“The Strategic Impact of Molecular Diagnostics: Insights from Game Theory”

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Duke Infectious Diseases Grand Rounds

January 14, 2013

Game Theory?

- A “game” is any situation with multiple parties who impact one another.
- Games are pervasive in the microbial world.
- Game theory can help one understand / anticipate game dynamics and shape outcomes via medical practice and policy.

Evolutionary Biology vs Game Theory

- **Evolutionary biology** describes *myopic* evolution.
- **Game theory** allows for a continuum of possibilities about how players make decisions, including:
  - Myopic evolution aka "0-level rationality"
  - "1-level rationality"
  - …
  - "Perfect rationality" [Nash equilibrium]

- I'll assume a mixture of myopes (e.g. microbes) and Game-Changers (e.g. public-health authorities).

Game Plan

1. **Intro: Myopic Evolution of Strategic Systems**
   - Application: Antigen Prevalence

2. Model: Games that Bacteria Play
   - Application: Carbapenem Resistance

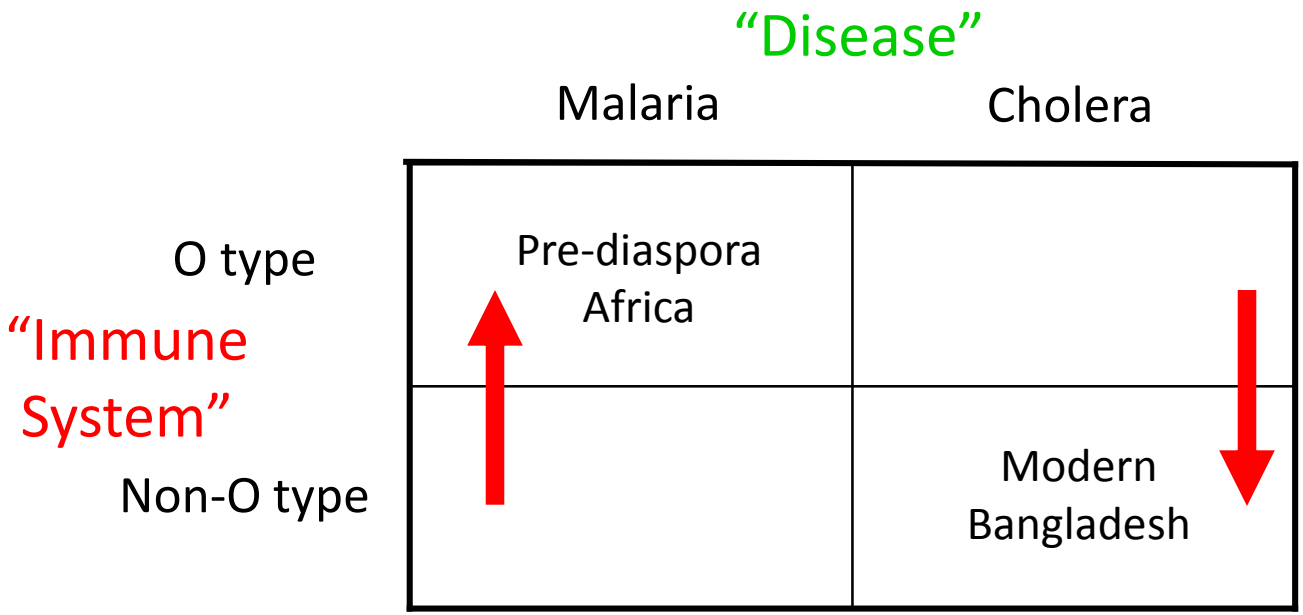
3. Game-Changer: Molecular Diagnostics
   - … and the severity of disease
   - … and the resistance of disease

Example: Blood-Group Antigens

Different blood-group antigens confer different advantages:

- O-type antigens are beneficial against malaria
- non-O-type antigens are beneficial against cholera

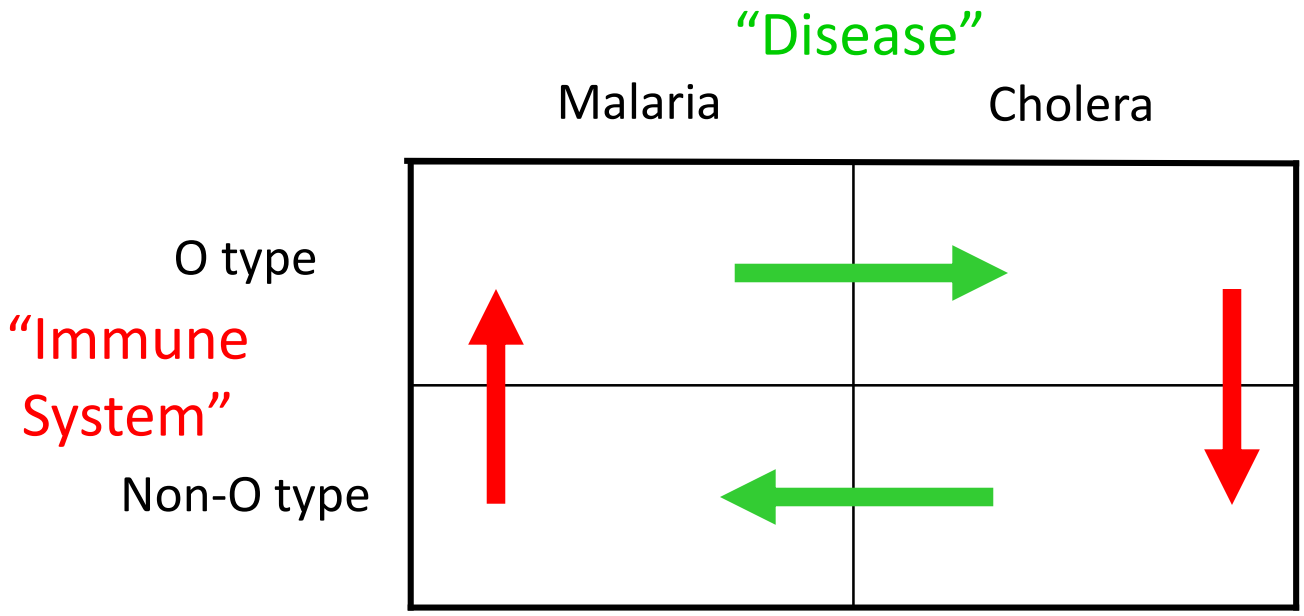
IF disease prevalence is given and varies across regions, evolution will select different blood-type across regions



Blood-Type Polymorphism

What about in regions where disease prevalence depends on blood-type prevalence?

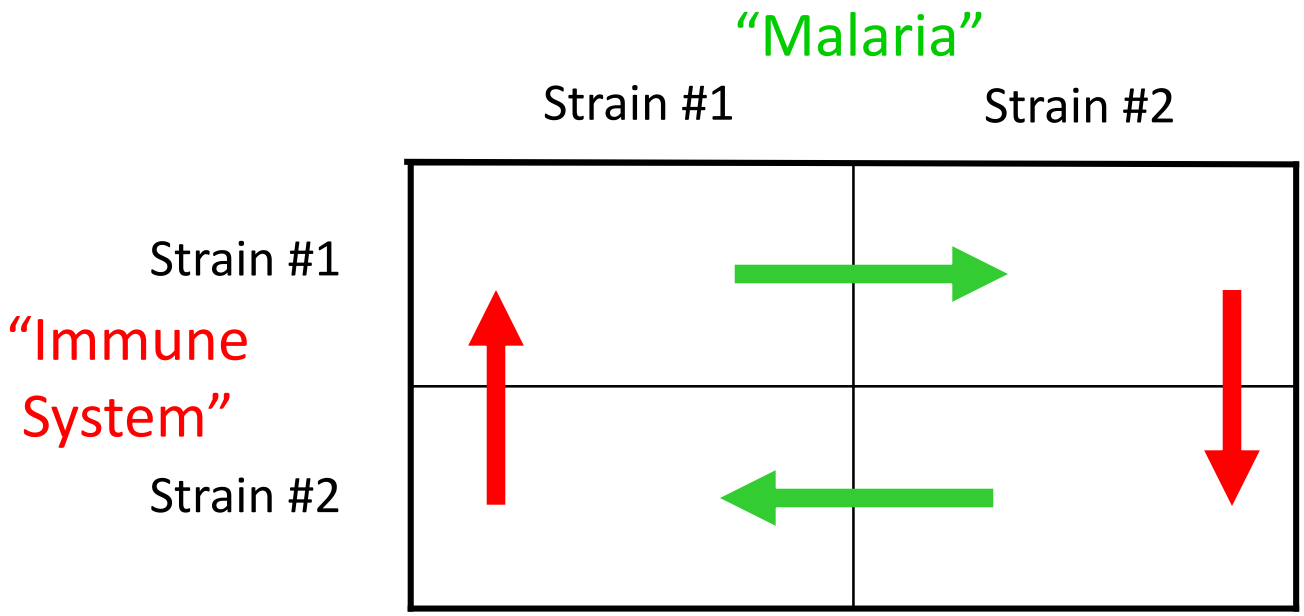
–under *co-evolution*, only a mixture of O / non-O blood types is evolutionarily stable.



