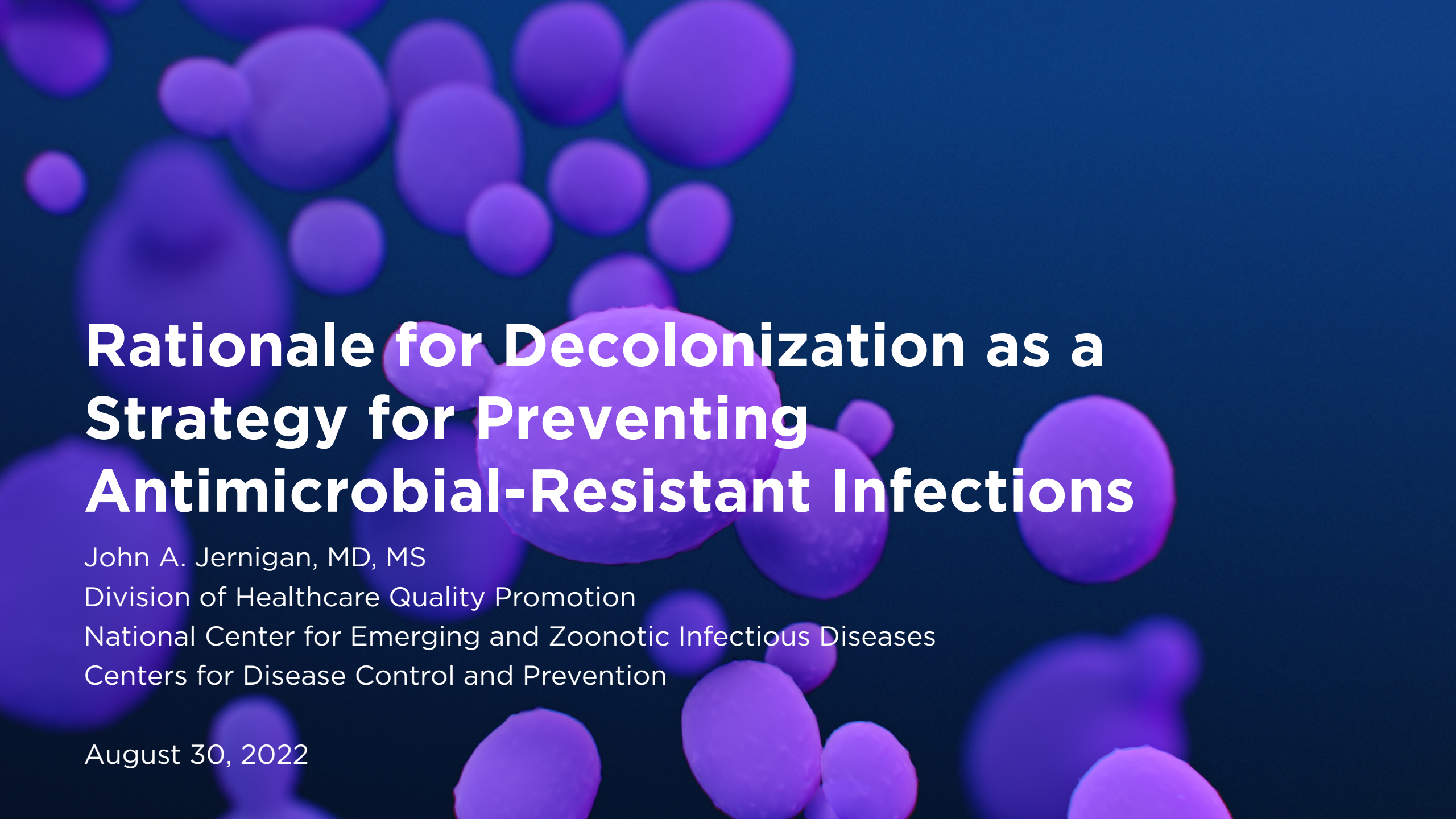

Rationale for Decolonization as a Strategy for Preventing Antimicrobial-Resistant Infections

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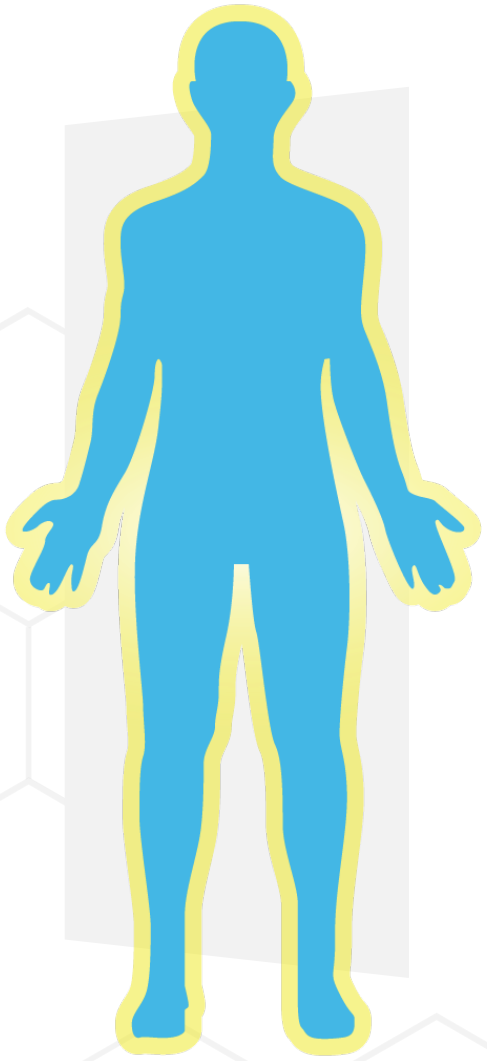
The findings and conclusions in this presentation are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention

Outline

- Definitions
- Colonization is important in the pathogenesis of healthcare-associated infections
- Bacterial transmission as an important driver of antimicrobial resistance burden
- Reducing colonization can prevent antimicrobial-resistant infection
  - Indirect benefit (through transmission prevention) likely much greater than direct benefit (preventing progression from colonization to infection)

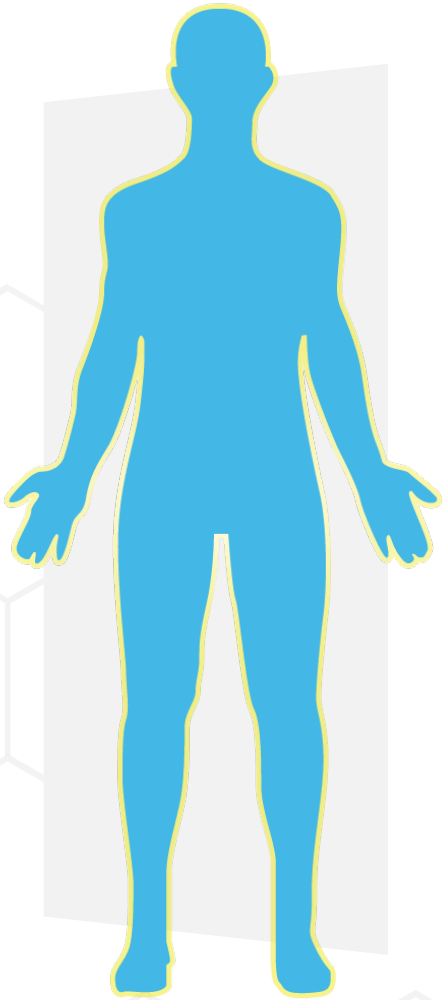
Definitions



COLONIZATION

- Presence of a microorganism living on or in a host in a non-sterile body site, but not causing disease or symptoms
- May be transient to life-long
  - Prolonged colonization usually involves sustained replication in one or more body sites
  - Body sites with prolonged colonization can serve as source of transient contamination of another body site (e.g., sustained colonization of GI tract can serve as a source of transient contamination of skin)
- Burden of colonization can by dynamic over time (e.g., microbial load of a bacterial pathogen might increase during/after exposure to an antibiotic)
- Colonizing microorganisms can and do transition from colonization to infection through various routes or mechanisms

Definitions (continued)

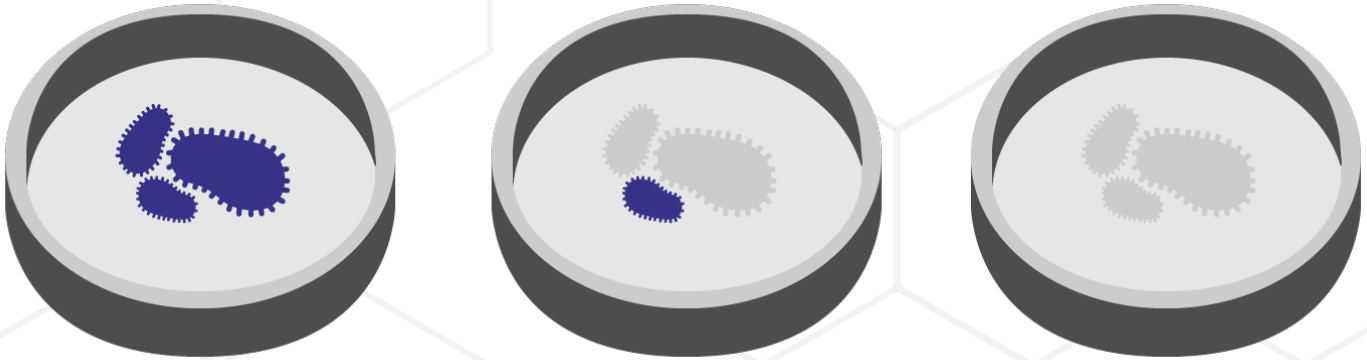


DECOLONIZATION

- Elimination of colonization (complete removal or inactivation/death of colonizing microorganism)

PATHOGEN BURDEN REDUCTION

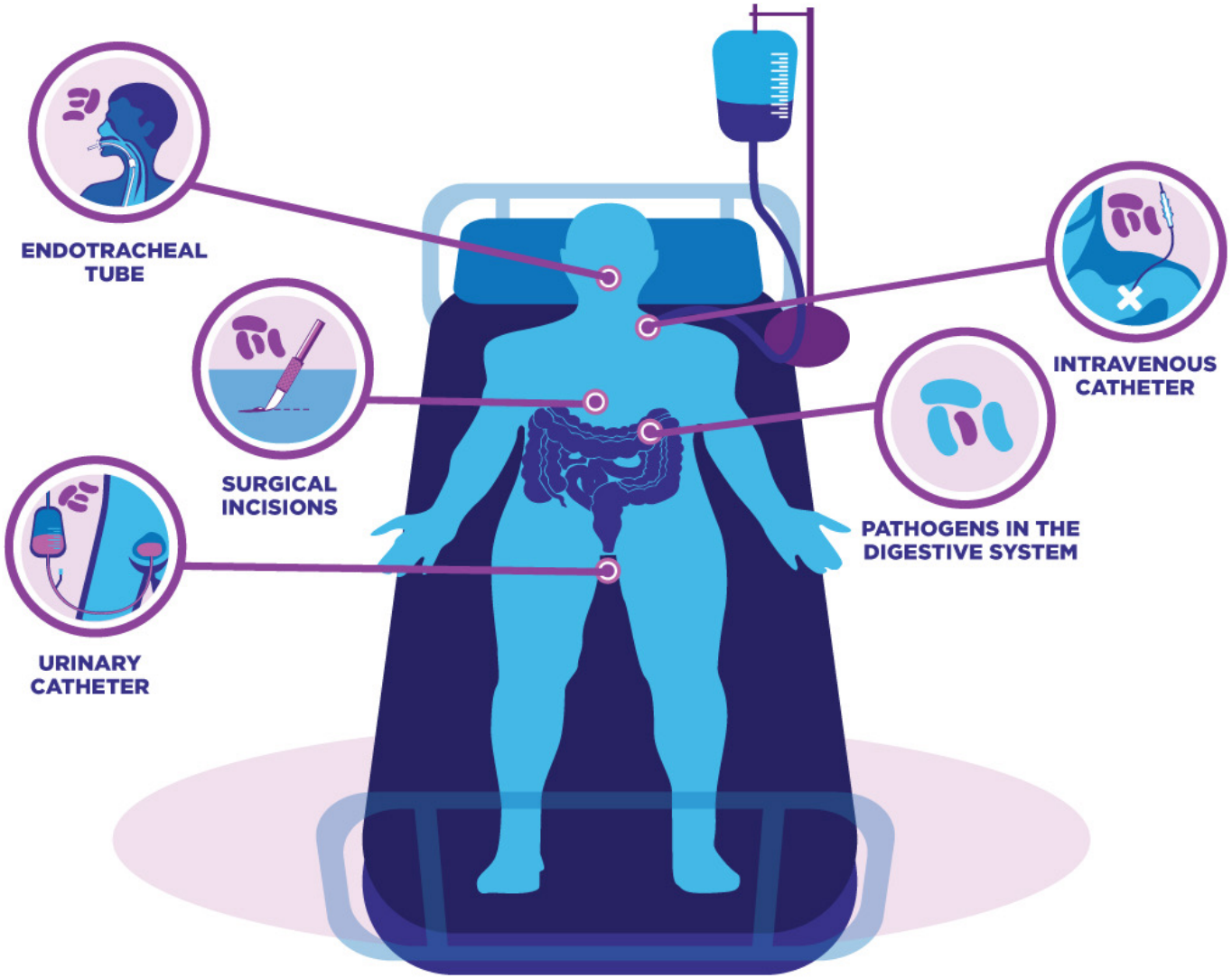
- Partial decolonization or reduction in microbial load of colonizing organism
- Even transient pathogen burden reduction may be beneficial (e.g., during a period of high risk for infection, such as peri-surgical period, ICU stay, or period of immunosuppression)



