

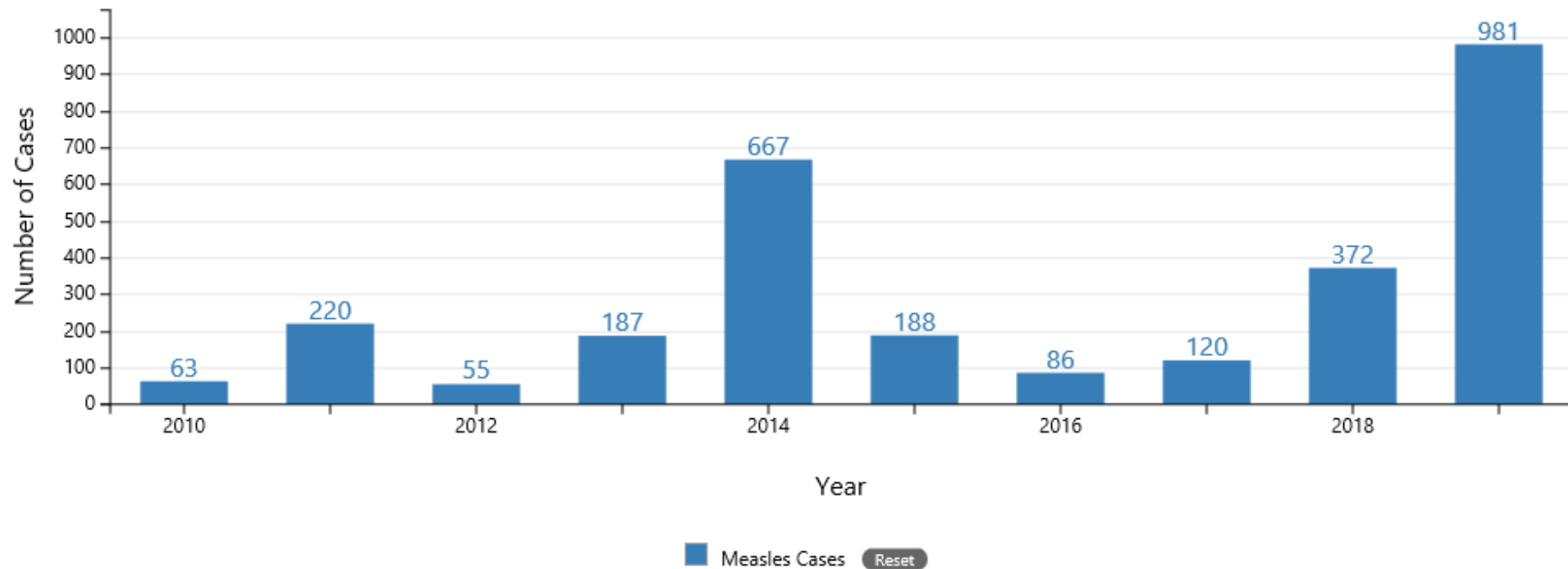


The Role of Vaccines in Combating Antimicrobial Resistance

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Number of Measles Cases Reported by Year

2010-2019**(as of May 31, 2019)



Measles in the Prevaccine Era

3-4 million

Illnesses annually in US

400-500

Deaths annually in US

???

>2 million

Illnesses annually in US

~23,000

Deaths annually in US

ANTIBIOTIC RESISTANCE

>2 million

Illnesses annually in US

~23,000

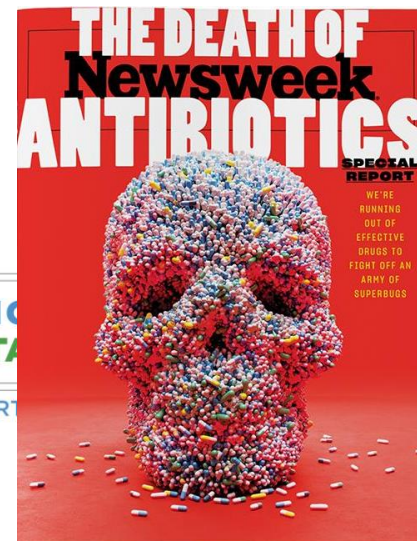
Deaths annually in US

CDC: Antibiotic Resistance Threats in the United States, 2013

<https://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf>



Antibiotic Resistance (AMR): A Global Health Emergency



2011

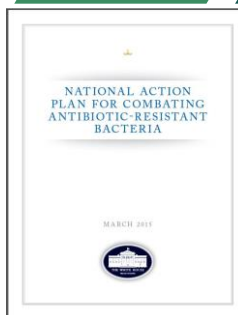
2013

2014

2015

2016

2019





Antibiotic Resistance (AMR): A Global Health Emergency

“Antimicrobial resistance is a global crisis that threatens a century of progress in health...There is no time to wait. Unless the world acts urgently, antimicrobial resistance will have a disastrous impact within a generation.”

<https://www.who.int/antimicrobial-resistance/interagency-coordination-group/final-report>

“Without urgent action, we are heading for a post-antibiotic era, in which common infections and minor injuries can once again kill.”