Example: Malaria Antigens

Malaria strains co-exist with different antigens:

– if any single strain becomes too prevalent, immune response will target that strain

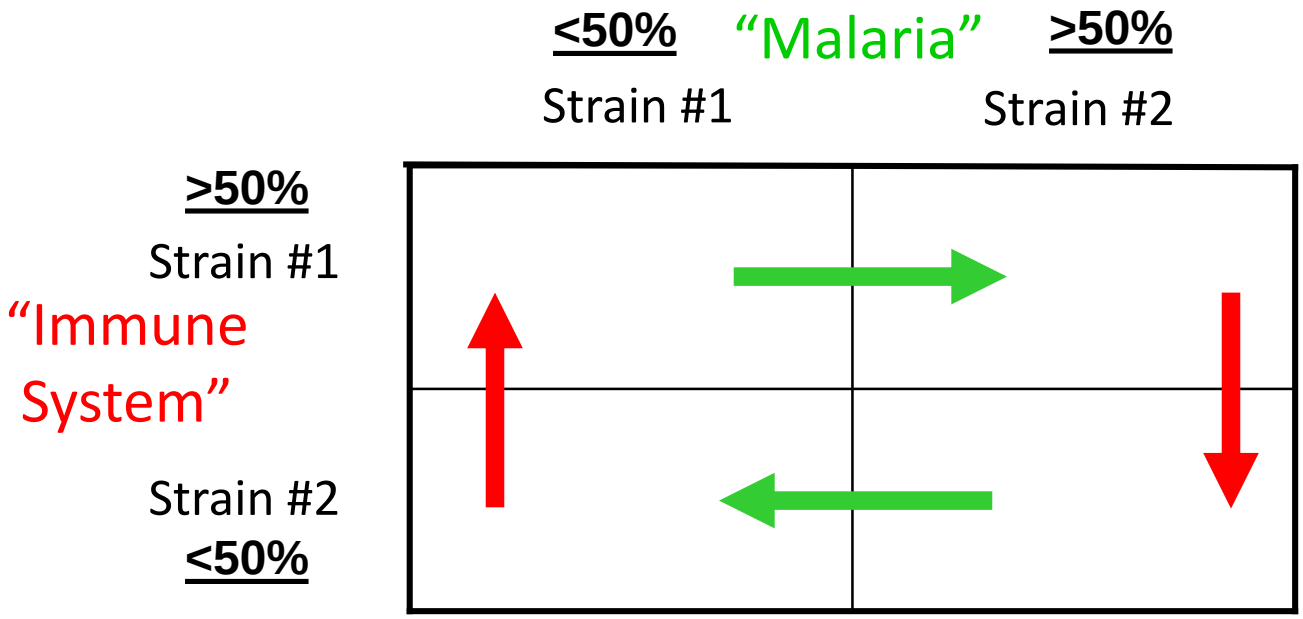


Assume: strains symmetric *except* Strain #1 more transmissible

Example: Malaria Antigens

"Equilibrium indifference" requires people to be *equally exposed* to both strains:

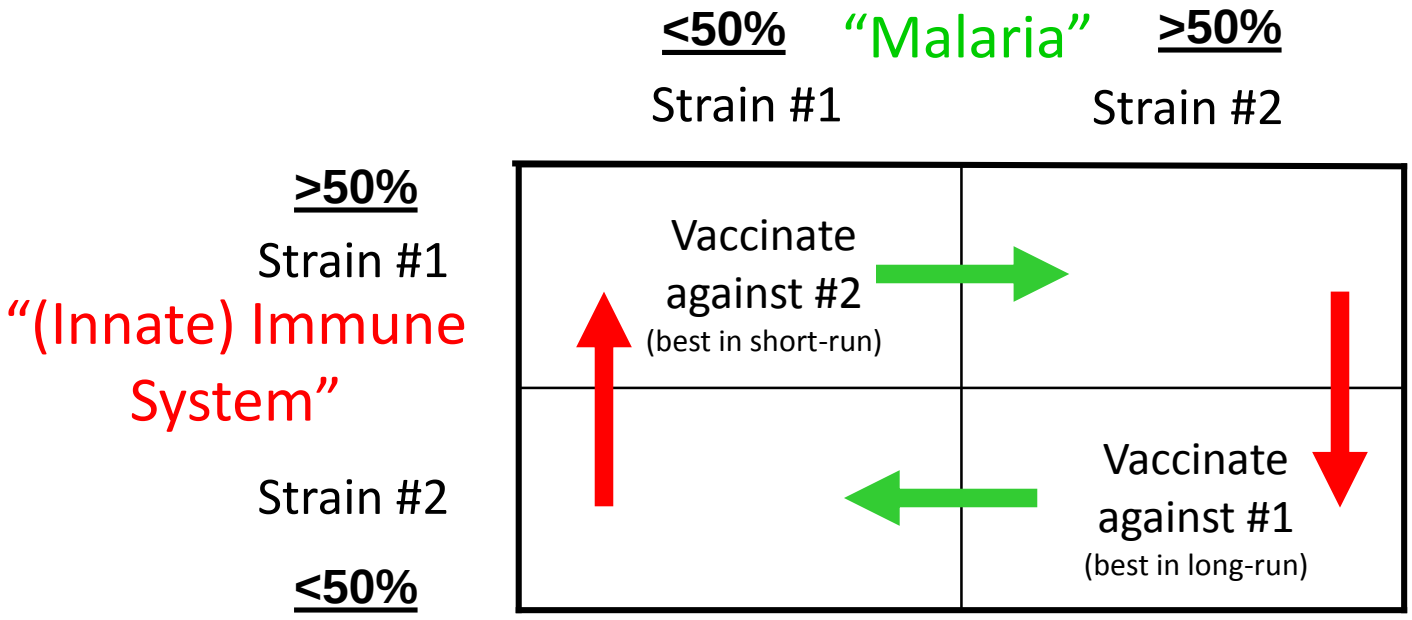
– more transmissible Strain #1 infects *fewer* people



Example: Malaria Antigens

In the long run, people will acquire immune protection against whatever strain is not targeted by vaccine.

– better to face less-transmissible Strain #2

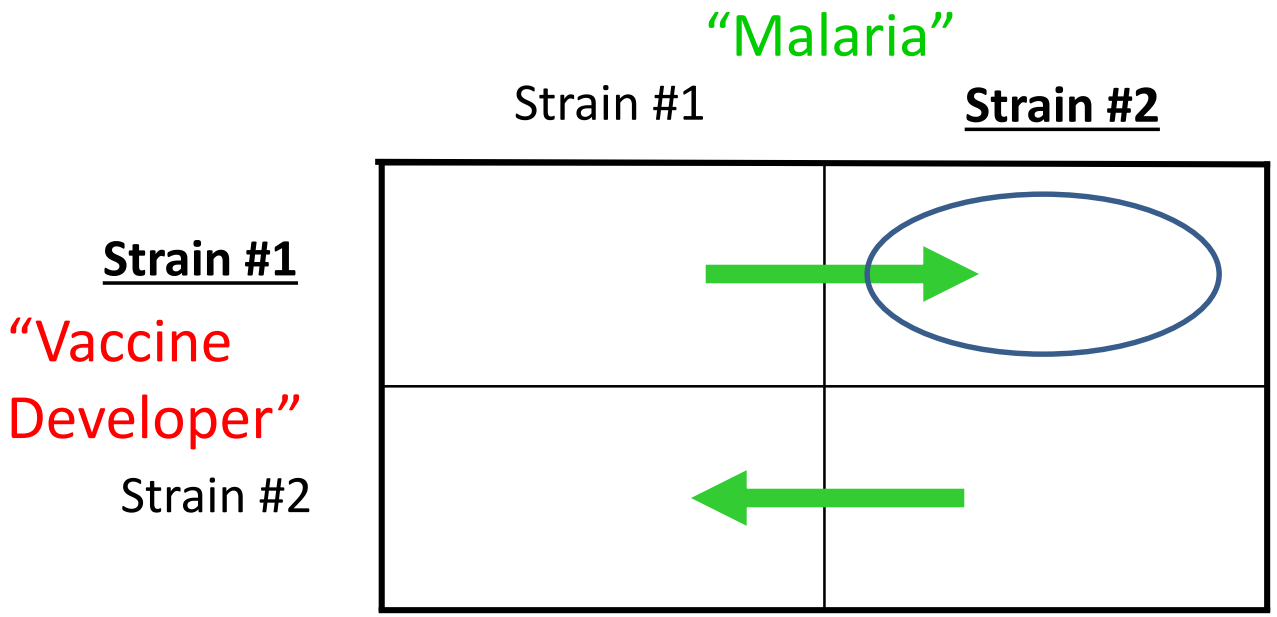


Value of a Strain-Specific Vaccine

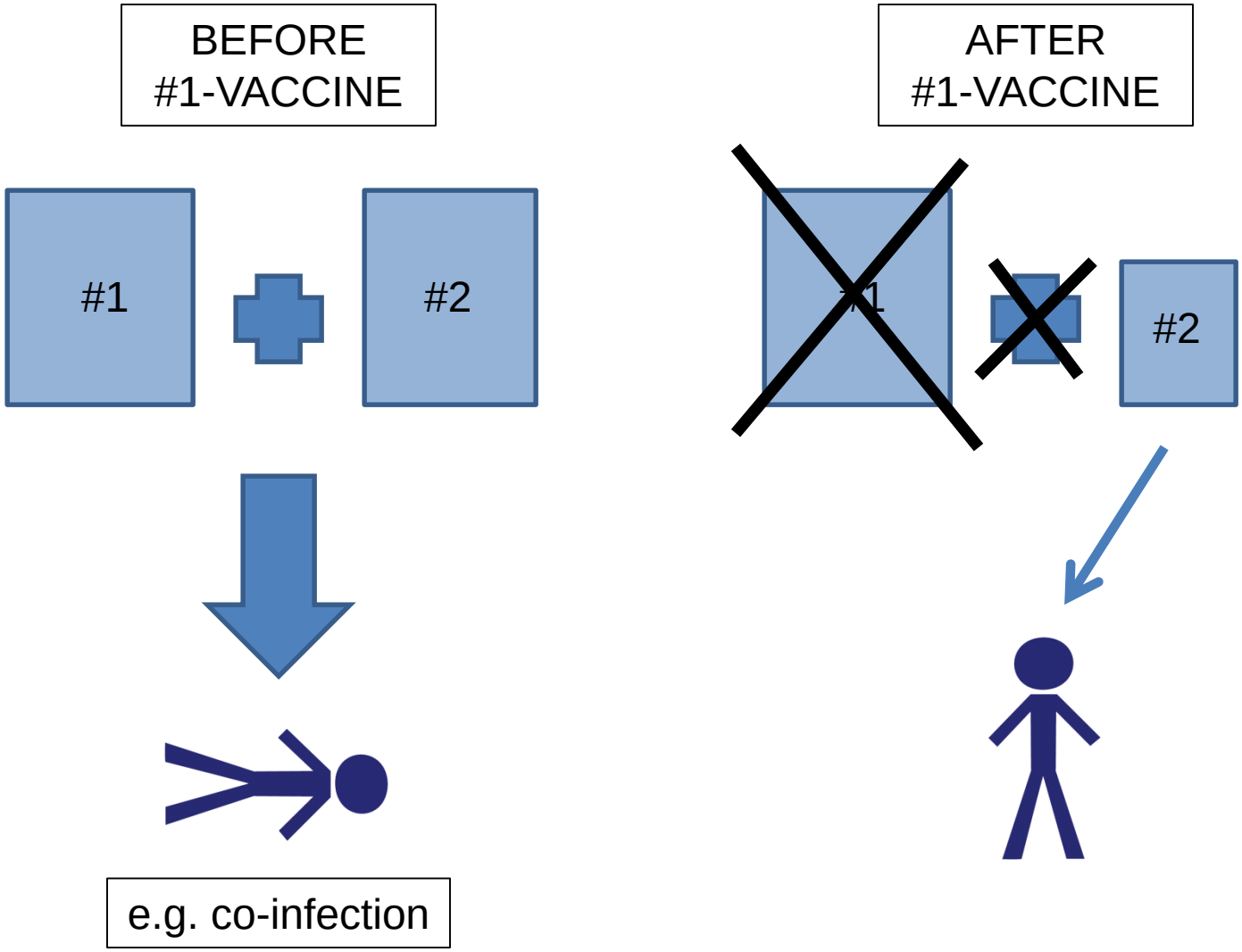
How beneficial is a vaccine that only protects against Strain #1? If administered:

