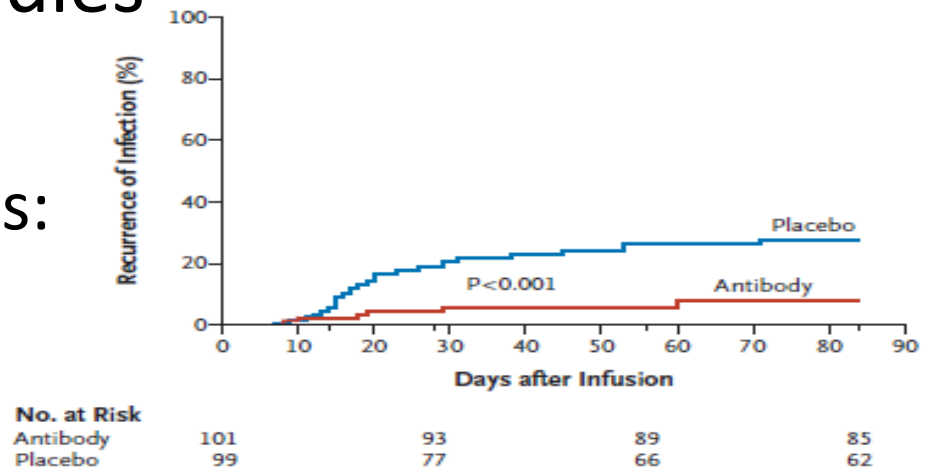
Enhance Anti-*C. difficile* Immunity

- Monoclonal antibodies
  - Recurrent CDI
  - Primary prophylaxis: cost-effectiveness



- Vaccination

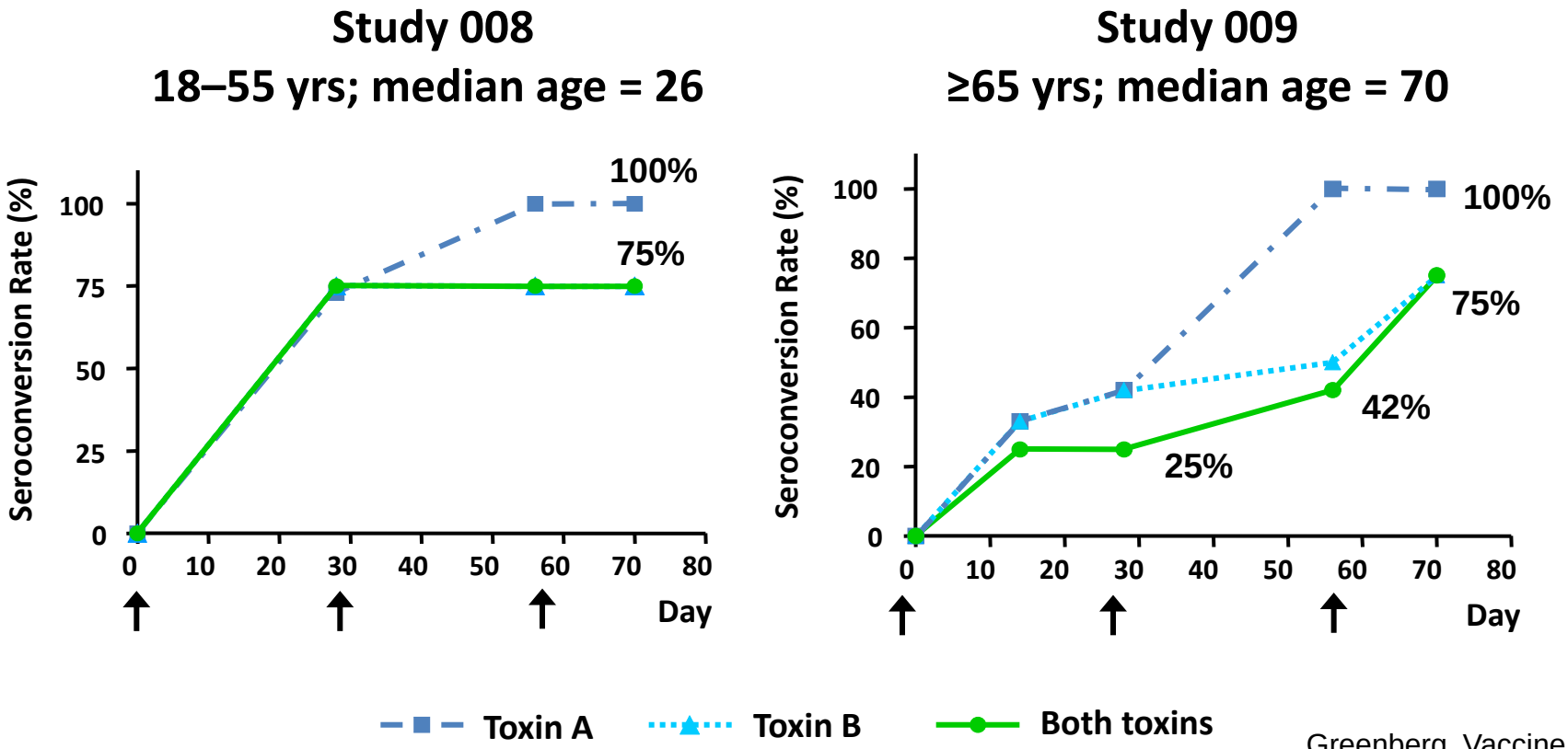
Lowy. *N Engl J Med*. 2010

Role of a Vaccine in CDI Prevention

- Oldest, sickest patients at risk for CDI
  - Repeated for infections / antimicrobial exposures
  - Repeated risk for hospitalization
- Huge reservoir of *C. difficile* in healthcare facilities and community
  - Not possible to prevent all transmission

Challenges for Vaccination

- First vaccine for healthcare-associated infection
  - Population to target
  - When to target



Greenberg. Vaccine. 2012

Conclusions

- Room for improvement
- Several potential targets
  - Prevent transmission from asymptomatic carriers
  - Prevent *C. difficile* colonization if transmission occurs
  - Prevent / restore antimicrobial induced microbiome perturbations
  - Enhance immunity against *C. difficile*