What We Know

Colonization is important in the pathogenesis of healthcare-associated infections

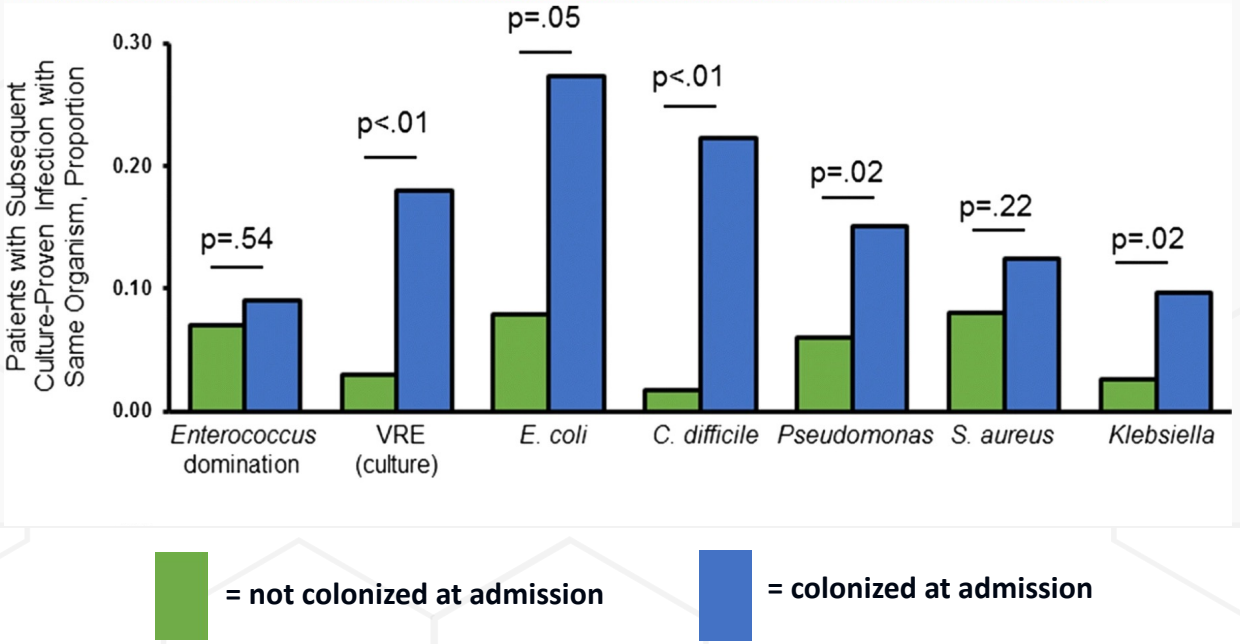
How colonizing pathogens gain entry



HAIs are usually caused by pathogens colonizing the patient prior to infection

- >80% of *S. aureus* bacteremia comes from colonizing strain[2]
- 85% of *S. aureus* surgical site infections come from colonizing strain[3]
- Patients with *Escherichia coli* and *Klebsiella pneumoniae* bloodstream infections have concomitant gut colonization with highly related phylogenetic strains of these organisms[1]
- VRE colonization commonly precedes infection among ICU and cancer patients[4,5]

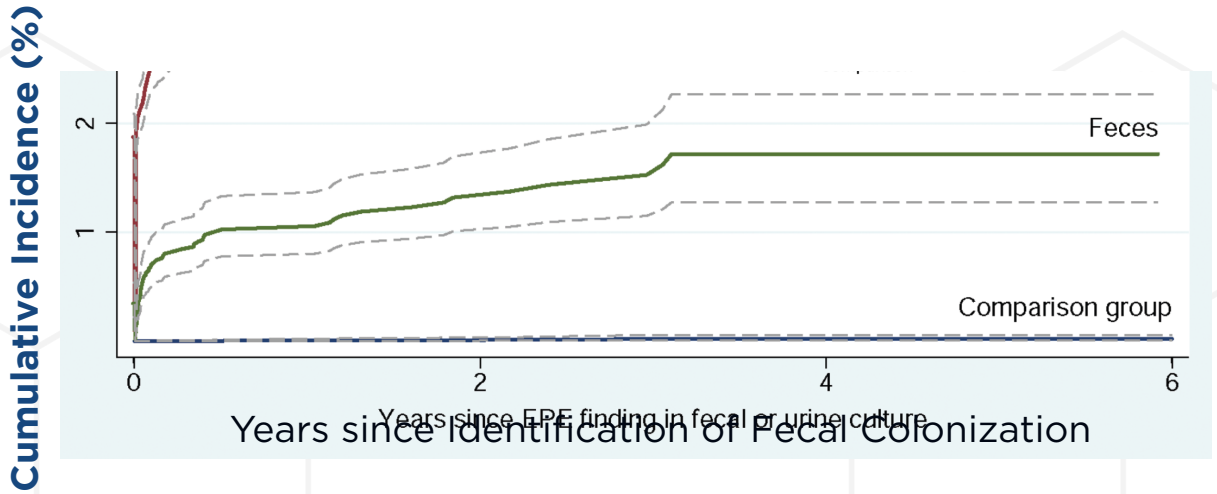
Colonization at ICU admission was associated with subsequent infection with the same organism[6]



1) Tamburin et alNat Med. 2018 December;24(12): 1809–1814. doi:10.1038/s41591-018-0202-8.
2) von Eiff N Engl J Med 2001 Jan 4;344(1):11-6.doi: 10.1056/NEJM200101043440102.
3) Perl et al N Engl J Med. 2002 Jun 13;346(24):1871-7. doi: 10.1056/NEJMoa003069)
4) Ziakas PD, et al. PLOS ONE 2013; 8 (9): e75658
5) Alevizakos, M et al. Open Forum Infect Dis 2016; 4 (1): ofw246
6) Freedburg et al. Intensive Care Med. 2018 Aug;44(8):1203-1211. doi: 10.1007/s00134-018-5268-8.

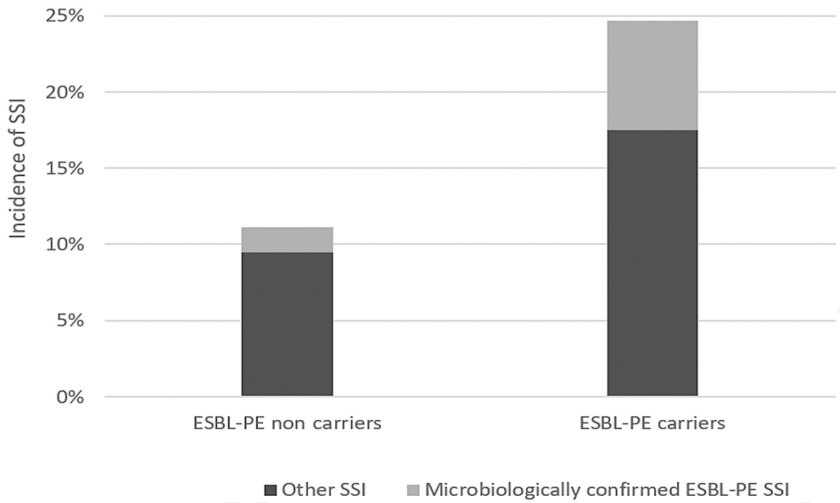
Colonization with pathogens increases risk of infection

Cumulative incidence of Bloodstream Infection Among Persons with Fecal ESBL-producing Enterbacterales Colonization (n=5513)[1]



32-fold increased risk of Bloodstream Infection Among Persons with Colonized with ESBL-producing Enterobacterales

Incidence of surgical site infection in ESBL-producing Enterbacterales carriers and noncarriers after colorectal surgery[2]



> 2-fold increase in SSI rate in carriers of ESBL-producing Enterobacterales

1) Isendahl et al. Clin Infect Dis 2019;68(4):641–9
2) Dubinsky-Pertzov et al. Clin Infect Dis 2019;68(10):1699–704

Colonization with pathogens increases risk of infection (continued)

- **Pre-operative *S. aureus* carriage associated with nearly 10 times the risk of wound infection following cardiac surgery[1]**
- **Risk of infection is associated with *microbial load* of colonization**
  - Relative abundance of carbapenemase-producing *K. pneumoniae* (C-Kp) in the intestinal microbiota of 22% was predictive of C-Kp bacteremia (relative risk = 4.2)[2]
  - Intestinal domination by *Enterococcus* (>30% of taxons in microbiota) increases risk of VRE bloodstream infection 9-fold among hematopoietic stem cell transplantation patients[3]

1) Kluytmans JA, Mouton JW, Ijzerman EP, et al. Nasal carriage of Staphylococcus aureus as a major risk factor for wound infections after cardiac surgery. J Infect Dis 1995;171:216-9.
2) Shimasaki et al Clin Infect Dis. 2019 May 30;68(12):2053-2059. doi: 10.1093/cid/ciy796. PMID: 30239622; PMCID: PMC6541703
3) Taur, Y, et al. Clinical Infectious Diseases 2012; 55(7): 905-914

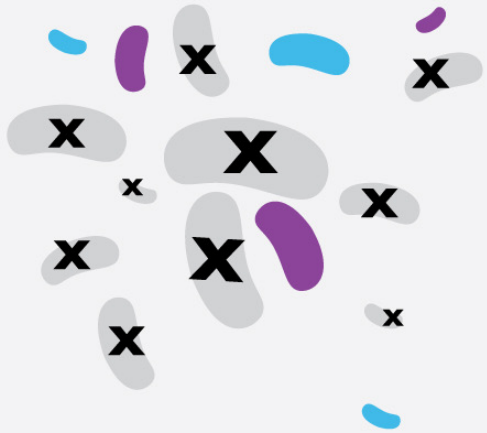
What We Know

Transmission is an important driver of antimicrobial resistance

How resistance emerges

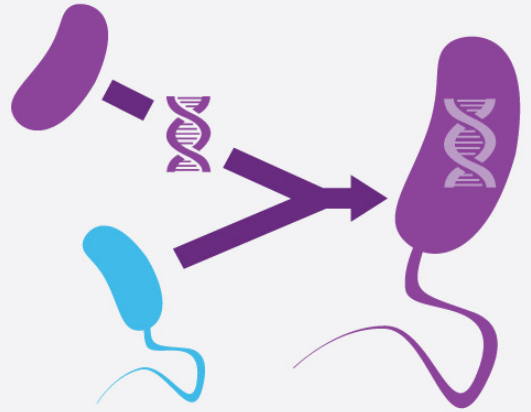
Resistant strains are often present due to:

- random genetic mutation
- acquisition of resistance genes from other bacteria
- acquisition of resistant strains through transmission