– burden of Strain #1 will fall

– burden of Strain #2 will rise / fall, depending on whether exposure to Strain #1 helps / hinders immune system response against Strain #2



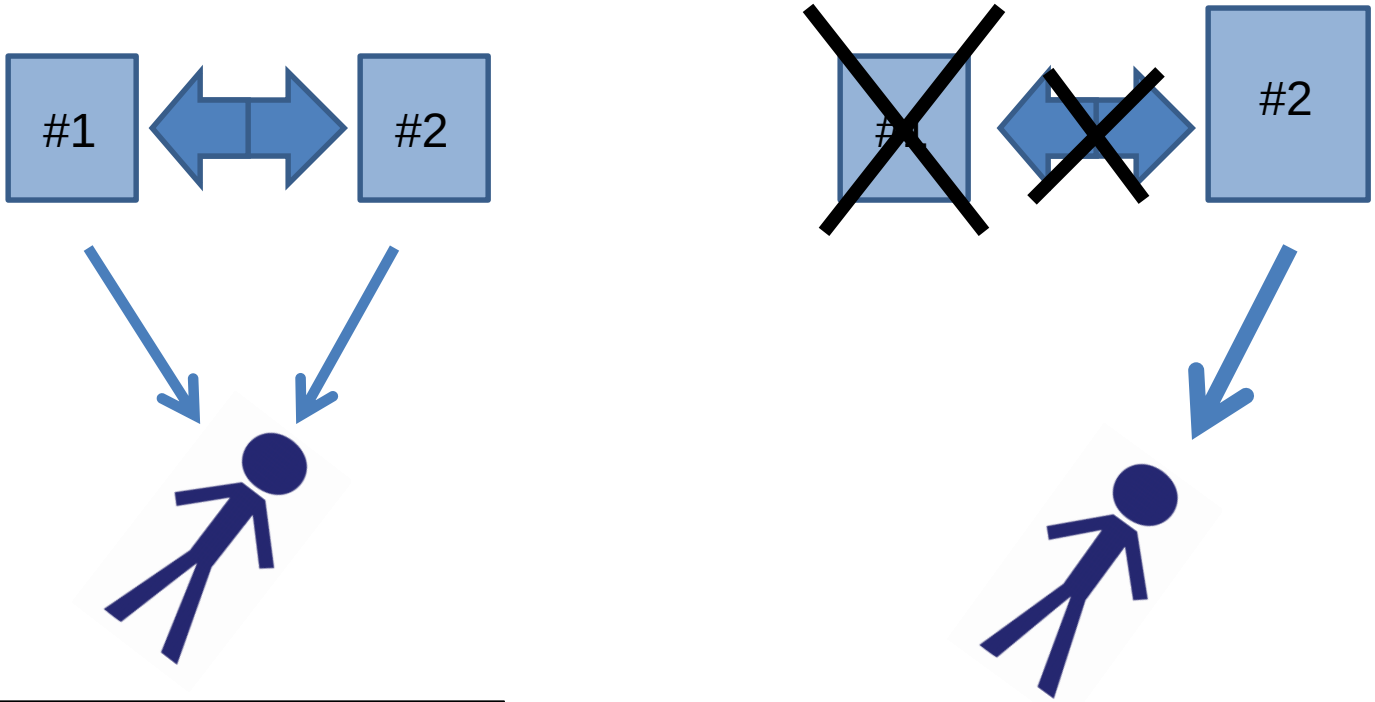
Case #1: “Cooperative” Strains



Case #2: “Competitive” Strains

BEFORE
#1-VACCINE

AFTER
#1-VACCINE



e.g. induced protection
from prior infection

Game Plan

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2. **Model: Games that Bacteria Play**
   - Application: Carbapenem Resistance

3. Game-Changer: Molecular Diagnostics
   - … and the severity of disease
   - … and the resistance of disease

The Games of Disease

Whether a strain's prevalence rises or falls depends on how well it plays three "Games of Disease":

1. The Infection Game [*virulence*]

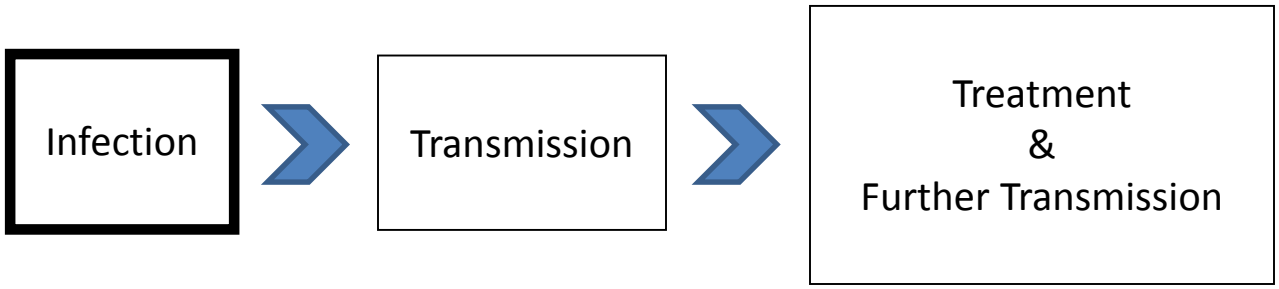
– Can the strain get past the human immune system?

2. The Transmission Game [*transmissibility*]

– Can the strain transmit itself to new hosts?

3. The Treatment Game [*resistance*]

– Can the strain survive medical treatment well enough to continue transmitting itself?



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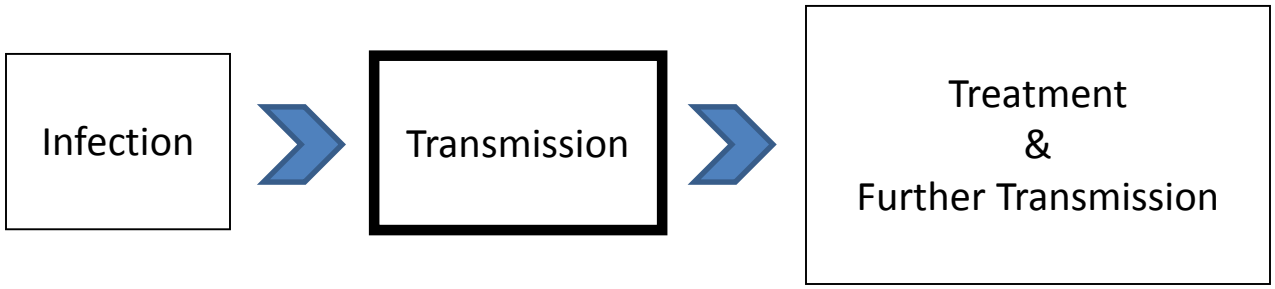

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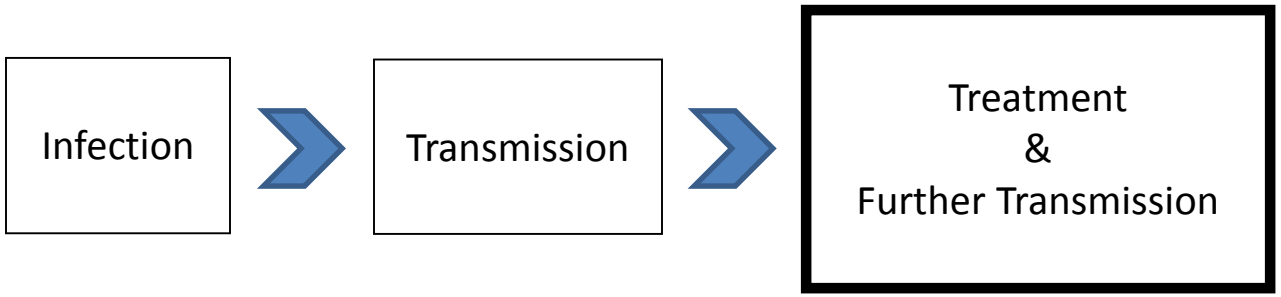

Tactics Against Disease

	GENERAL	TARGETED
INFECTION	Healthful Lifestyle	Vaccine
TRANSMISSION	Hand-washing	Quarantine Contact Tracing
TREATMENT	Sterilization of Medical Devices	Antibiotics

Table: Examples of disease-fighting tactics

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Carbapenem Resistance

In 1992, hospitals began to detect cases of Carbapenem-resistant Enterobacteriaceae (CRE), e.g. E. coli and Salmonella:

- Carbapenem class includes many “drugs of last resort”
- CRE can be extremely deadly [mortality rates of 40%-50%]

RESISTANT

SUSCEPTIBLE

TREATMENT

RESISTANT

SUSCEPTIBLE

“Detect and Protect” (CDC 2012)

In June 2012, CDC published guidance on a proven* “Detect and Protect” strategy** that hospitals can use to eradicate CRE:

1. **MONITOR** to identify cases in your hospital;

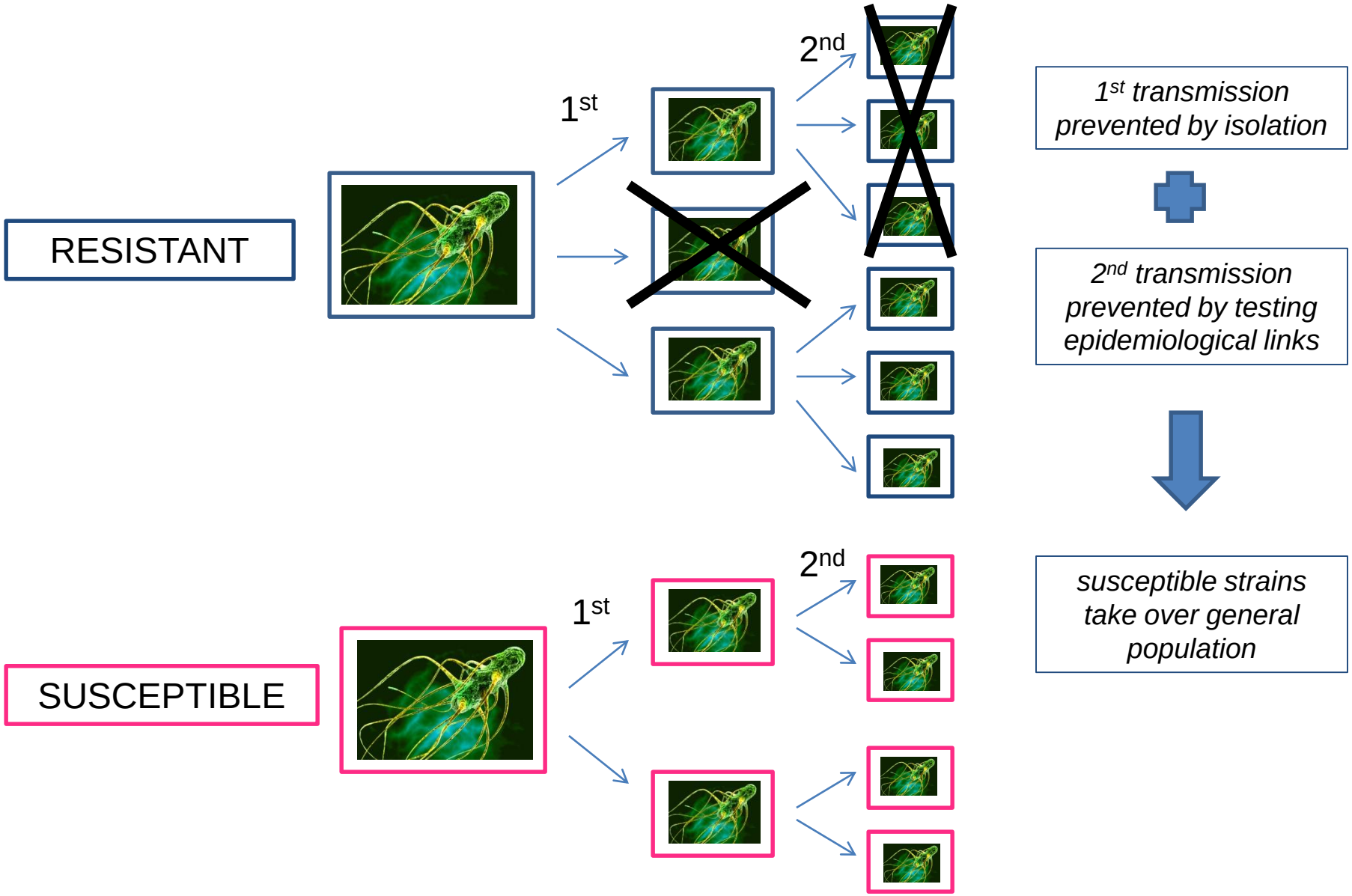
2. **ISOLATE** identified CRE sufferers; and

3. **SCREEN** all patients who are “epidemiologically linked” to any identified CRE sufferer (e.g. shared room, shared machine)

* “Containment of a Country-wide Outbreak of Carbapenem-resistant Klebsiella pneumonia in Israeli Hospitals via a Nationally Implemented Intervention” by Mitchell Schwaber, Boaz Lev, Avi Israeli, et al, *Clinical Infectious Diseases*, 2011.

** “Guidance for Control of Carbapenem-resistant Enterobacteriaceae (CRE): 2012 CRE Toolkit”, CDC Division of Healthcare Quality Promotion, June 2012.

“Detect and Protect” (CDC 2012)



“Detect and Protect” (CDC 2012)

“Detect and Protect” is NOT just a containment strategy:

- Carbapenem resistance testing is imperfect.* So, some CRE will always escape any attempt at containment.
- (And even a little “loose CRE” can potentially wreak havoc.)

Detect and Protect works by putting“loose CRE” at a disadvantage in the *general* population:

- **Isolation** limits CRE’s advantage in the Treatment Game [as loose CRE has less *opportunity* to transmit itself after being discovered]

- **Screening** puts CRE at a disadvantage in the Transmission Game [as susceptible bacteria are freer to hop between hosts]

* “Clinical microbiology laboratories have often found it difficult to achieve accurate susceptibility testing results for carbapenem drugs”. See “Carbapenem Resistance in Klebsiella pneumoniae Not Detected by Automated Susceptibility Testing” by Tenover, etal, *Emerging Infectious Diseases*, 2006.

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Molecular Diagnostics: Emerging Tool for Medical Practice

"Innovations in diagnostic testing that incorporate molecular biology into the routine care of the patient are ringing in the millennium. The Cepheid GeneXpert system [allows] a health-care worker [to] take a sample from a patient, place the sample into the instrument, and have an answer within an hour. The rapid diagnosis of childhood meningitis, sepsis, or even antibiotic resistance will soon be available in 'real-time.' There is great potential to identify infections faster, treat patients better, and save patient admissions to the hospital, resulting in cost savings to the health-care system."

-- Dr. Beverly Rogers, Chief of Pathology at Children's Medical Center of Dallas , September 2002

GeneXpert System: Timeline

- 1983: Kary Mullis invents PCR (1993 Chemistry Nobel)
- 2001: Cepheid delivers first prototype GeneXpert system to the Army (USAMRIID)
- 2004: first deployment (anthrax)
- 2006: first clinical Xpert tests (Group B Streptococcus & EV-associated Meningitis)
- 2007: first resistance-detecting Xpert test (Methicillin-resistant Staphylococcus aureus)
- 2009: Xpert MTB/RIF (that detects rifampin-resistant TB) to be sold “at cost”
- 2012: PEPFAR/USAID/UNITAID/Gates action reduces cost of MTB/RIF cartridges to $9.98 per test.

GeneXpert as “Game-Changer”

	GENERAL	TARGETED	TARGETED AT SUSCEPTIBILITY
INFECTION	Healthful lifestyle	Vaccine	N/A
TRANSMISSION	Hand-washing	Quarantine Contact Tracing	*Targeted* Transmission Control
TREATMENT	Sterilization of Medical Devices	Antibiotics	*Targeted* Antibiotics

Table: Molecular Diagnostics Creates *New Targeted Strategies* Against Disease

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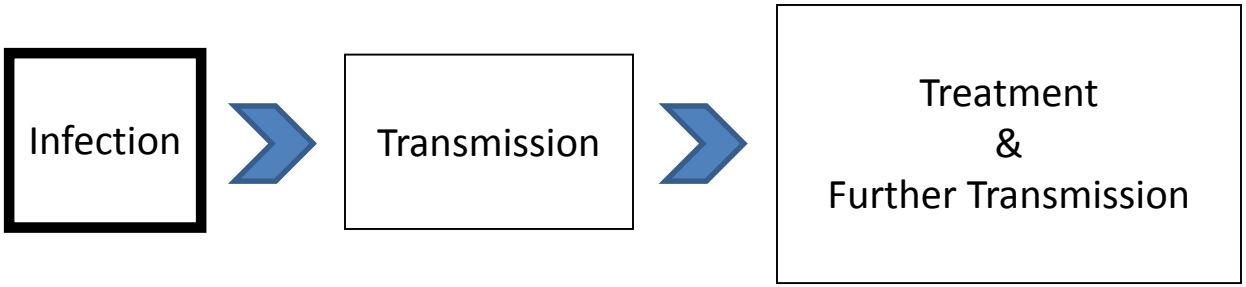
Before: What Incentive to be Severe?