<https://www.who.int/antimicrobial-resistance/publications/surveillancereport/en/>

CDC's Four Core Actions to Prevent AMR

1 PREVENTING INFECTIONS, PREVENTING THE SPREAD OF RESISTANCE



Avoiding infections in the first place reduces the amount of antibiotics that have to be used and reduces the likelihood that resistance will develop during therapy. There are many ways that drug-resistant infections can be prevented: immunization, safe food preparation, handwashing, and using antibiotics as directed and only when necessary. In addition, preventing infections also prevents the spread of resistant bacteria.

Immunization!

2 TRACKING



CDC gathers data on antibiotic-resistant infections, causes of infections and whether there are particular reasons (risk factors) that caused some people to get a resistant infection. With that information, experts can develop specific strategies to prevent those infections and prevent the resistant bacteria from spreading.

3 IMPROVING ANTIBIOTIC PRESCRIBING/STEWARDSHIP



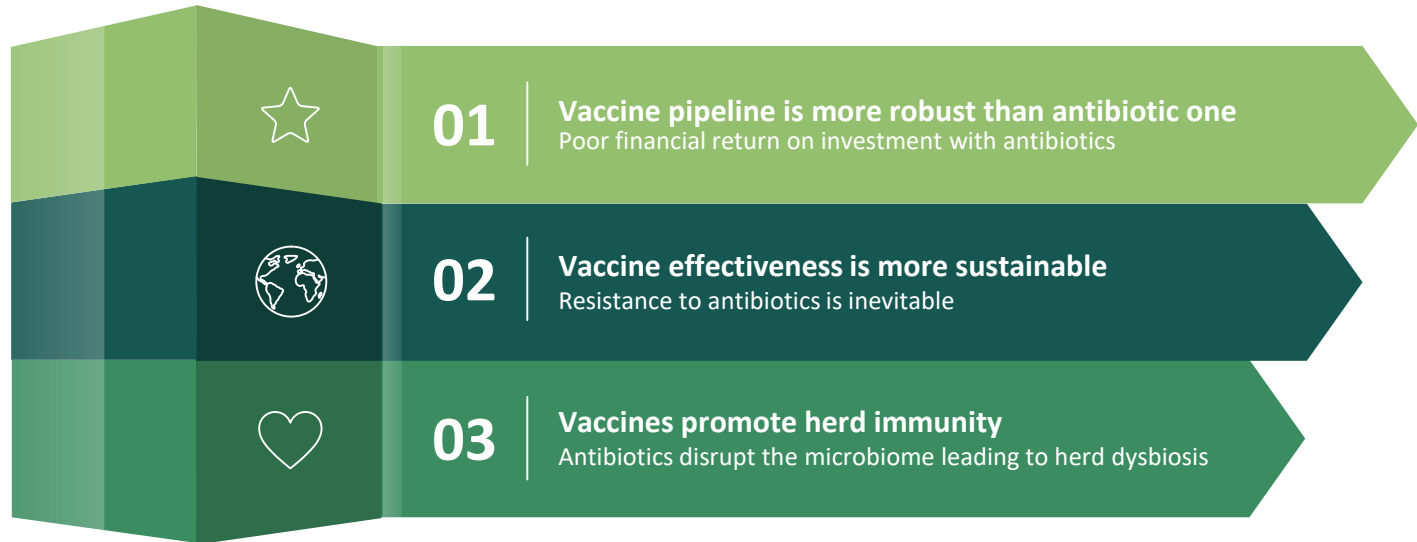
Perhaps the single most important action needed to greatly slow the development and spread of antibiotic-resistant infections is to change the way antibiotics are used.