Antibiotics, antifungals and other therapeutics create a selective advantage for the resistant organisms

Both proportion and total burden of **resistant organisms increase**

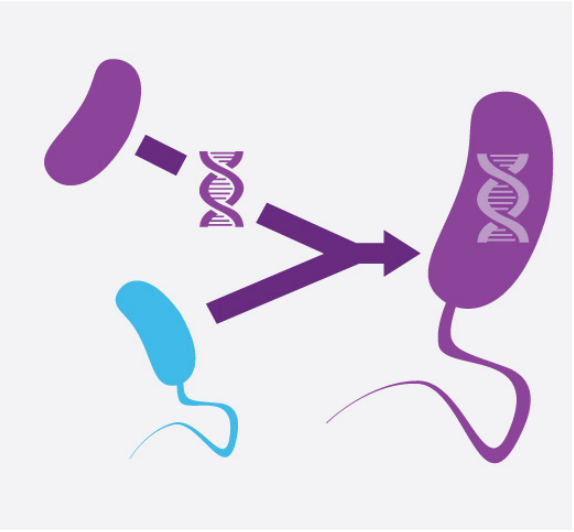


Increase in burden of resistant organisms increases **risk of:**

- **Direct and indirect transmission among people**
- **Horizontal transmission of genetic resistance elements among bacteria**

Serious resistance problems often result from transmission of highly fit clonal strains

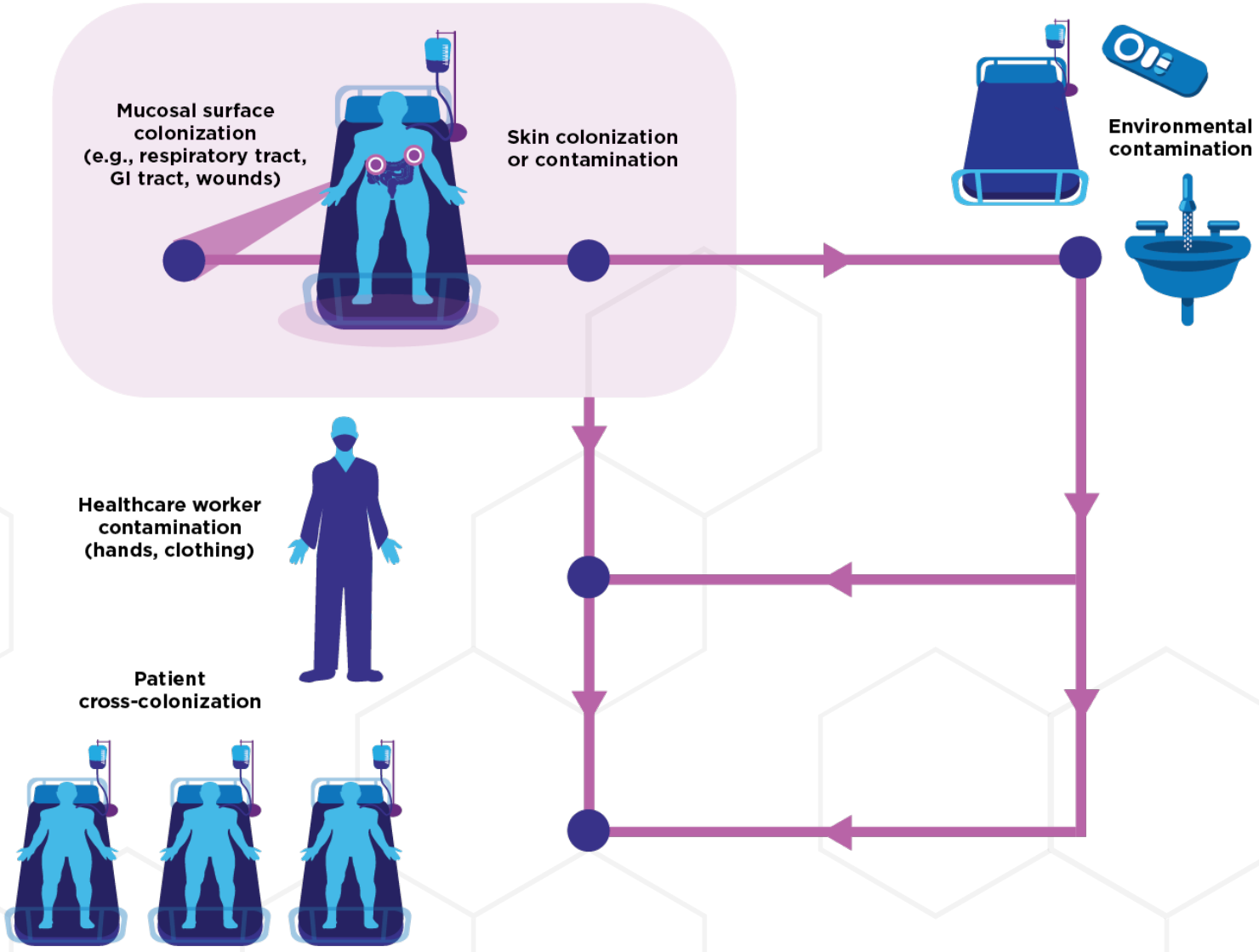
- **Highly fit resistant clones result when genetic resistance elements are acquired by susceptible strains adept at colonization, transmission, and/or causing infection**
- Examples:
  - Healthcare associated MRSA primarily associated with clonal group USA100
  - Community-associated MRSA primarily associated with clonal group USA300
  - International spread of KPC-producing *K. pneumoniae* primarily associated with clonal group ST258 and its related variants
  - ESBL *E. coli* associated with clonal group ST131
  - Rapid emergence of *C. difficile* associated with ribotype O27



What We Know

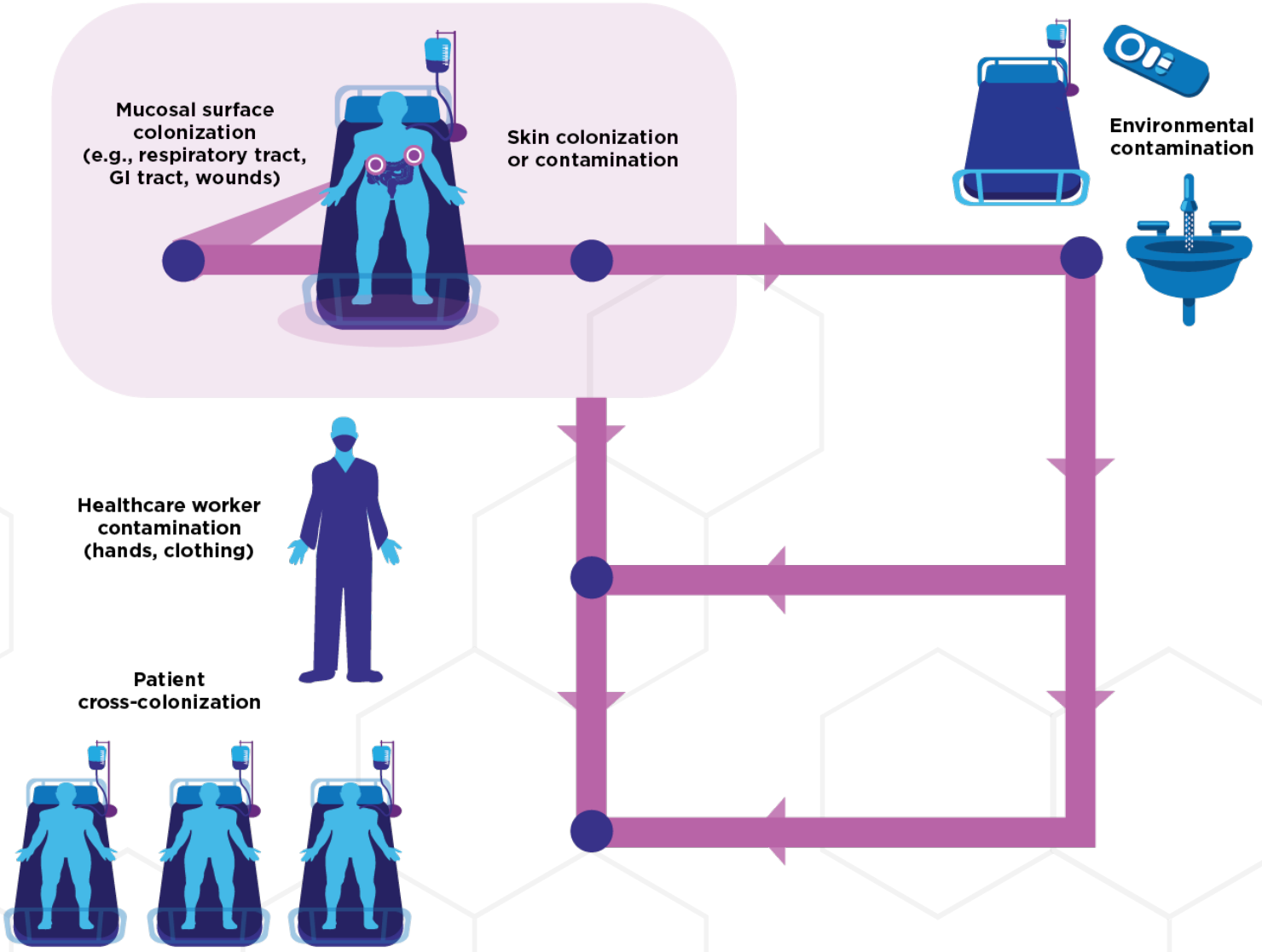
Colonization drives transmission of antimicrobial-resistant organisms in healthcare settings

A model of colonization & healthcare transmission



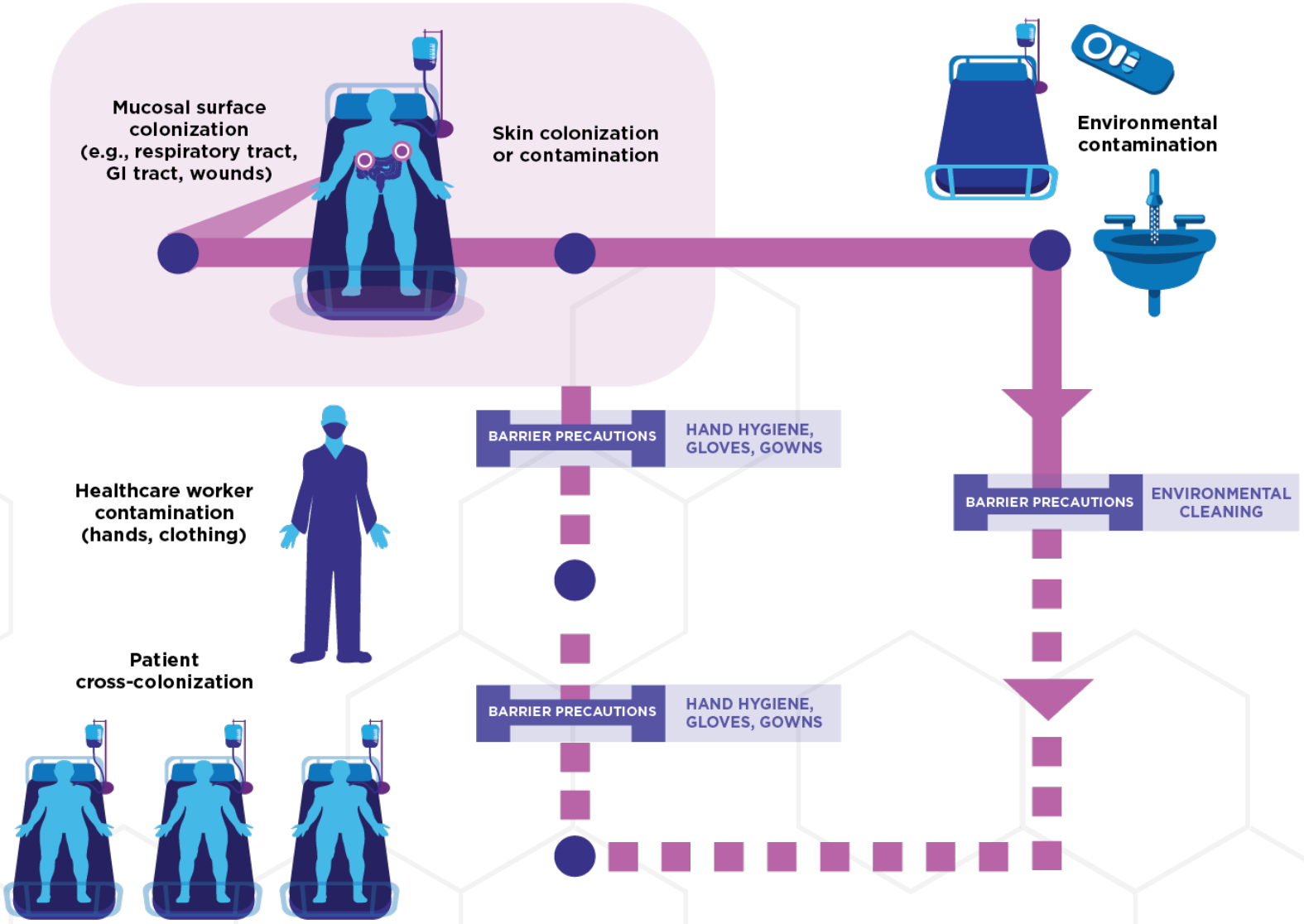
*Line thickness denotes magnitude of transmission