Causing severe symptoms may sometimes be advantageous for bacteria, for several reasons:

1. **Enhanced virulence (e.g. quorum attacks)**
2. Enhanced transmissibility (e.g. diarrhea)
3. Hospitalization itself (e.g. hospital-acquired infections)



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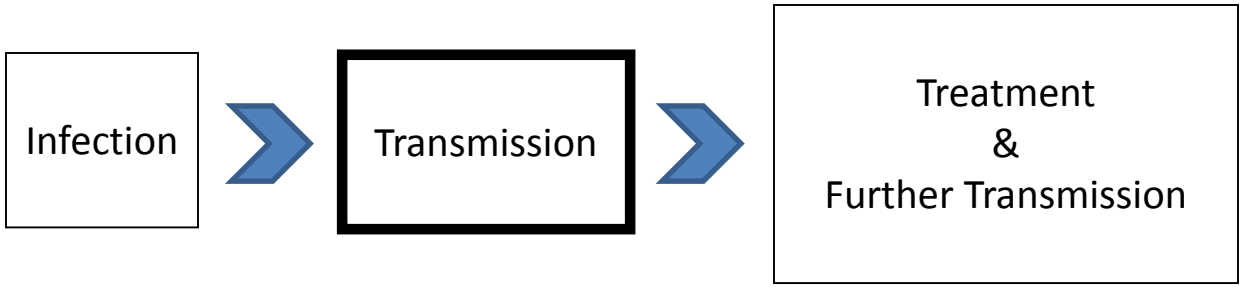

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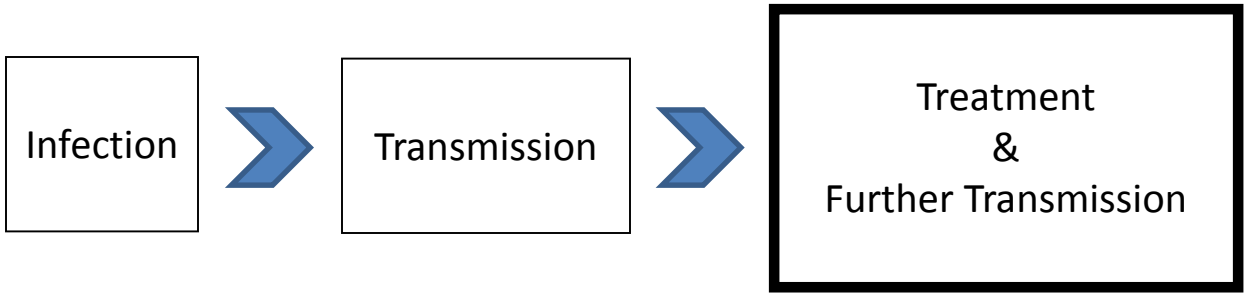

After: What Incentive to be Severe?

Once GeneXpert testing becomes widespread, doctors will quickly and accurately diagnose the antibiotic susceptibility of disease.

KEY IDEA: *With GeneXpert, disease has a stronger "incentive" than before to AVOID TREATMENT.*

After: What Incentive to be Severe?

Once GeneXpert testing becomes widespread, doctors will quickly and accurately diagnose the antibiotic susceptibility of disease.

KEY IDEA: *With GeneXpert, more "incentive" to AVOID TREATMENT.*

IMPLICATION: Expect to see a bifurcation in the severity of disease:

1. *Milder diseases* that succeed by maximizing the window before infected people CHOOSE to receive medical attention.

After: What Incentive to be Severe?

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KEY IDEA: *With GeneXpert, more "incentive" to AVOID TREATMENT.*

IMPLICATION: Expect to see a bifurcation in the severity of disease:

1. *Milder diseases* that succeed by maximizing the window before infected people CHOOSE to receive medical attention; and

2. *More severe diseases* that succeed by exploiting the window before infected people CAN receive medical attention.

Shaping Disease Severity

Whether mild or severe disease will thrive in the post-GeneXpert world depends on how patients receive diagnosis and treatment:

1. **Can people *choose* when their disease is diagnosed?** If "no", expect MORE SEVERE disease.

Why?

- Diagnosis unrelated to severity → treatment-avoidance is irrelevant.
- The most successful disease strains will therefore focus just on maximizing virulence and transmissibility during the window that they are given, prior to being discovered by the health authorities.

Why might people not choose when to be diagnosed? Examples:

- Poor village where medical treatment available only when aid-workers come through town, at which time everyone comes for a check-up.
- High-tech metropolis where everyone is automatically diagnosed while travelling on mass transit.

Shaping Disease Severity

Whether mild or severe disease will thrive in the post-GeneXpert world depends on how patients receive diagnosis and treatment:

1. **Can people *choose* when their disease is diagnosed?** If "no", expect MORE SEVERE disease.

2. **Can people *easily* (but not too easily*) access medical care?** If "yes", expect MILDER disease.

Why?

- Access → severely affected patients will quickly seek out treatment
- Diseases that create mild symptoms will have an advantage

* If medical care can be accessed at zero cost / zero inconvenience, people will seek care at the onset of even the mildest symptoms. Milder disease would then enjoy no advantage.

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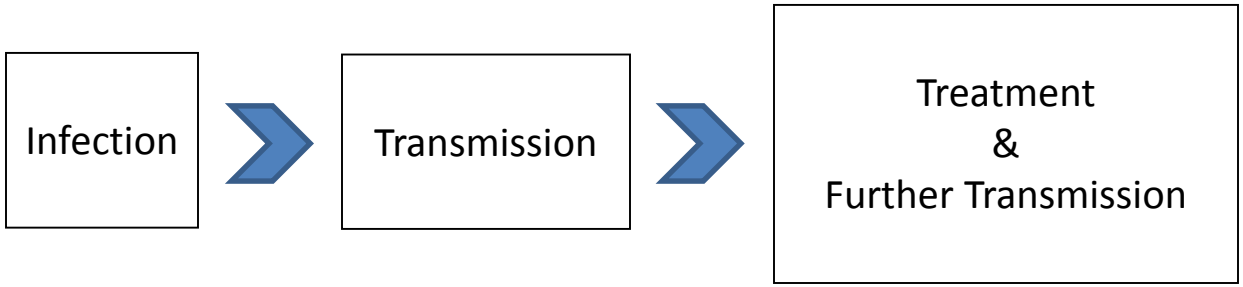
Antibiotic Resistance – Overview

THE PROBLEM: Resistant strains will come to dominate the bacterial population *IF* the following three conditions are satisfied:

1. ***Equal Virulence***
2. ***Equal Transmissibility***
3. ***Uniform Treatment***

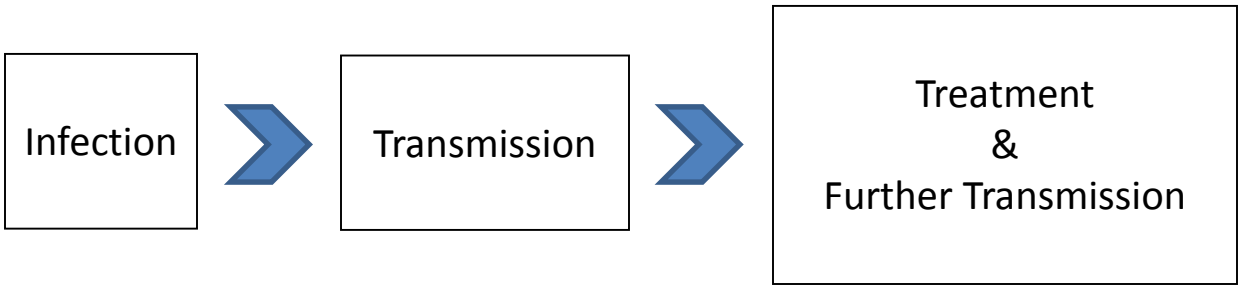


Best-practices can decrease resistant strains' treatment advantage but, as long as all strains are treated the same, (equally virulent and transmissible) resistance will always "win" in the end.

Antibiotic Resistance – Overview

THE SOLUTION: We can reverse resistance by exploiting AND/OR CREATING at least one of the following conditions:

1. ***Greater Virulence of Susceptible Strains***
2. ***Greater Transmissibility of Susceptible Strains***
3. ***Non-Uniform Treatment that Disfavors Resistant Strains***



Idea #1: Reduce Antibiotic Use

When strains mutate to acquire resistance, they sometimes become *less virulent / less transmissible*. To beat such "unstable resistance", it suffices to reduce antibiotic use:

1. **Vaccines** that target all strains of a disease will induce fewer infected people to seek medical attention

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2. **Fewer unnecessary prescriptions**, e.g. CDC's "Get Smart: Know When Antibiotics Work" program

3. **Restrictions**, e.g. "drugs of last resort" and temporary bans (e.g. cefiximine for gonorrhea)

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4. **Molecular diagnosis of drug susceptibility**, e.g. GeneXpert

Not Enough?

Unfortunately, reducing antibiotic use alone cannot reverse resistance, once it has "stabilized":

"Resistance might be reversible, provided antibiotic use is reduced. However, several processes act to stabilize resistance, including compensatory evolution [reducing the disadvantages associated with resistance] … and genetic linkage or co-selection between the resistance markers and other selected markers [making it costly to lose resistance as then the bacteria would lose other benefits]."

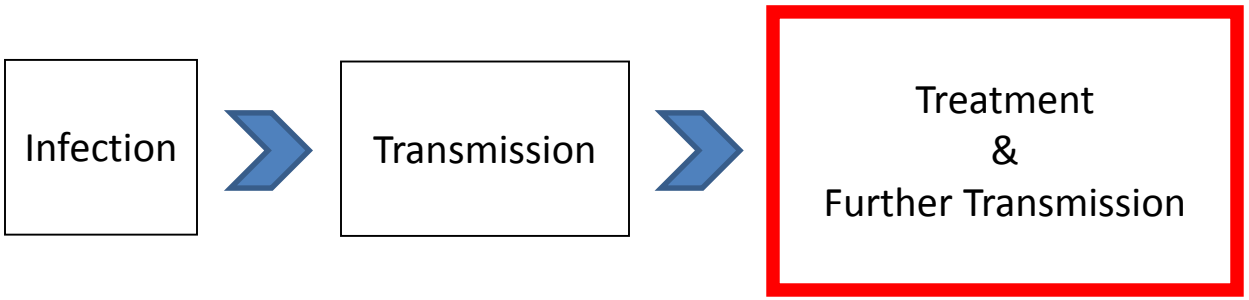
-- Dr. Dan Andersson, Fellow of American Academy of Microbiology, in *Current Opinion in Microbiology*, 2006

Idea #2: Targeted Treatment

To defeat stably-resistant disease, we must TARGET resistant strains during Infection, Transmission, and/or Treatment.

One possibility is to TREAT resistant strains more intensively:

- Screen all patients with GeneXpert to identify drug susceptibility
- After treating with best antibiotic for their susceptibility status,
  - RELEASE patients with susceptible disease
  - HOLD AND MONITOR patients with resistant disease, until confirmed eradication
- Isolating resistance neutralizes its advantage and, depending on the effectiveness of treatment, could advantage susceptible strains.