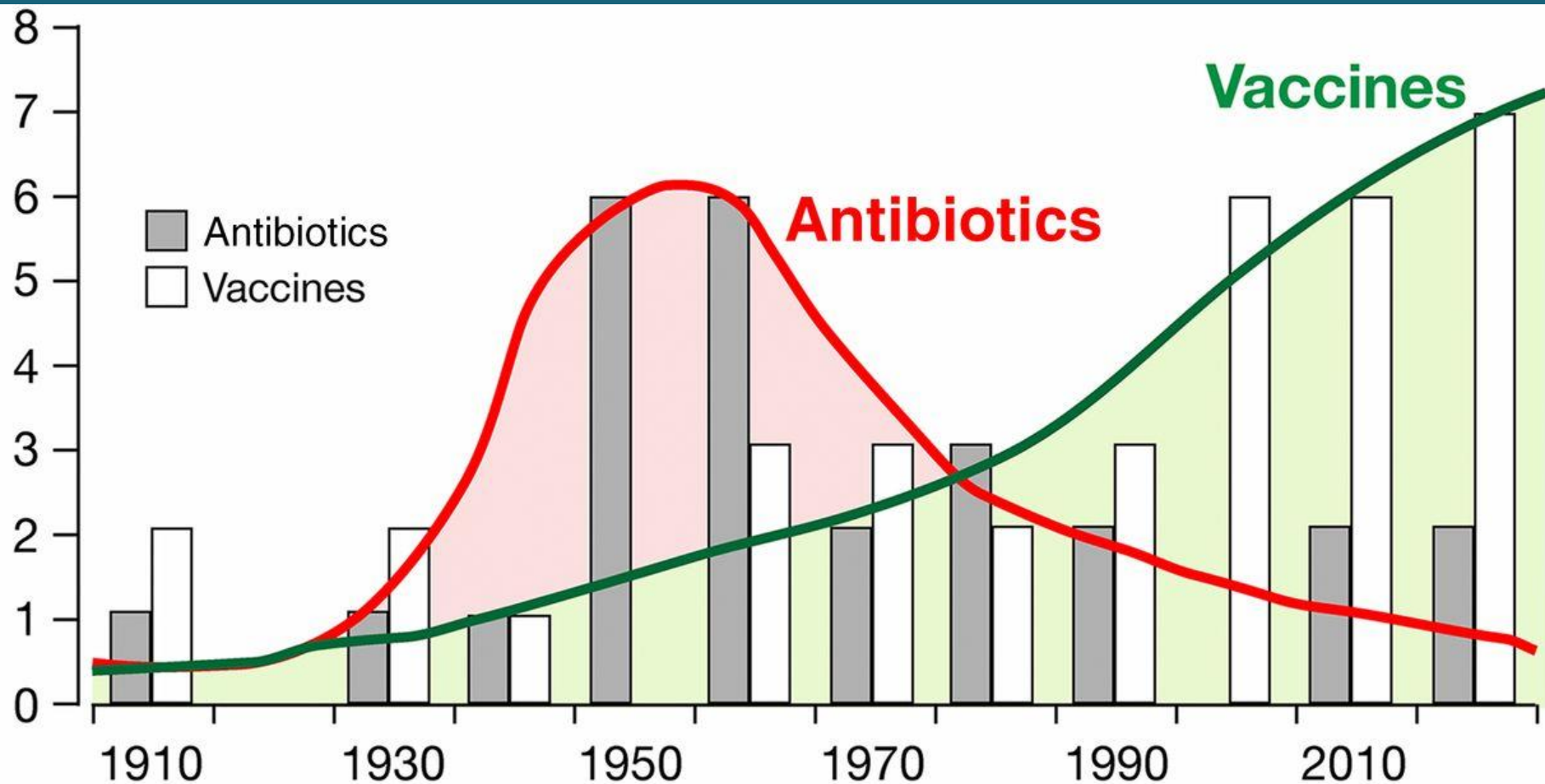
4 DEVELOPING NEW DRUGS AND DIAGNOSTIC TESTS



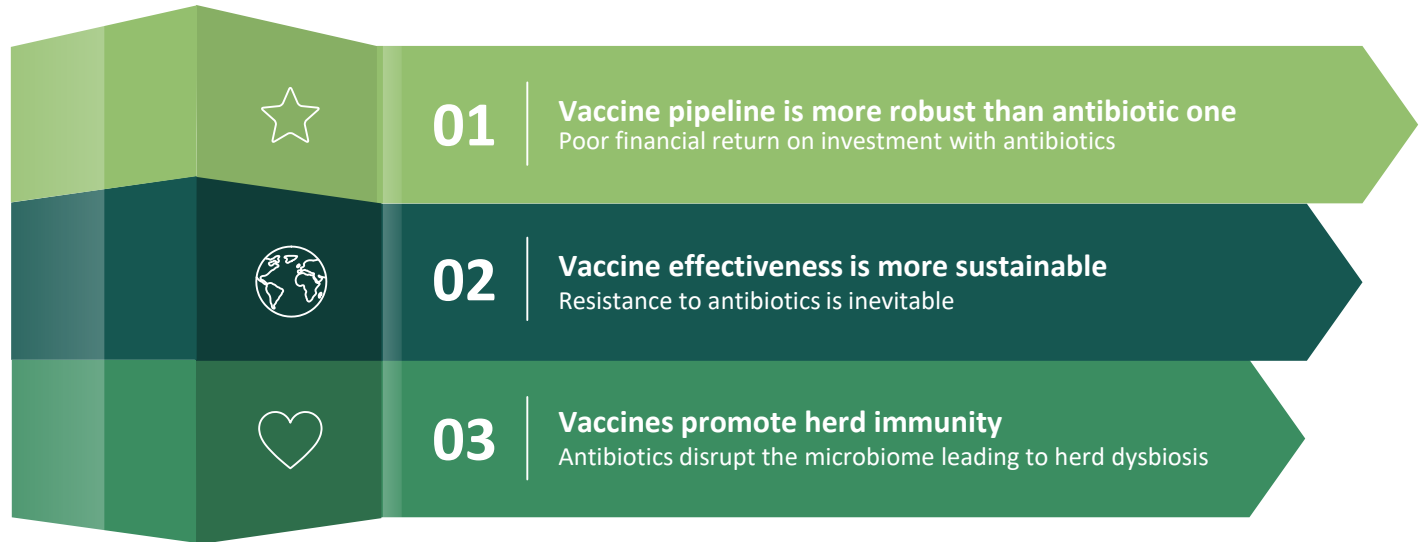
Because antibiotic resistance occurs as part of a natural process in which bacteria evolve, it can be slowed but not stopped. Therefore, we will always need new antibiotics to keep up with resistant bacteria as well as new diagnostic tests to track the development of resistance.