Under conditions of HIGH colonization burden



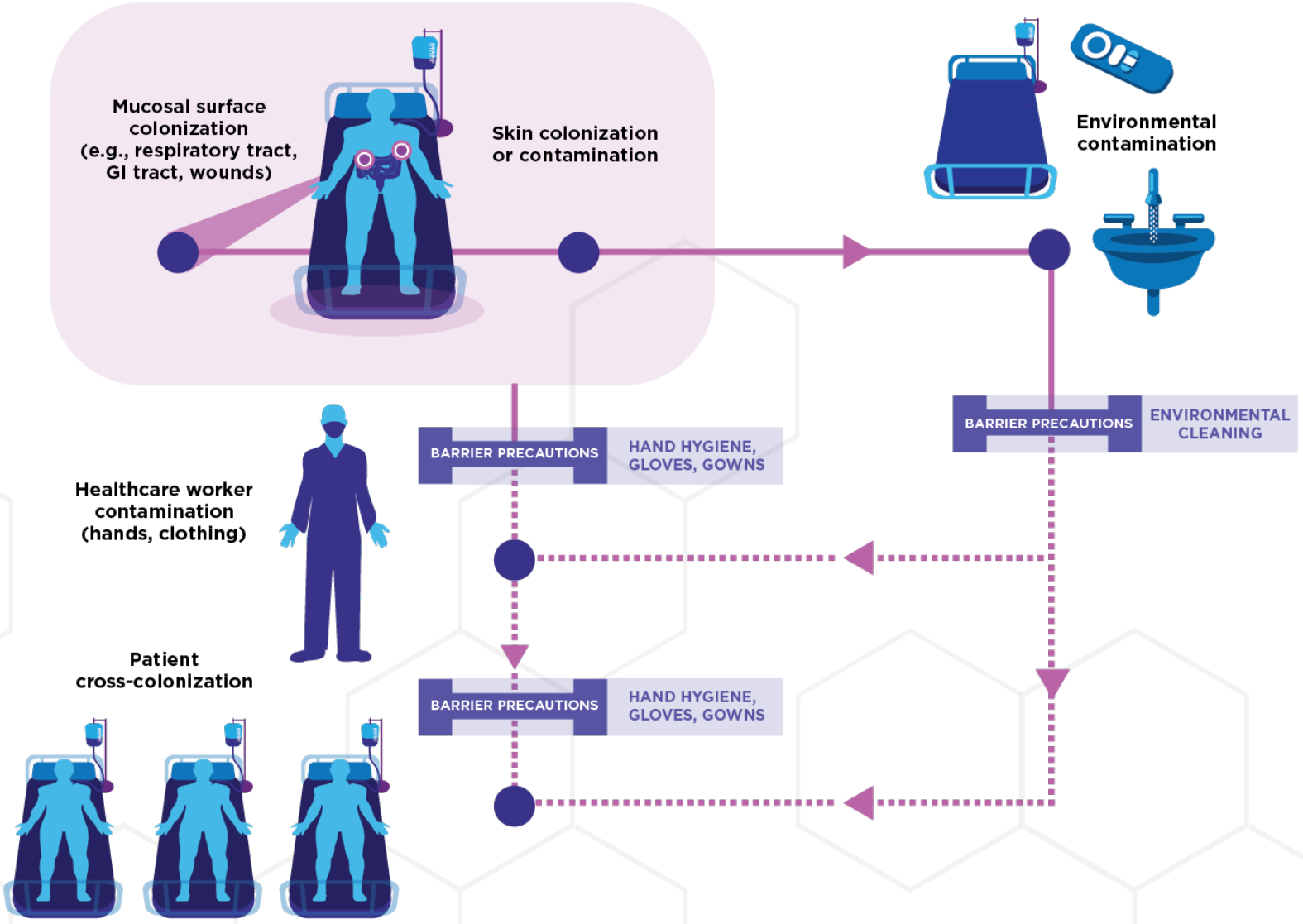
*Line thickness denotes magnitude of transmission

Under conditions of HIGH colonization burden, with infection control precautions



*Line thickness denotes magnitude of transmission

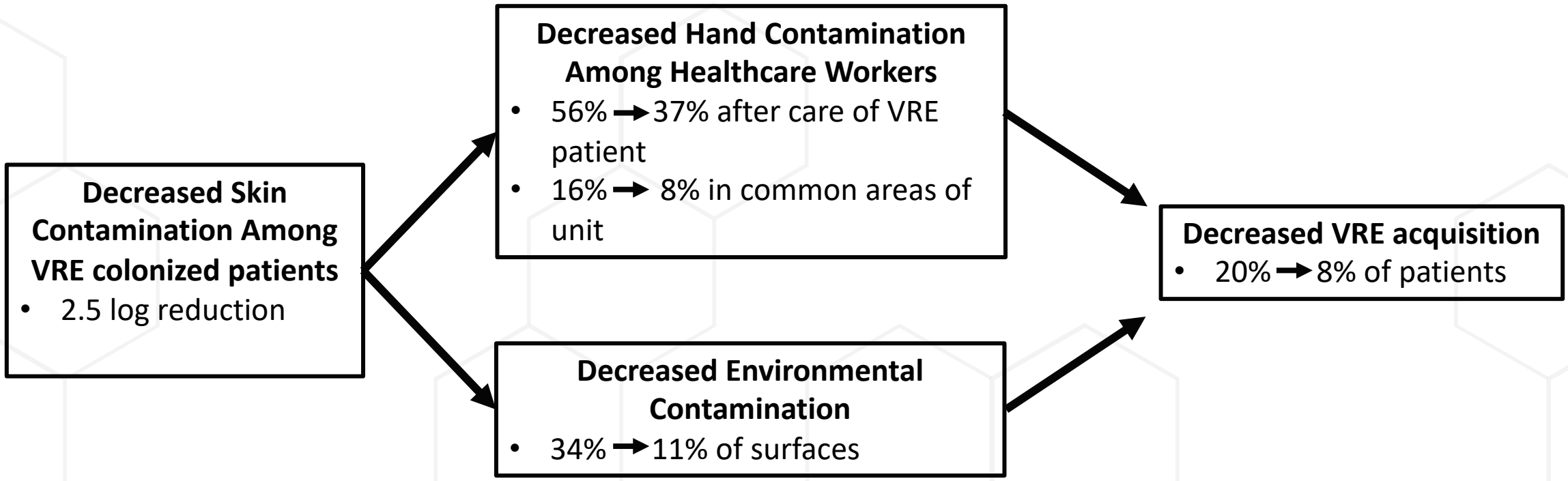
Under conditions of LOW colonization burden, with infection control precautions



*Line thickness denotes magnitude of transmission

Reducing burden of colonization can prevent transmission in healthcare settings

Effect of daily chlorhexidine bathing on skin and environmental contamination and acquisition of vancomycin-resistant enterococci (VRE) in an ICU



Vernon et al. Arch Intern Med. 2006;166:306-312

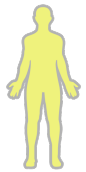
Reducing burden of colonization can prevent infection in healthcare settings

Evidence from Randomized Trials

- REDUCE MRSA Trial
  - Huang SS, et al. NEJM 2013; 368 (24):2255-65
- ABATE Trial
  - Huang SS, et al. Lancet 2019; 393 (10177):1205-1215
- Project CLEAR
  - Huang SS, et al. Lancet 2019; 393 (10177):1205-1215
- PROTECTS
  - Miller et al. ID week abstract 2021
- MARS Study
  - Perl et al. NEJM 2002; 346 (24): 1871-7
- Bode et al. NEJM 2010; 362 (1): 9-17

Theoretical mechanisms of action

- Reduces risk of transitioning from colonization to infection in treated colonized individual (direct benefit)
- Reduced risk in other untreated individuals through decreasing shedding/transmission from colonized individual (indirect benefit)
- Reducing risk of acquiring colonization in treated, uncolonized individual