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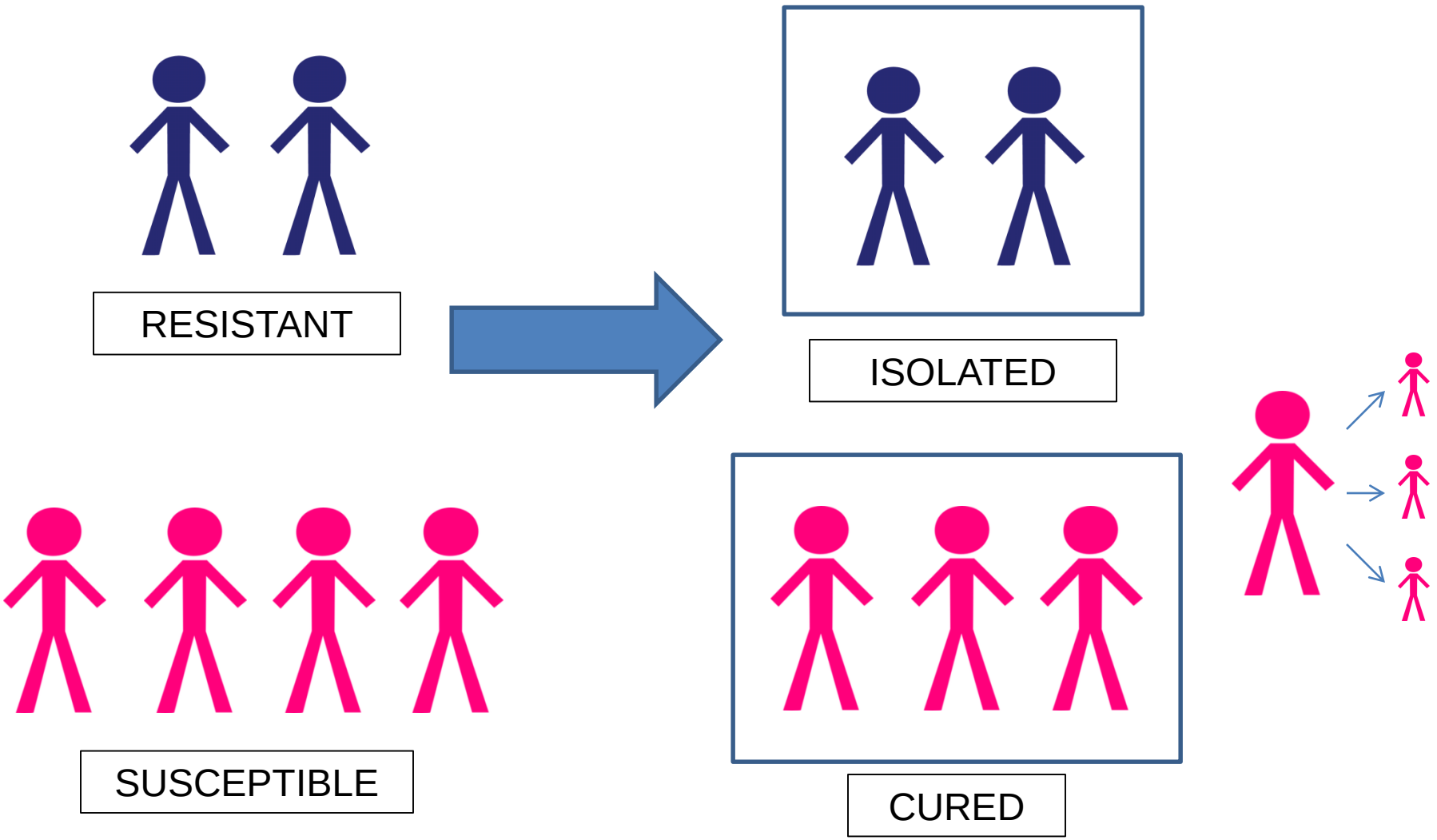
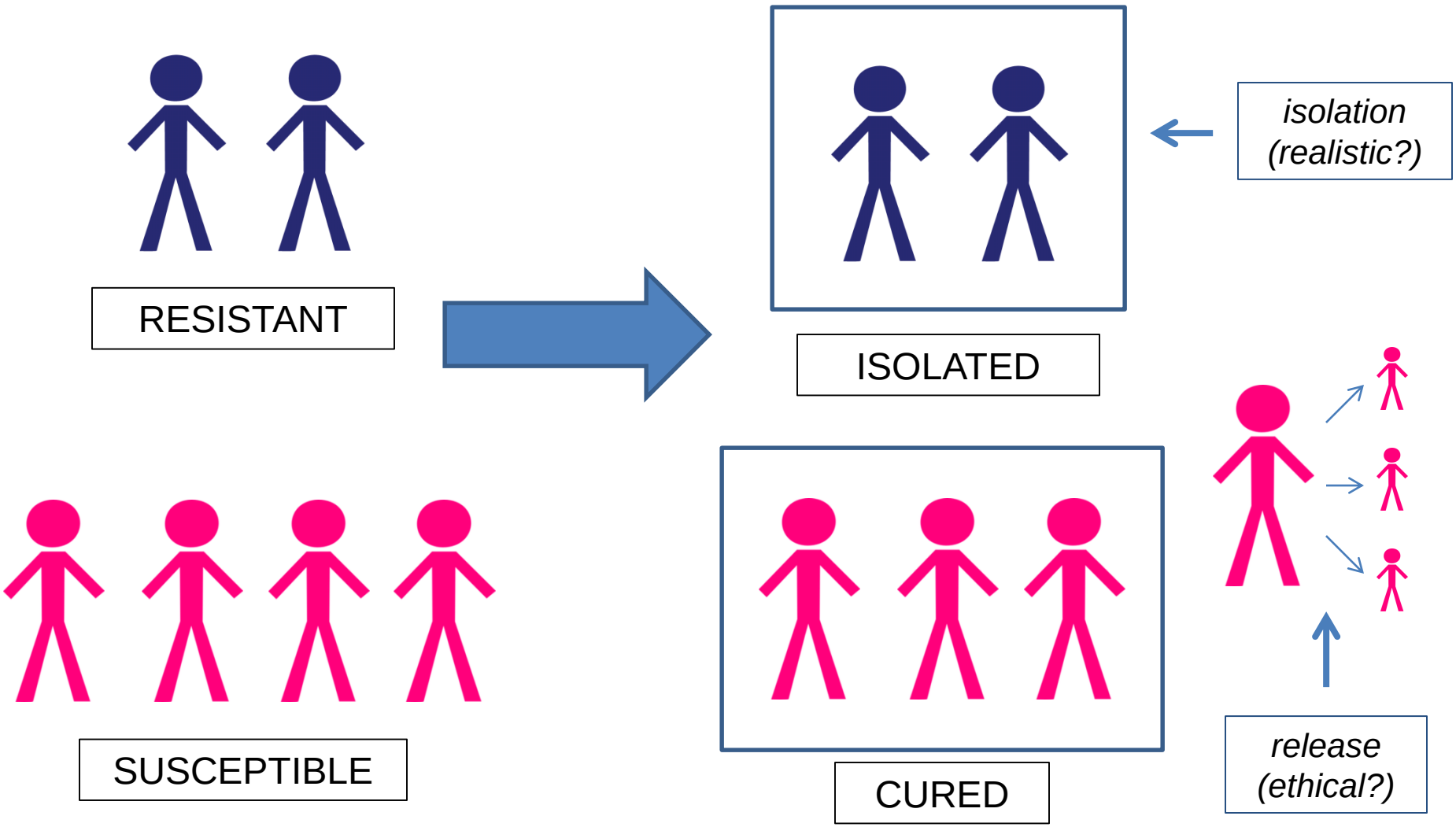


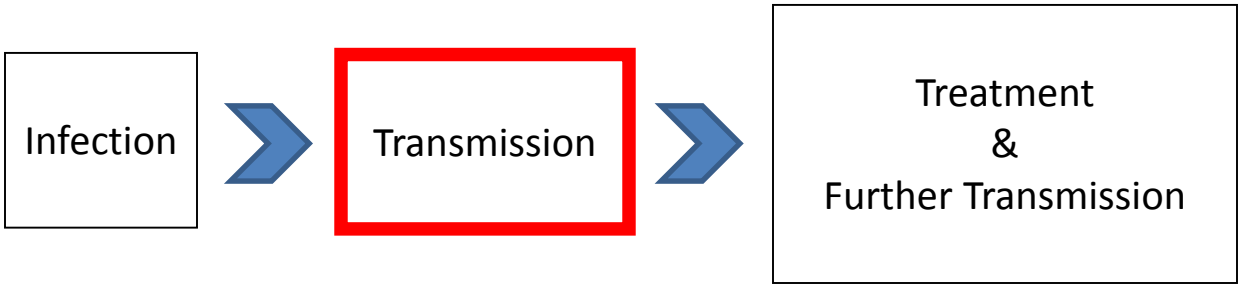
Unrealistic? Unethical?