Advantages of Vaccines

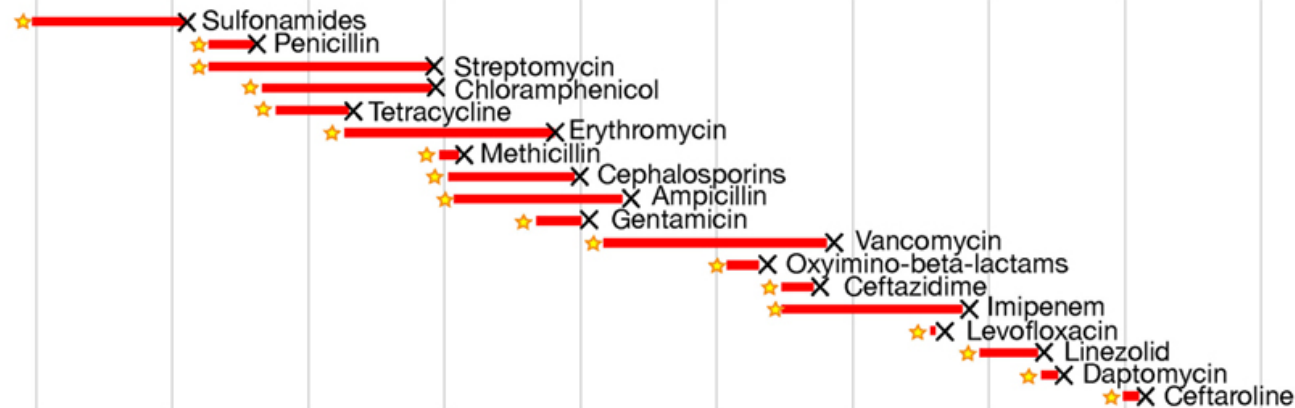




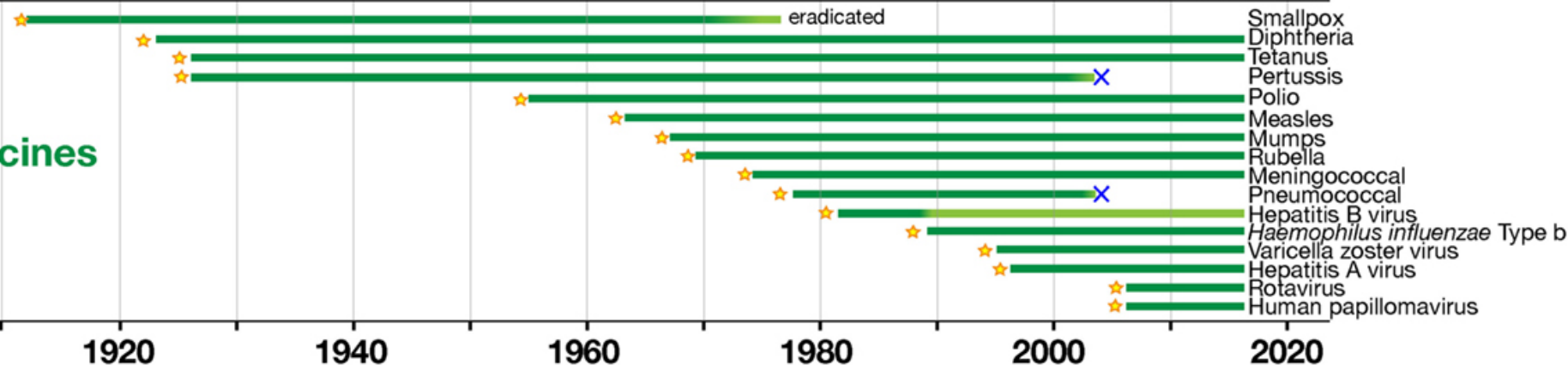
Advantages of Vaccines



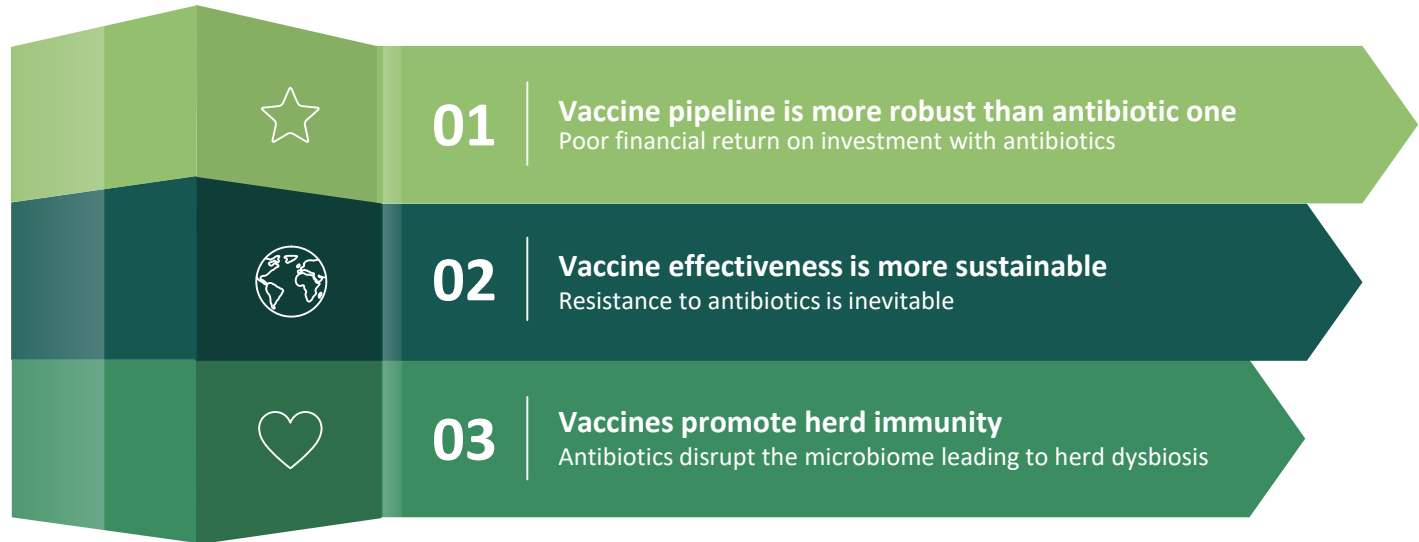
Antibiotics



Vaccines

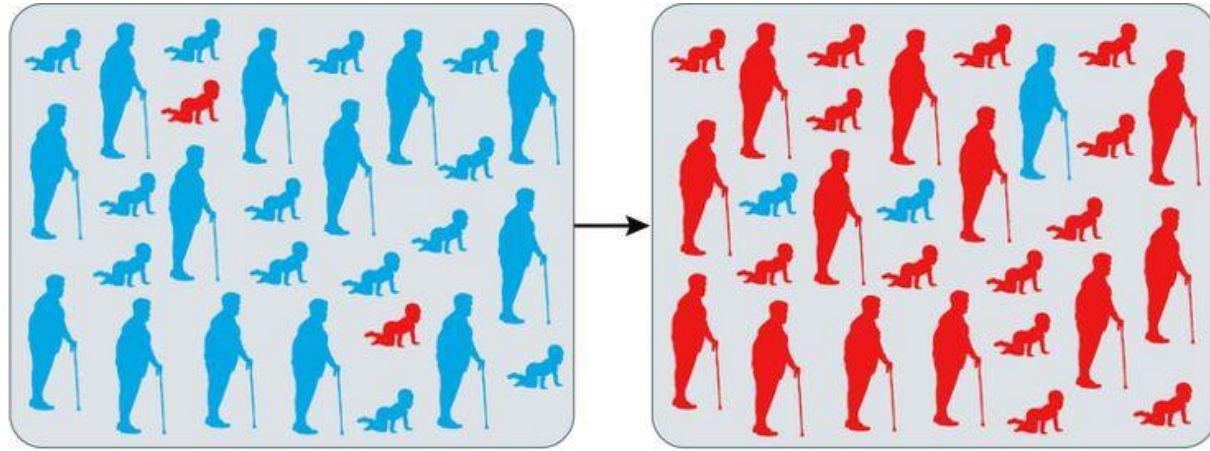