Decolonized

Colonized

Infected

Deceased

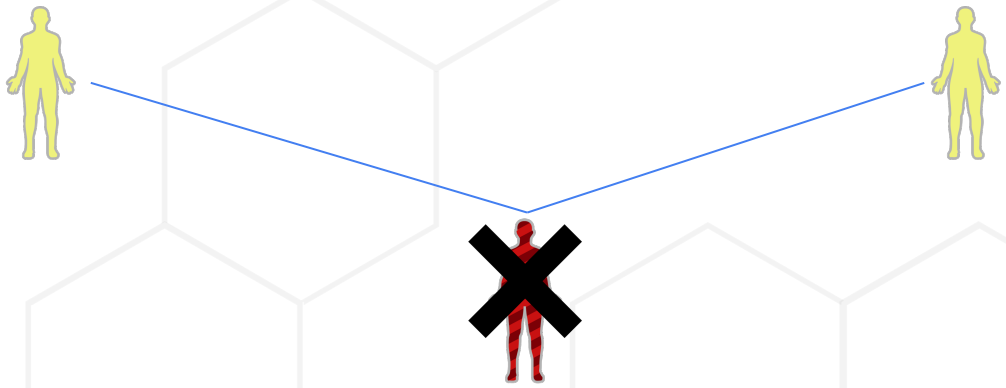
Decolonized

Colonized

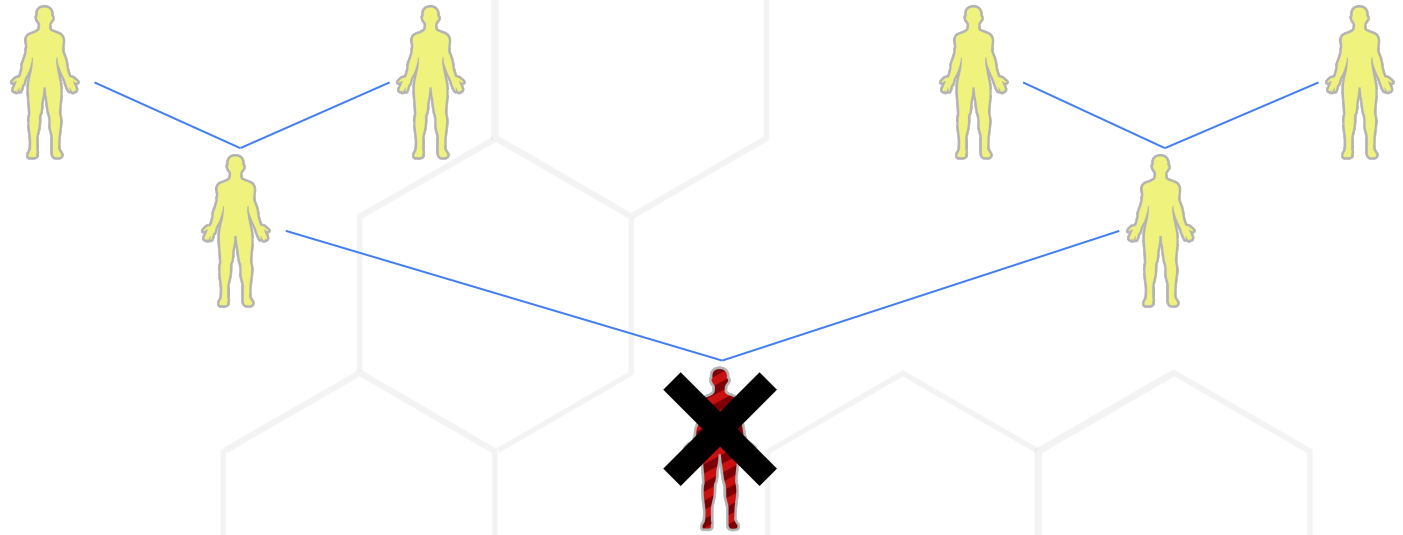
Infected

Deceased

Decolonized Colonized Infected Deceased



Decolonized Colonized Infected Deceased

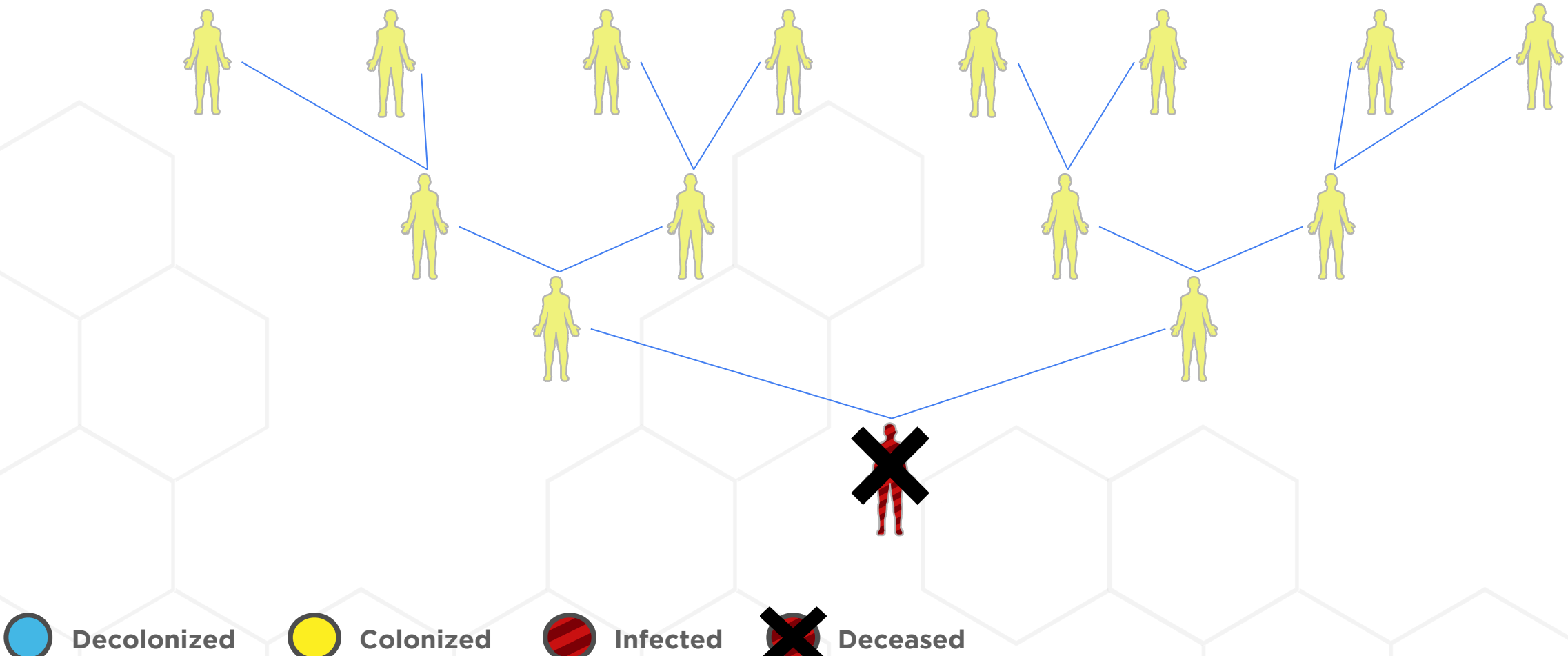


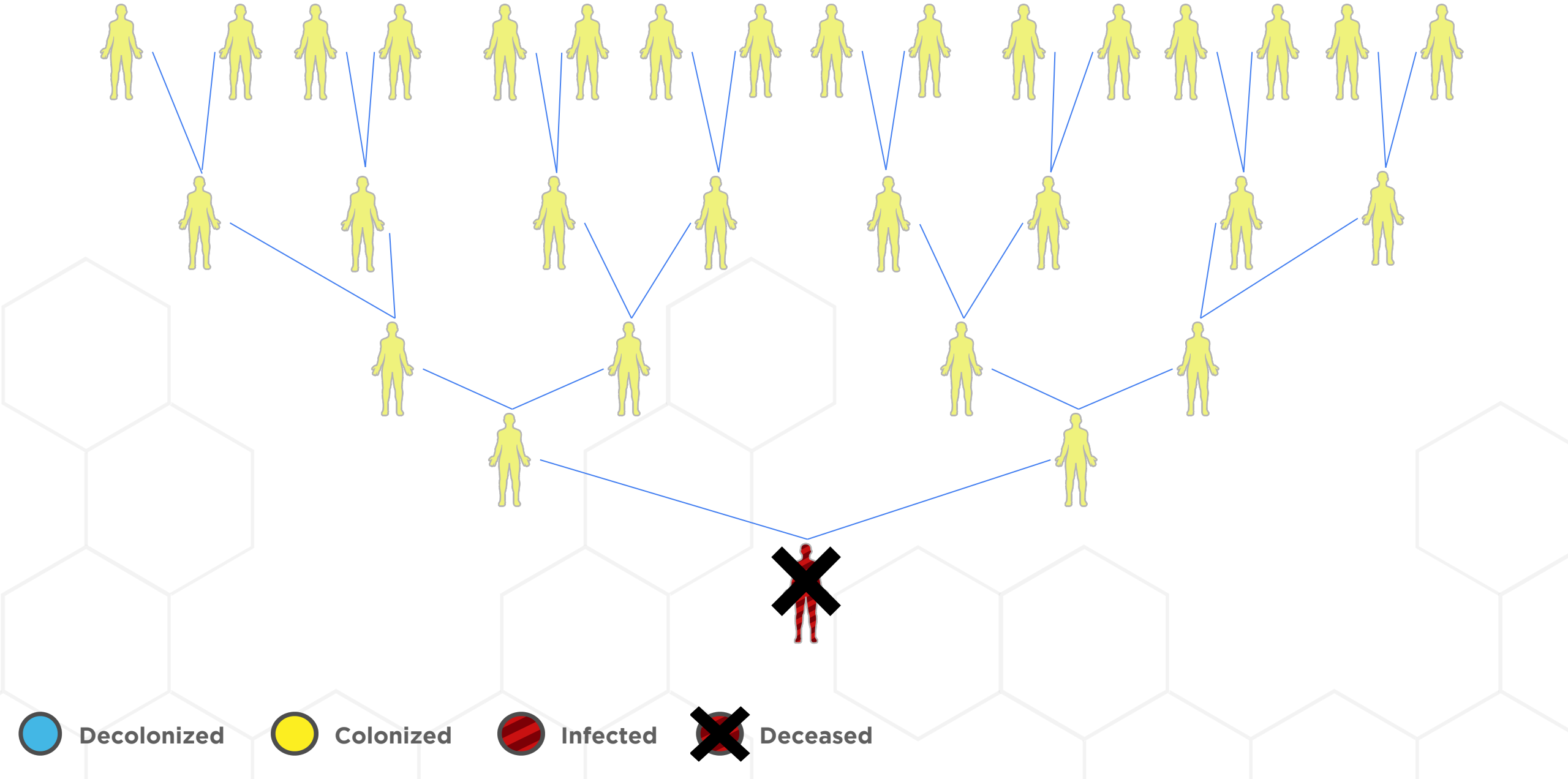
Decolonized

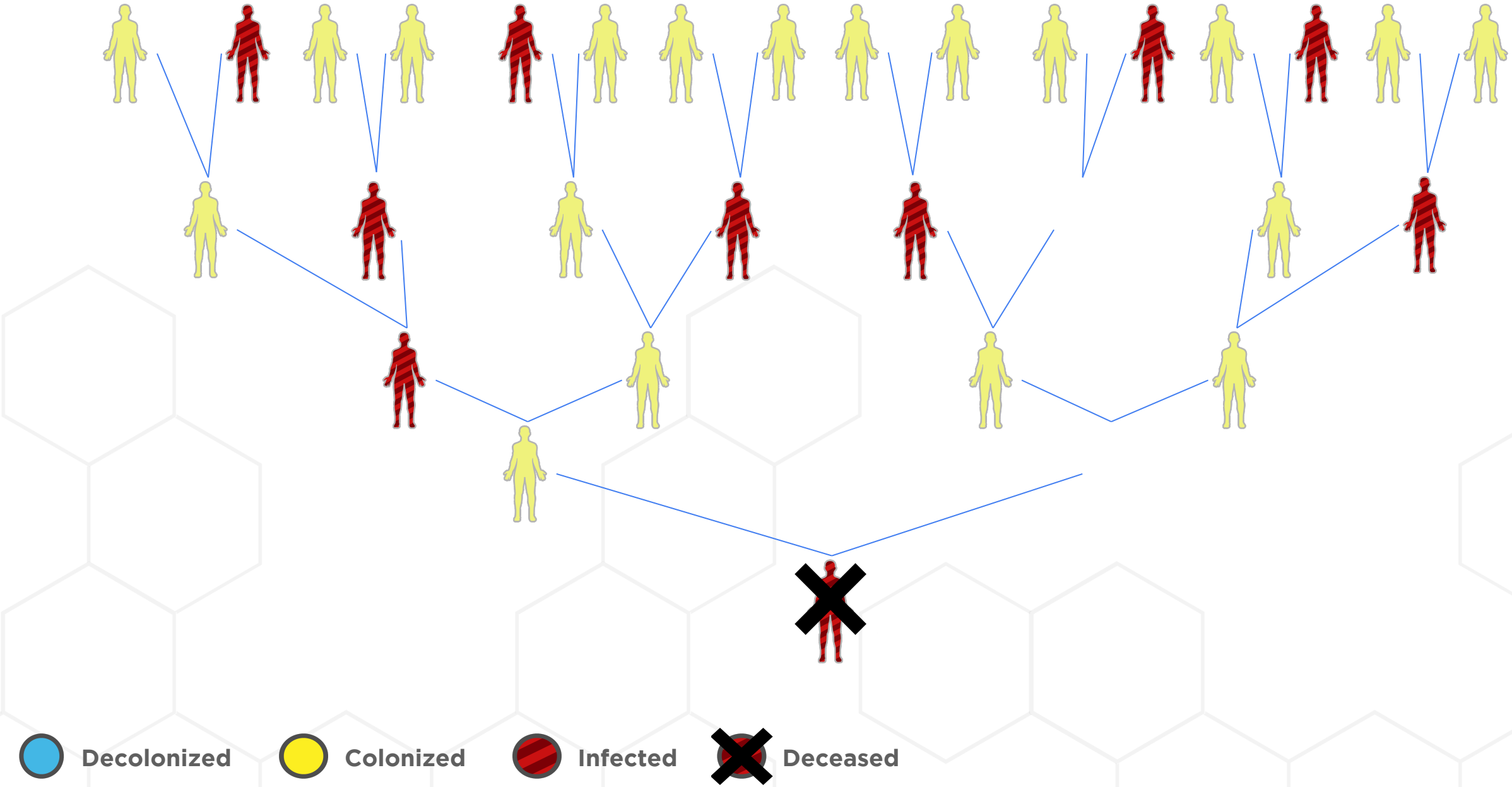
Colonized

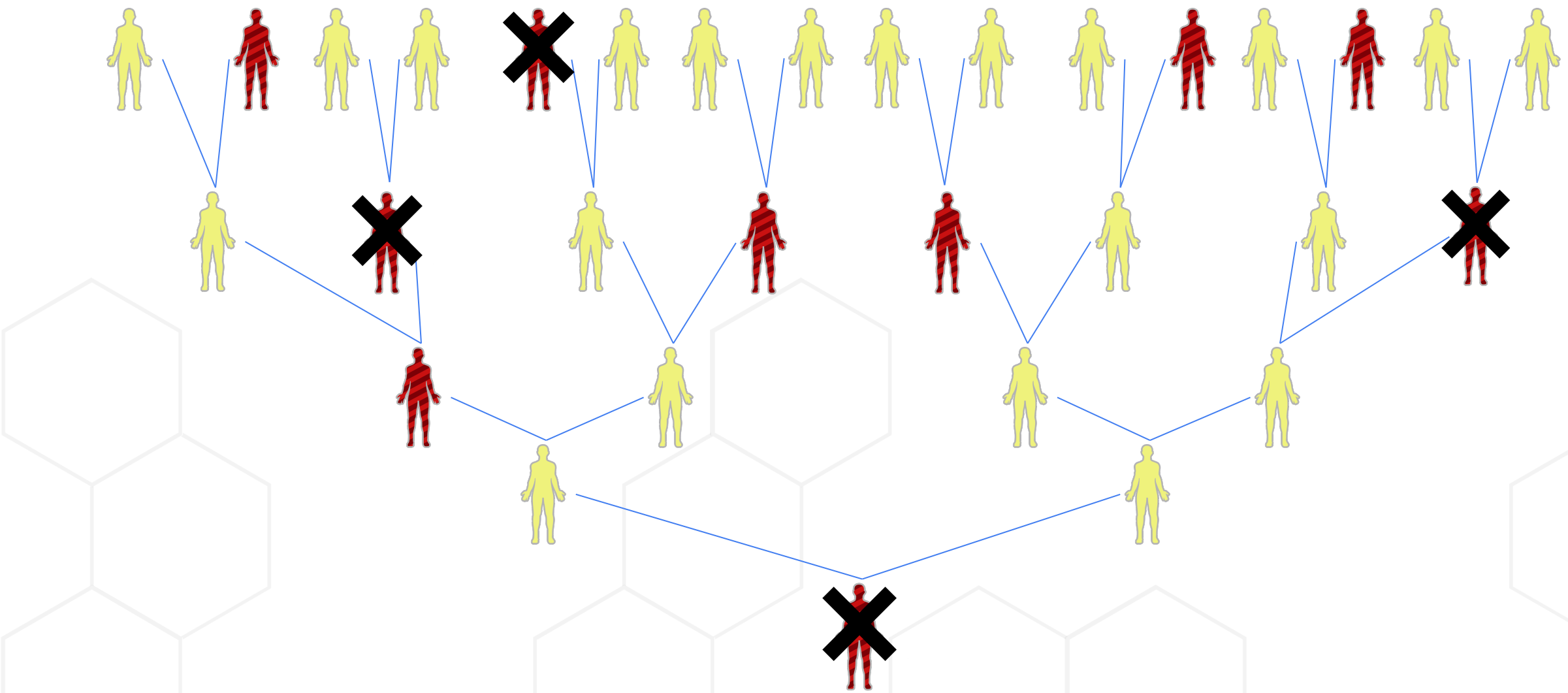