Idea #3: Targeted Contact Tracing

Quick diagnosis of resistance in a patient can also enable medical professionals to target OTHERS who may soon transmit / be infected with resistant disease:

- Screen all patients with GeneXpert to identify drug susceptibility
- ONLY if infectious disease with extensive resistance is detected:
  - dispatch a "transmission-fighting team" of field epidemiologists to test for the disease in all those in close contact with the patient
  - prescribe prophylaxis and/or hospitalize as appropriate



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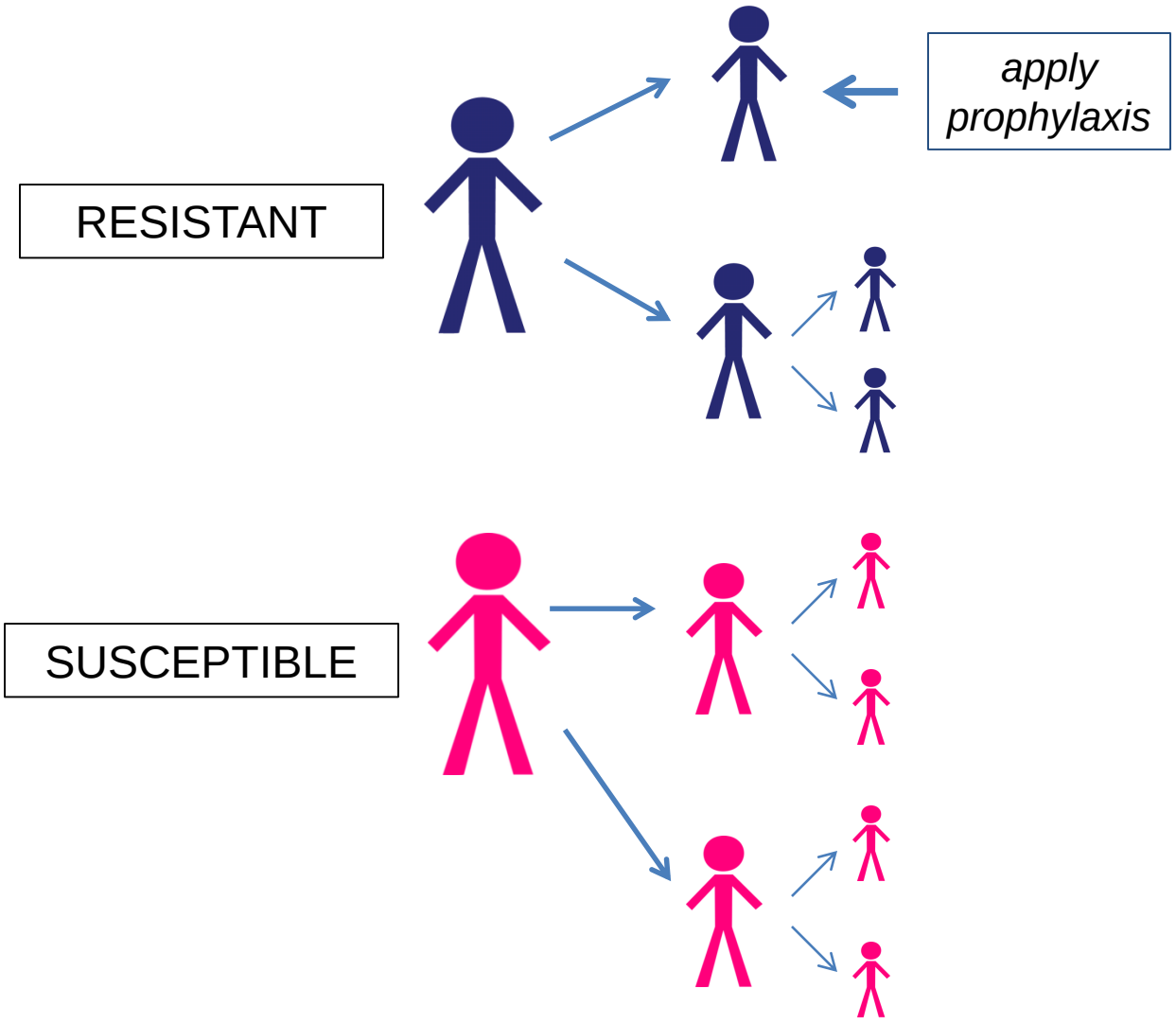

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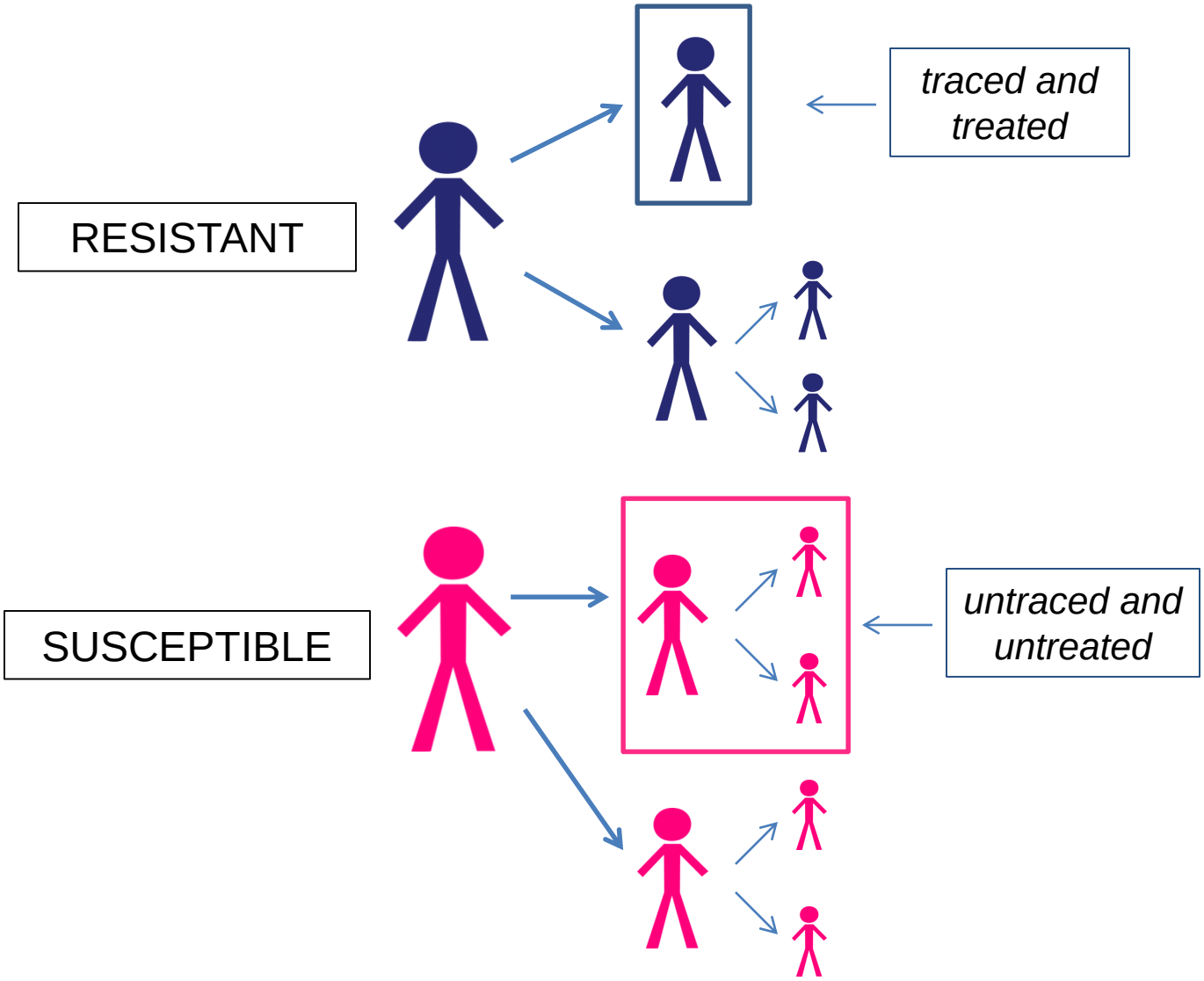
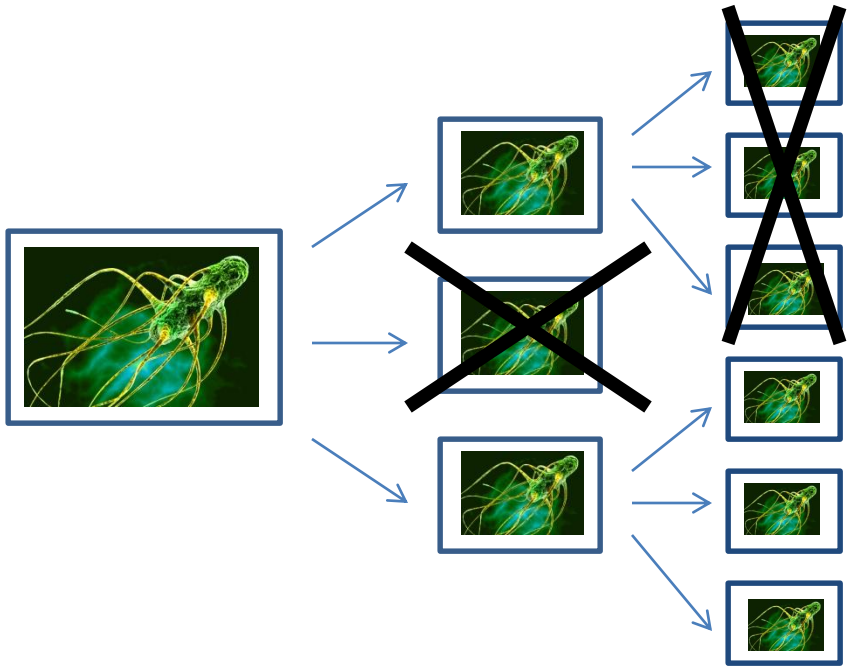
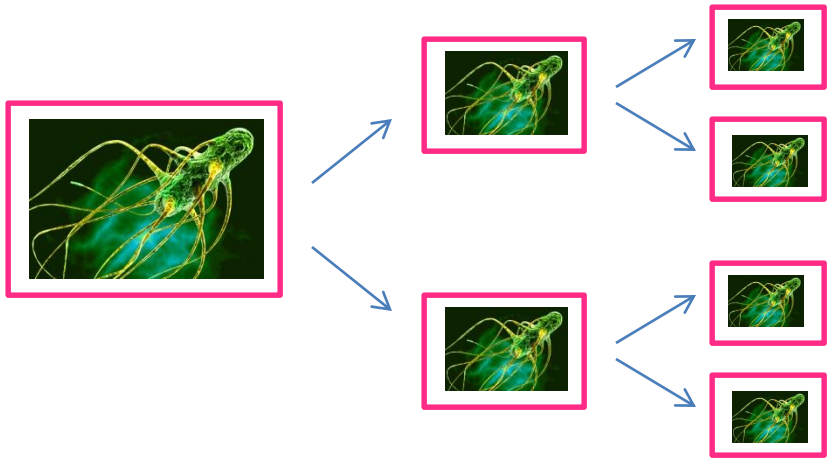