Advantages of Vaccines



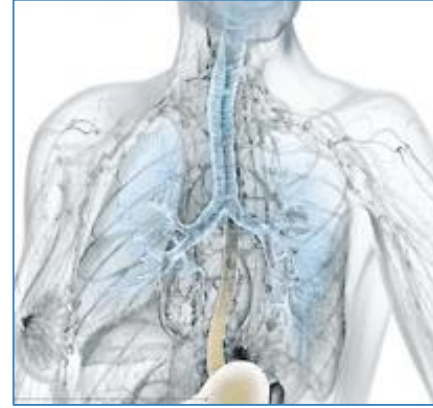
a

Poorly
immunized
population



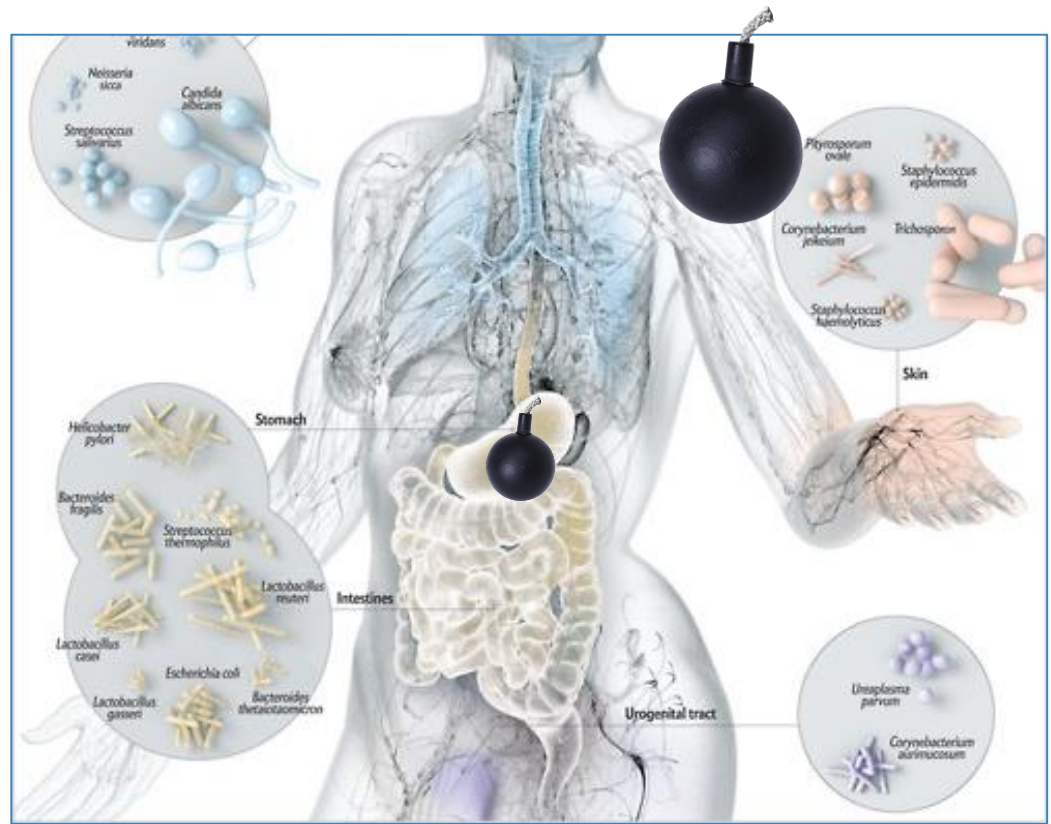
Immunized
population:
herd immunity

Antibiotics: Silver Bullet?



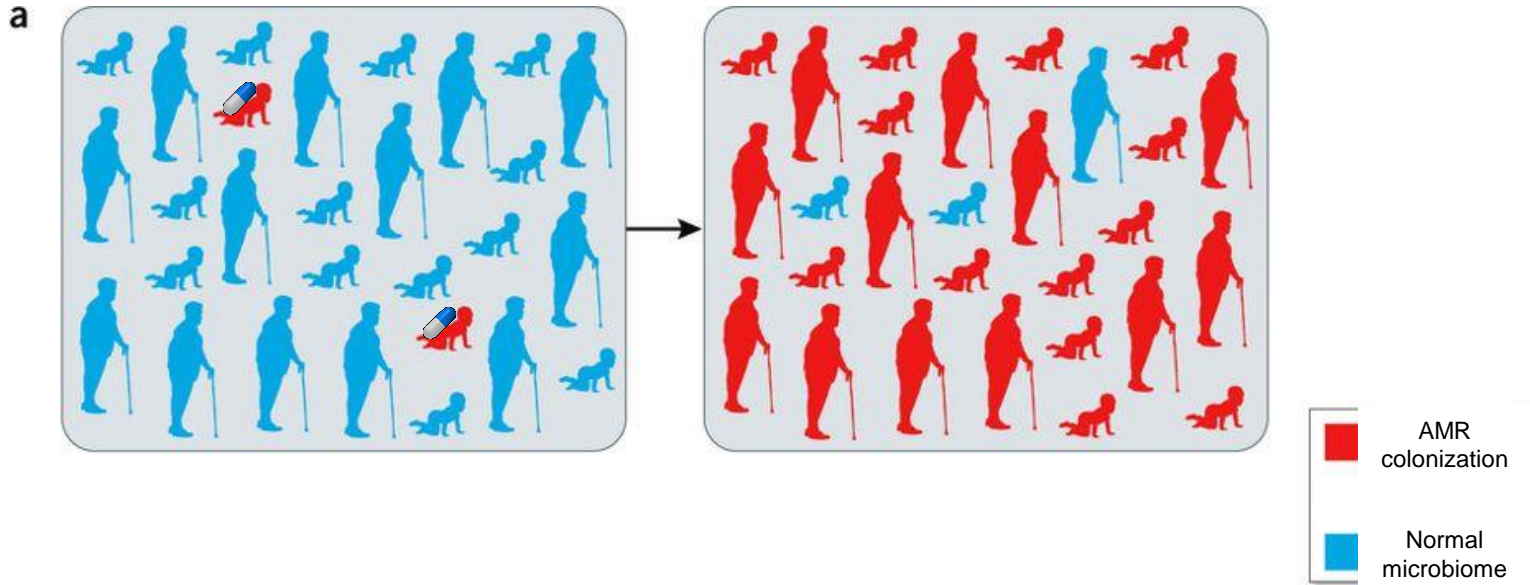
Antibiotics: Cluster Bomb

Antibiotic use, both appropriate and inappropriate, damages the normal microbiome



Vaccines don't cause this broad disruption

Antibiotic
exposure:
herd
dysbiosis



How do vaccines impact antibiotic resistance?