Infected

Deceased


Decolonized
Colonized
Infected
Deceased


Decolonized
Colonized
Infected
Deceased


Decolonized
Colonized
Infected
Deceased



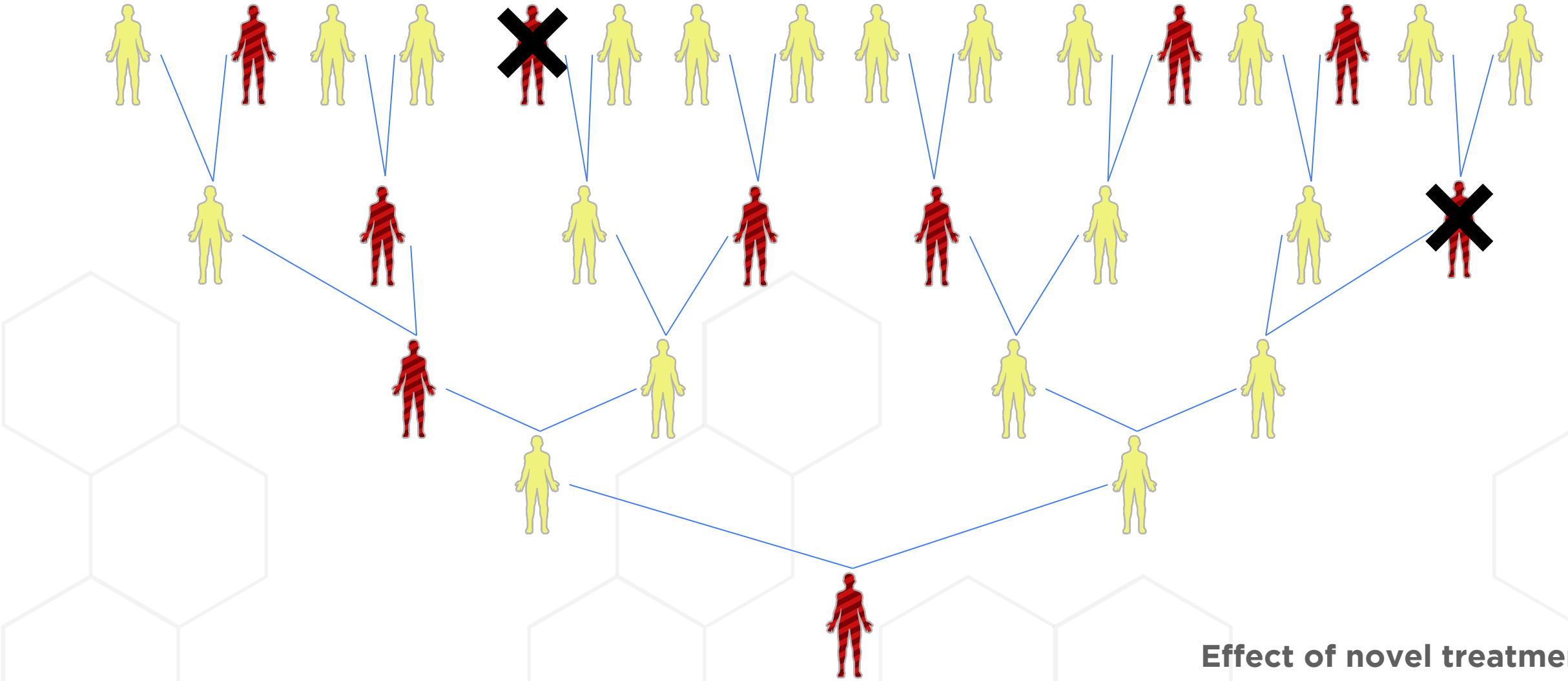
Decolonized

Colonized

Infected

Deceased

Mortality with currently available treatment for infection= 40%



Decolonized

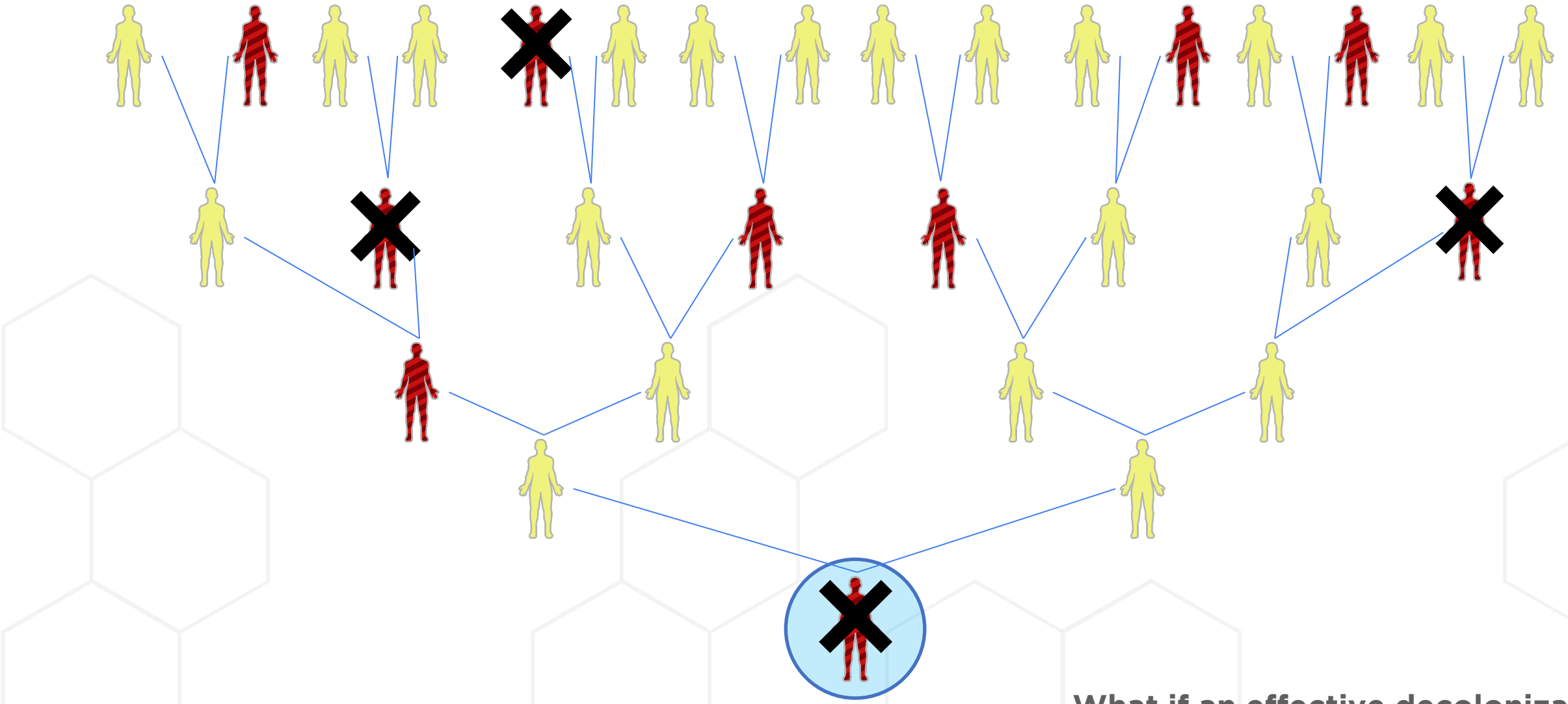
Colonized

Infected

Deceased

Effect of novel treatment drug (mortality 20%):