Proof of Concept: CRE

RESISTANT



SUSCEPTIBLE



1st transmission prevented by isolation

2nd transmission prevented by testing epidemiological links

Example of "Targeted Contact Tracing"

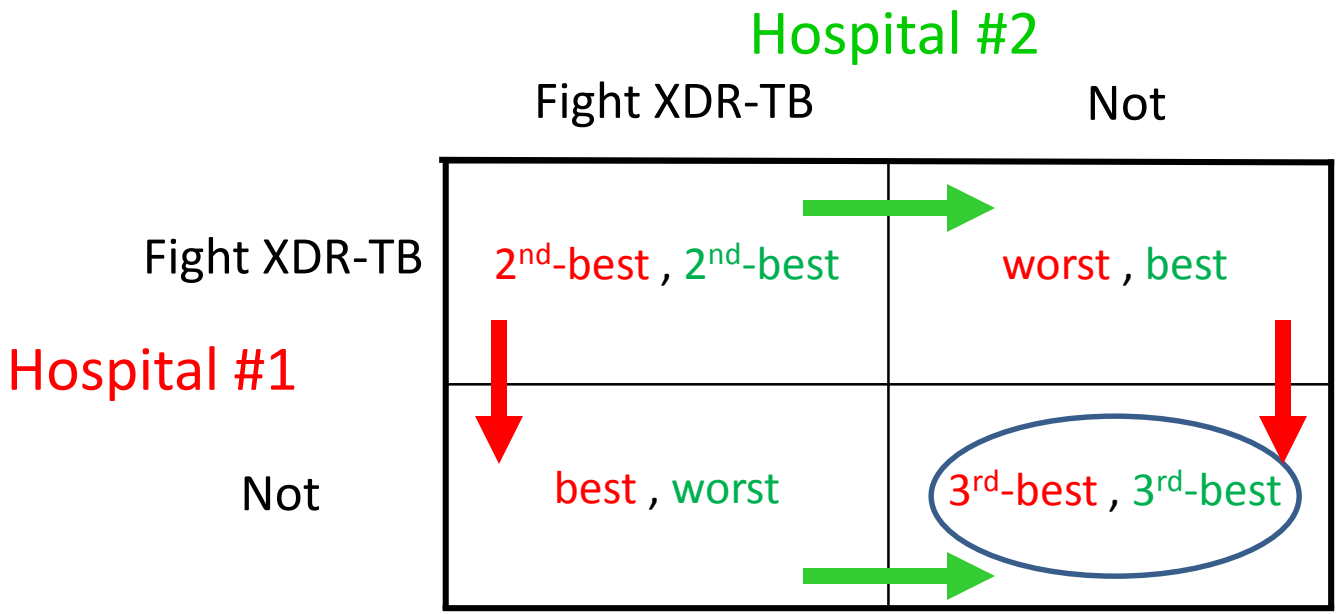
Free-Rider Problem?

Hospitals "own" Carbapenem-resistance within their own facilities.

- Each hospital has ample incentive to implement "Detect and Protect".

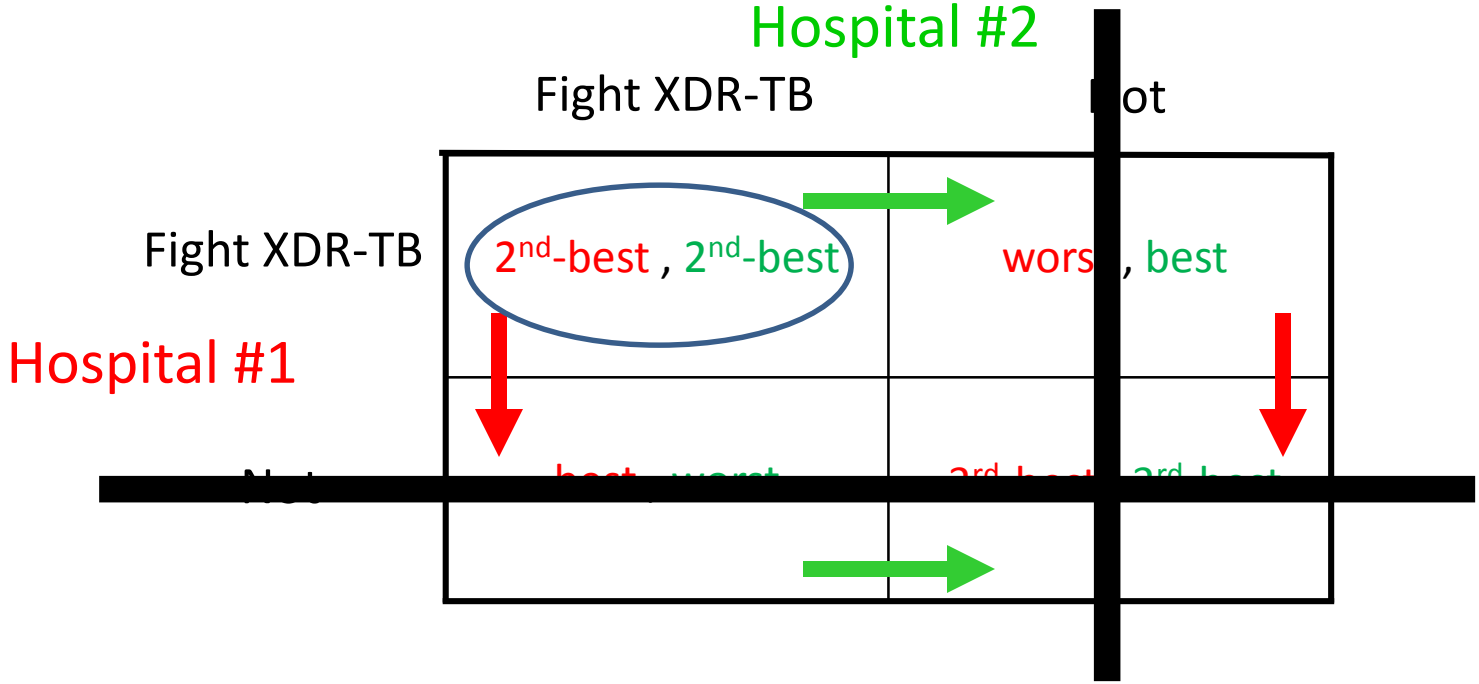
What about widely-circulating disease like **tuberculosis**?

- 2012: extensively drug-resistant Tuberculosis (XDR-TB) reported in India
- BUT no individual hospital can make a dent against XDR-TB
- Hospitals appear stuck in a free-rider trap (aka "Prisoners' Dilemma")



Free-Rider Problem?

To overcome the free-rider problem, coordination and/or regulation likely needed at the national level, i.e. CDC in US, Ministry of Health and Family Welfare in India, etc.



XDR-TB: Additional Challenges

1. Lengthy transmission window prior to detection
   - more difficult to get ahead of the disease via contact tracing

2. Prophylaxis already given to family members of any TB-sufferer, regardless of susceptibility
   - resistance-targeted approaches must provide greater protection to family members and/or more extensive protection beyond family

3. Others?

Summary and Next Steps

Recent advances in molecular diagnostics have created new STRATEGIC options in our fight against disease.

If deployed wisely, with an understanding of their implications on “the games of disease”, these new tools could help us fight (and perhaps even reverse) antibiotic resistance.

The natural next step would be for a credible third-party (e.g. WHO or Gates Foundation) to develop guidelines on how best to deploy molecular diagnostics, in combination with other strategies, at a facility, national, and regional level.

THANK YOU!!

Game Theory in the ED

Many hospitals focus on maximizing patient "satisfaction," e.g.

- in 2007, Duke created "Patient Satisfaction University" for managers, with the CEO personally reviewing patient satisfaction scores monthly*

Pro: Greater satisfaction-focus has led to improved care in some areas, e.g. venipuncture

Con: … but has likely harmed care in other areas, e.g. emergency medicine

*Source: "Duke University Hospital: Organizational and Tactical Strategies to Enhance Patient Satisfaction" by Sharon Silow-Carroll, *Commonwealth Fund Case Study*, December 2008.

Downside of "satisfaction": *Inappropriate care*

According to an (unscientific) survey conducted by *Emergency Physicians Monthly* in December 2009:

1. "Nearly one in eight respondents had their **employment threatened** due to low patient satisfaction scores."
2. "More than 40% [of respondents] had **altered treatment** [to avoid] a negative patient satisfaction survey. Of those, 67% gave treatment that was probably not medically necessary more than half of the time."
3. "81% were aware of instances in which patients intentionally provided inaccurate derogatory information on a satisfaction survey and 84% felt that patients used the **threat of negative** satisfaction surveys to obtain inappropriate medical care."

Downside of "satisfaction": *Greater cost and mortality*

According to a (scientific) study published in *Archives of Internal Medicine* in March 2012:*

"Higher patient satisfaction was associated with … greater total health care expenditures, higher expenditures on prescription drugs, [and] statistically significantly **greater mortality risk**."

*Source: "The Cost of Satisfaction: A National Study of Patient Satisfaction, Health Care Utilization, Expenditures, and Mortality" by Dr. Joshua Fenton, et al, *Archives of Internal Medicine*, 2012. [Based on over 50,000 respondents to the Medical Expenditure Panel Survey during the period 2000-2007.]

Downside of "satisfaction": *Over-focus on non-acute patients*

ED satisfaction surveys (by Press Ganey) are only sent to patients who are discharged into their own care

- by design, **<u>urgent and emergent patients mostly NOT surveyed</u>**!!

Best way to improve "ED satisfaction" is to shorten the wait-time of non-acute patients, e.g. Press Ganey praised

- Allentown Memorial of Waterloo, Iowa who (i) set aside four ED beds exclusively for non-acute patients and (ii) got ED staff to transport discharged patients to hospital care
- "It wasn't the most popular thing, but it's what the patients wanted. That's our rationale to the doctors on the floor and to the hospital board"