Directly

Decreasing the need for antibiotics by reducing the burden of bacterial disease

Directly

Decreasing carriage of and infection with AMR organisms

Indirectly

Decreasing viral febrile illnesses and their associated antibiotic use

1

Pneumococcus

(*Streptococcus pneumoniae*)



Burden of Pneumococcal Disease in the Prevaccine Era

Otitis media

7 million cases/year

Pneumonia

500,000 cases/year

Bacteremia

50,000 cases/year

Meningitis

3,000 cases/year

Death

40,000 deaths/year

Pneumococcal Vaccines

Polysaccharide vaccine

- PPS23 developed in 1970s
- Poorly immunogenic in infants and young children
- No immunologic memory
- No effect on mucosal carriage

Conjugate vaccine

- PCV7 introduced in 2000, followed by PCV13 in 2010
- Immunogenic
- Induces immunologic memory
- Reduces mucosal carriage (herd immunity)

Impact of PCV7 & PCV13 on Otitis Media

- Nationwide study on the impact of PCV7 & PCV13 on otitis media-associated ambulatory visits in children

Impact of PCV7 & PCV13 on Otitis Media

		Pre-PCV7 to PCV7	PCV7 to PCV13	Pre-PCV7 to PCV13
<2 years of age	MD office visit	-29%	-31%	-51%
	Hospital ED	-32%	-22%	-47%
2-4 years of age	MD office visit	-17%	-23%	-37%
	Hospital ED	-18%	-20%	-34%
5-18 years of age	MD office visit	-24%	-15%	-35%
	Hospital ED	-22%	-12%	-32%



7 million OM episodes annually



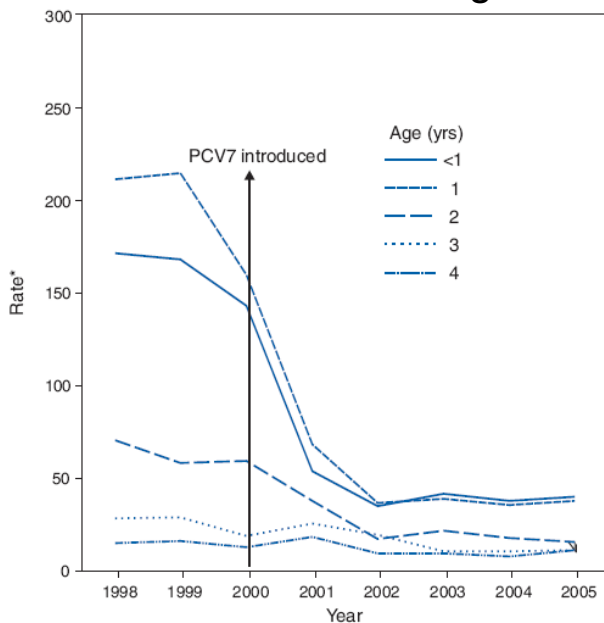
~40% of OM visits prevented annually



>2 million antibiotic courses avoided!

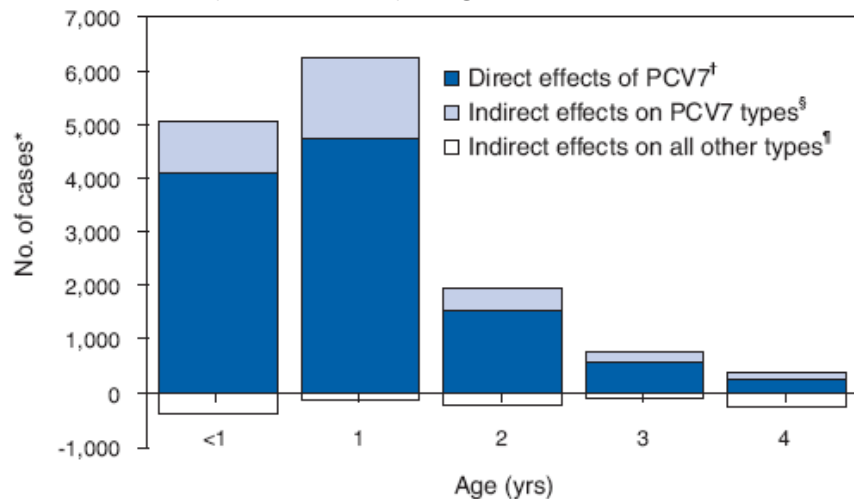
Impact of PCV7 on Invasive Pneumococcal Disease (IPD)

Incidence of IPD in Children Aged <5 years



* Per 100,000 population.

Estimated Number of IPD Case Prevented By PCV7 by Age Group (2005)



Impact of PCV13 on Invasive Pneumococcal Disease (IPD)

	PCV13-Only Serotypes	Non-PCV13 Serotypes	All Serotypes
<5 years	-93%	-2%	-64%
5-17 years	-75%	-2%	-53%
18-49 years	-72%	+13%	-32%
50-64 years	-62%	+26%	-18%
>64 years	-58%	+7%	-12%