- **Deaths Prevented=2**
- **Infections Prevented=0**



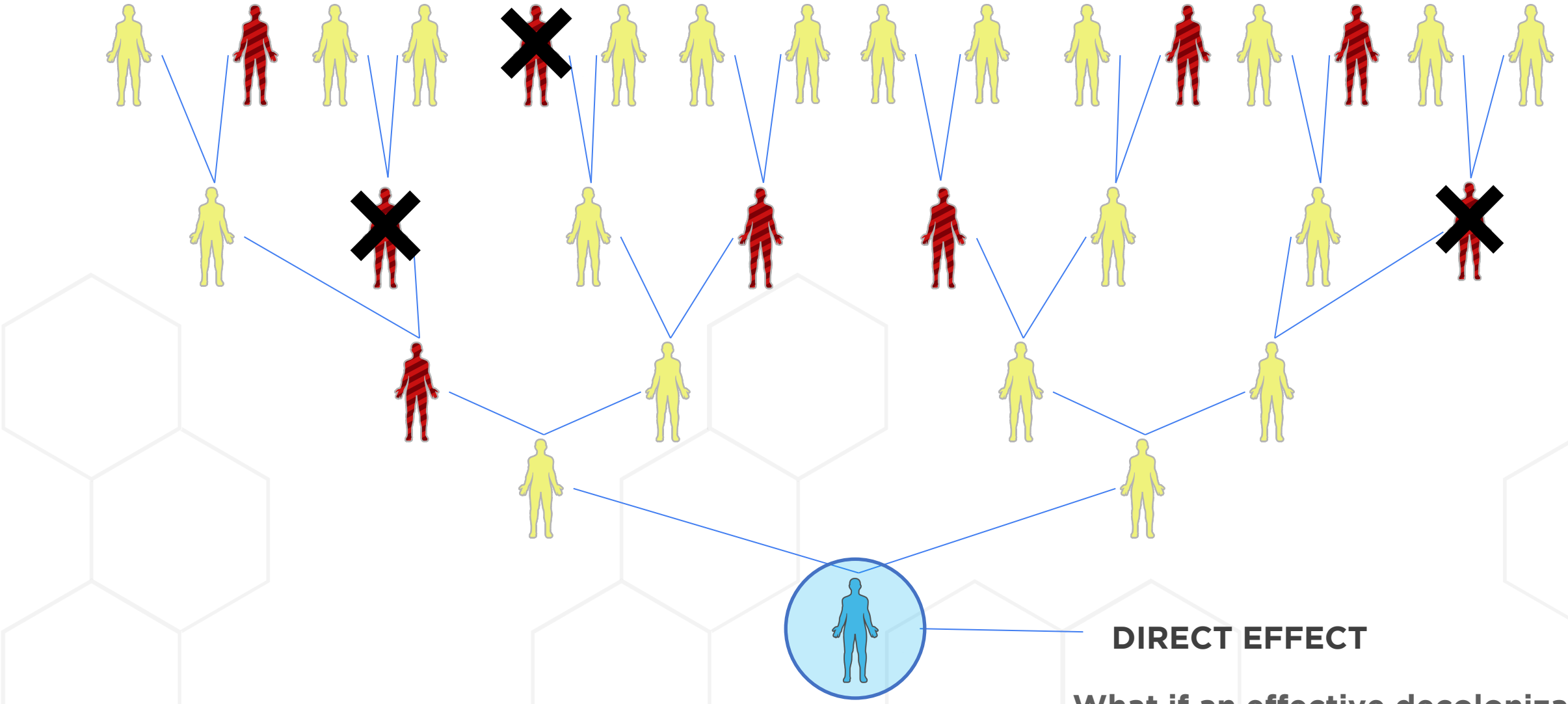
Decolonized

Colonized

Infected

Deceased

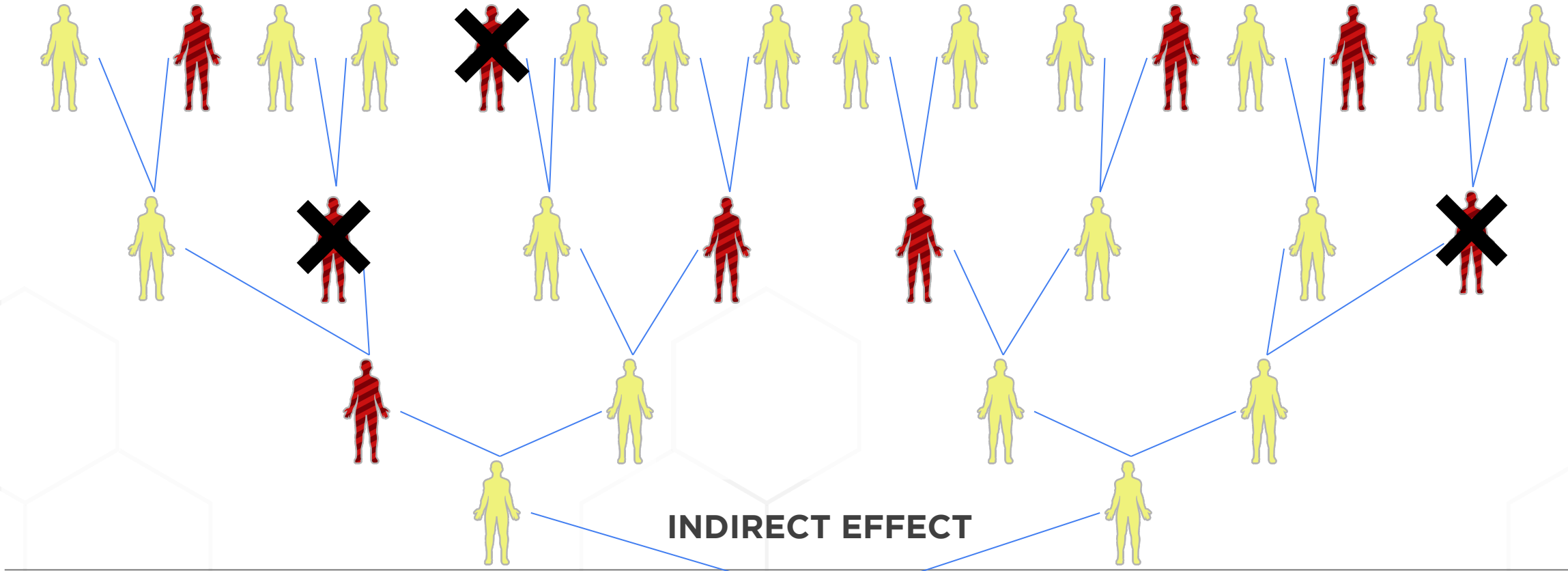
What if an effective decolonization agent had been used for index patient?



DIRECT EFFECT

What if an effective decolonization agent had been used for index patient?

Decolonized Colonized Infected Deceased



INDIRECT EFFECT

DIRECT EFFECT

What if an effective decolonization agent had been used for index patient?

Decolonized

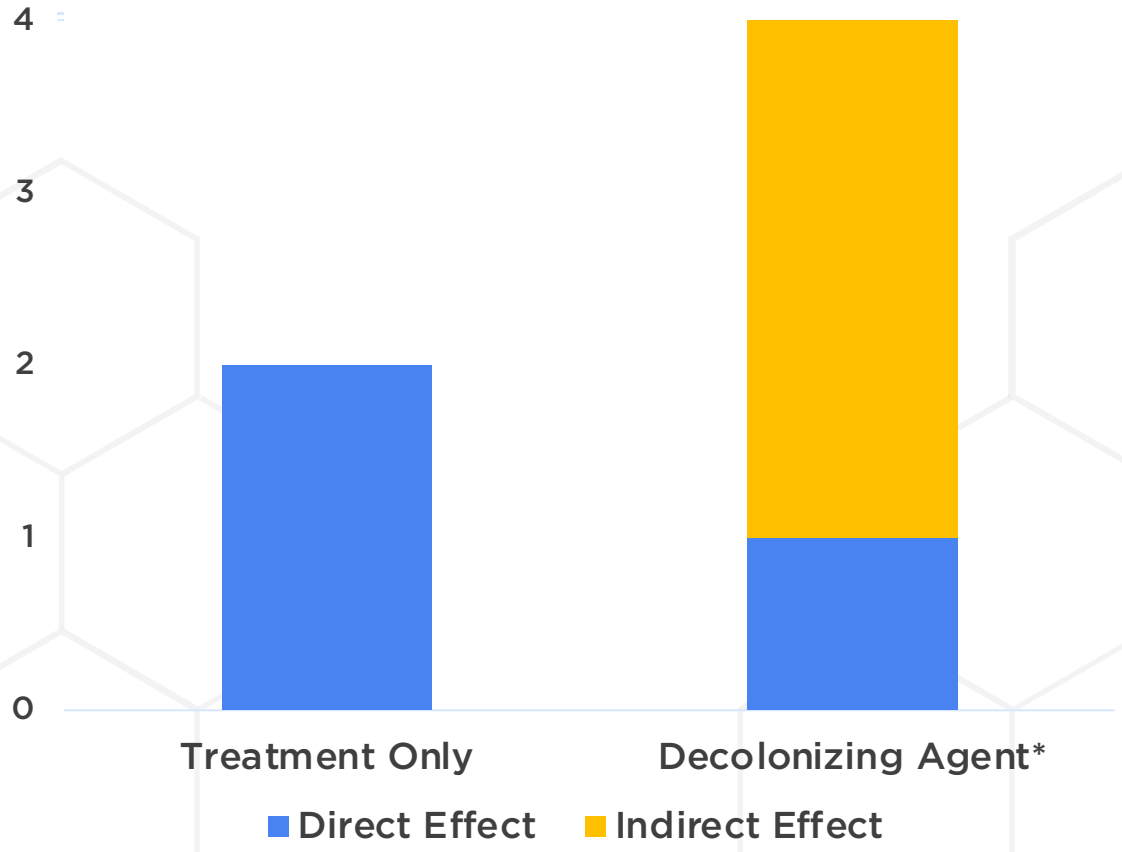
Colonized

Infected

Deceased

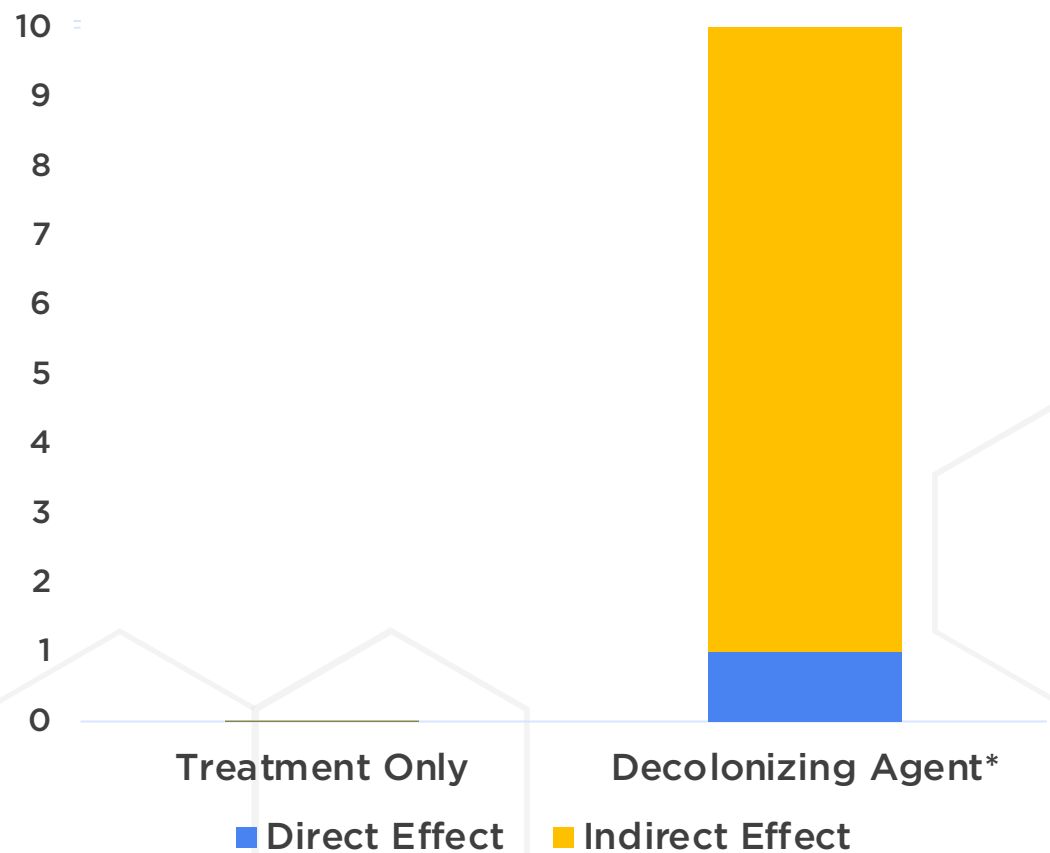
Potential Impact

Deaths Prevented



*All infected patients receive treatment for infections

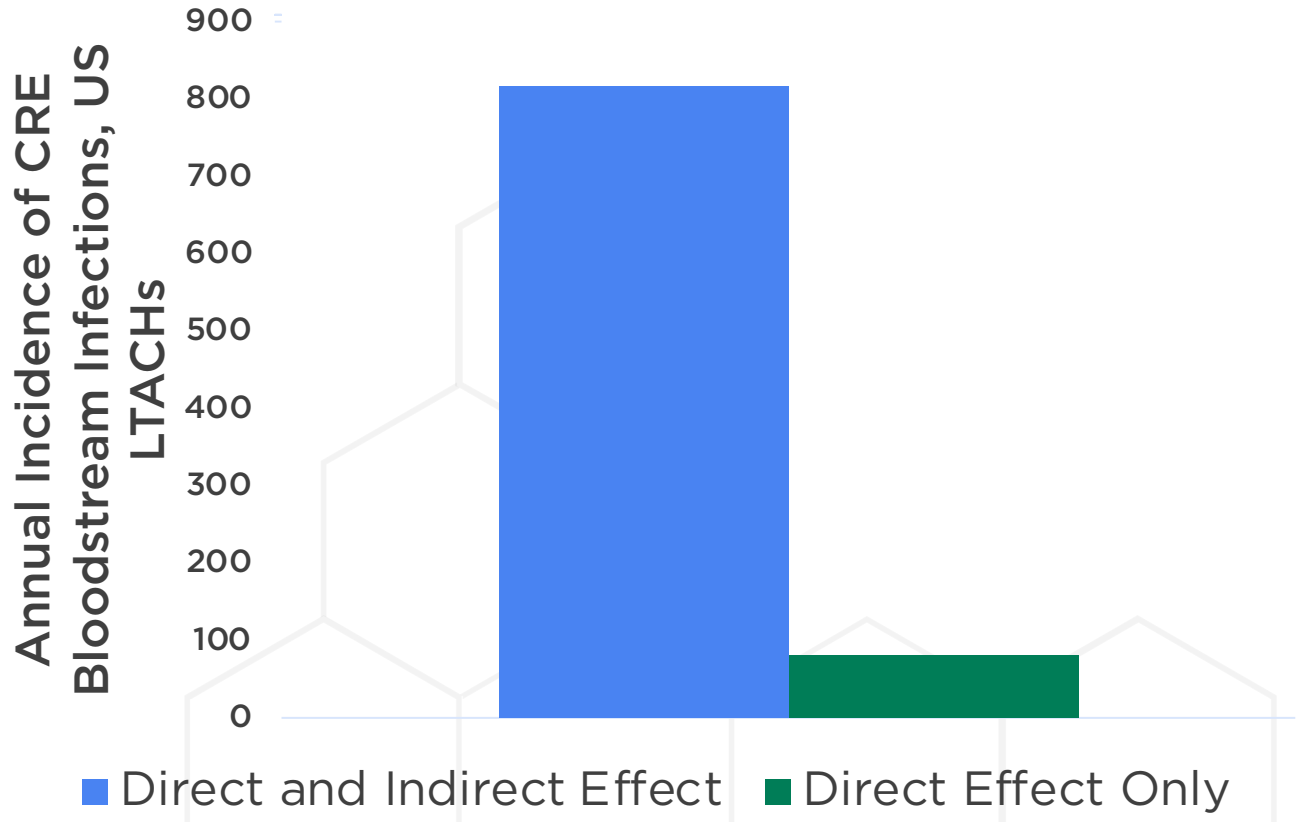
Infections Prevented



*All infected patients receive treatment for infections

How Impactful Might the Indirect Effect of Effective Decolonization Therapy be in the Real World?

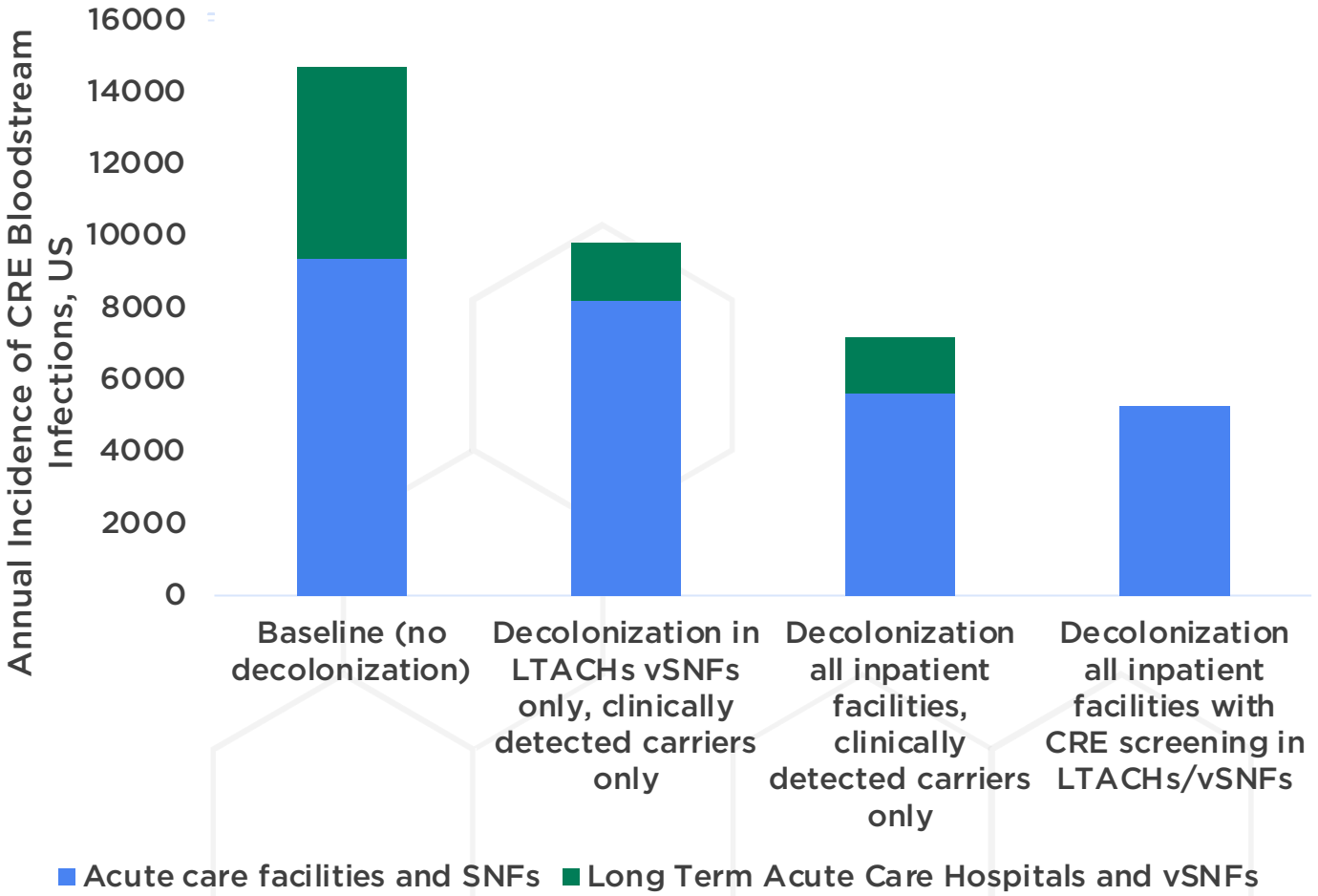
National Estimates of CRE Bloodstream Infections Prevented if Effective CRE Decolonization for Known Carriers Was Implemented in All US Long Term Acute Care Hospitals*



*Damon Toth, unpublished adaptation of model published in Toth et al. Clinical Infectious Diseases 2021;72(S1):S34–41

How Impactful Might the Indirect Effect of Effective Decolonization Therapy be in the Real World?

National Estimates of CRE Bloodstream Infections Prevented, By Decolonization Strategy, US Healthcare Facilities *



* Prabasaj Paul and Hannah Wolford, unpublished adaptation of model published in Toth et al. Clinical Infectious Diseases 2021;72(S1):S34–41

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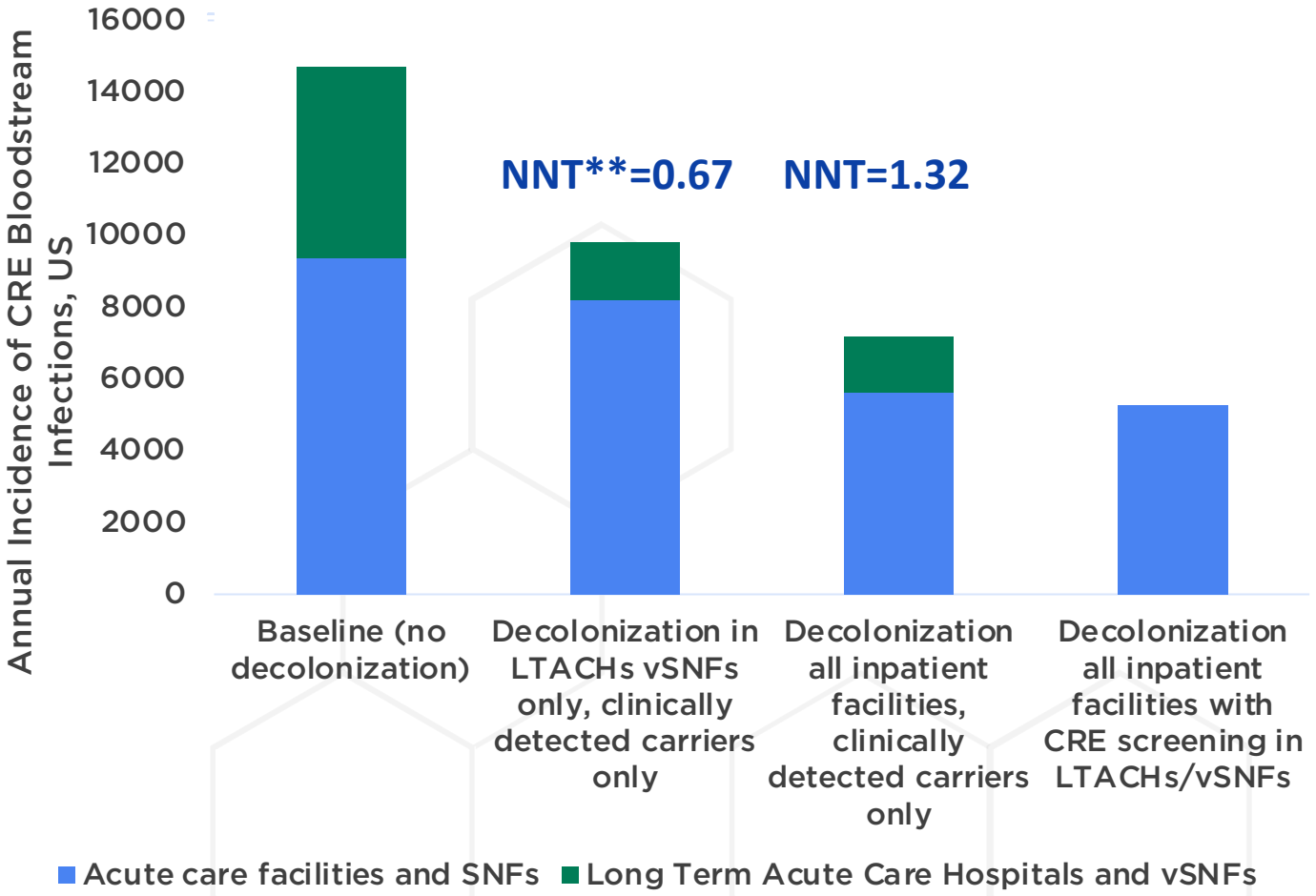

**NNT=number needed to treat with decolonization agent to prevent 1 Bloodstream infection

* Prabasaj Paul and Hannah Wolford, unpublished adaptation of model published in Toth et al. Clinical Infectious Diseases 2021;72(S1):S34–41

Summary

- **Colonization by pathogens increases risk of infection**
- **Colonization is an important driver of AR infection burden**
  - Increases risk of infection in colonized individuals
  - Amplifies burden through transmission
- **Reducing colonization may be a potent strategy for preventing antimicrobial-resistant infections**
  - Largest impact may be result from indirect benefit (preventing transmission)

What We Need

Industry/academia to pursue more research and development for agents that reduce or eliminate the burden of colonizing pathogens, based on:

- Potential benefit of decolonizing agents, particularly in controlling antimicrobial resistance
- Existence of a clear and feasible approach for regulatory approval for such agents
    - Development of endpoints and trial designs that consider population-based benefit should be a priority

Thank you

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