Nearly **400,000** IPD cases prevented



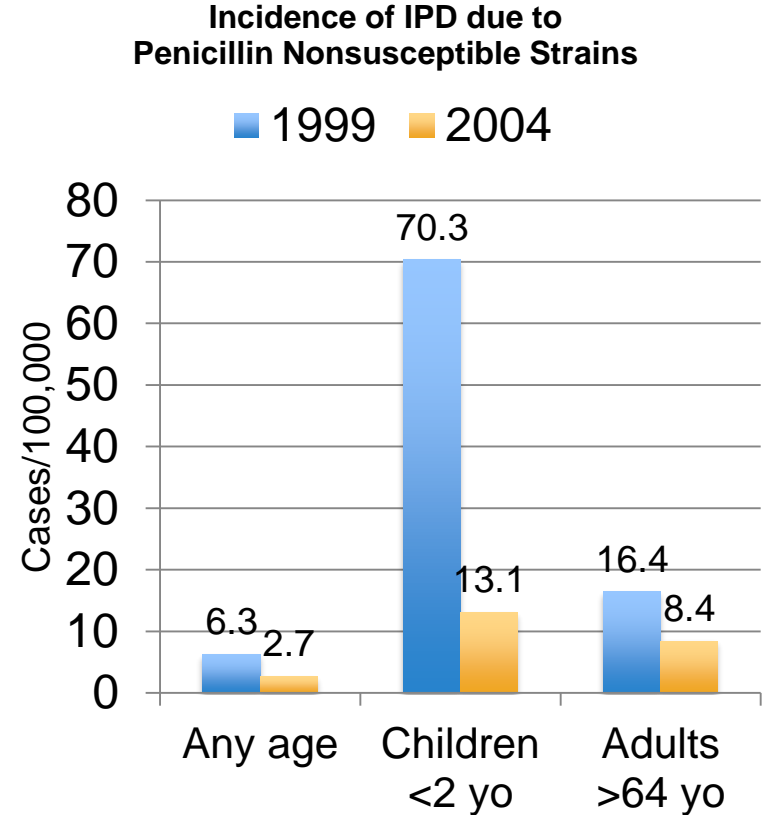
About **30,000** deaths prevented



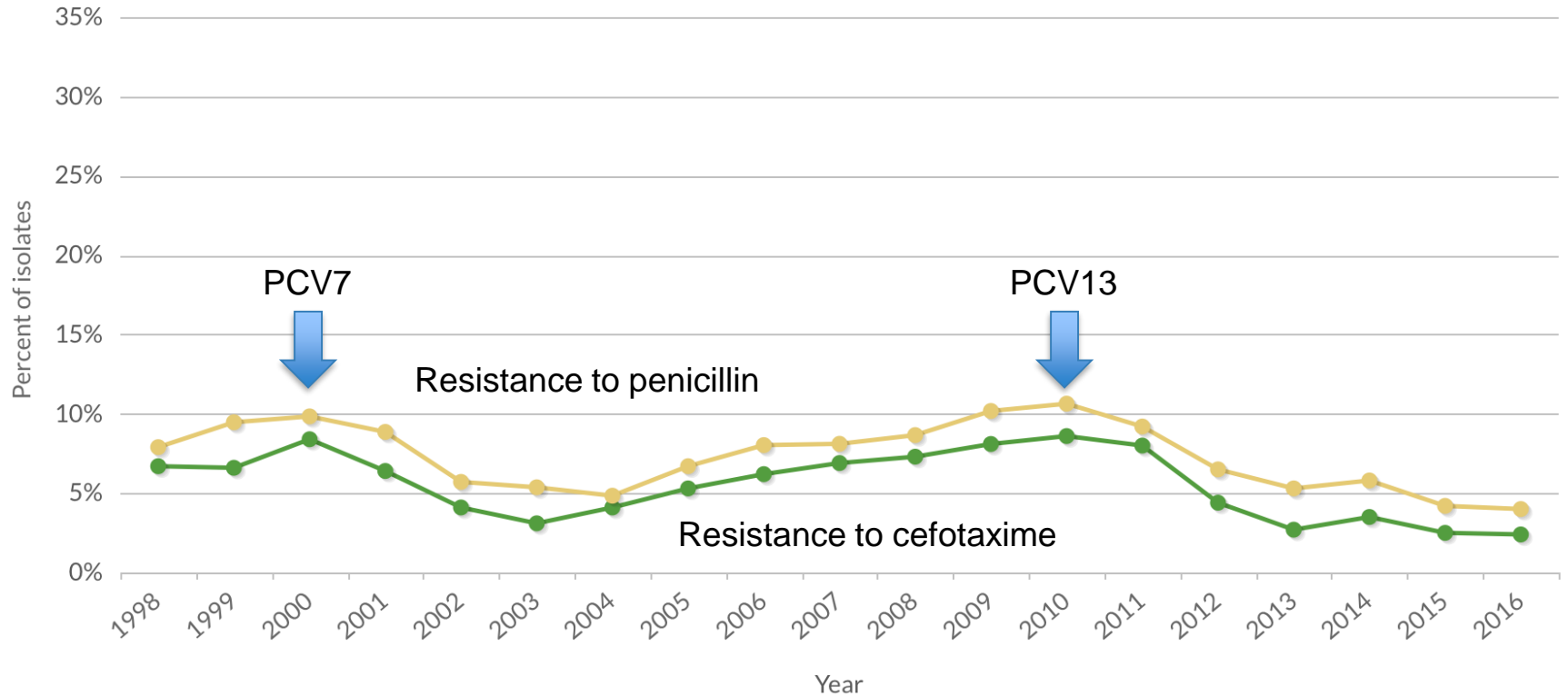
A LOT of antibiotic courses avoided!

Impact of PCV7 on IPD Due to Antibiotic-Resistant *S. pneumoniae*

- 57% decrease in IPD due to PCN-NS *S. pneumoniae*
 - 81% decrease in <2 yo
 - 49% decrease in ≥65 yo
- 59% decrease in IPD due to multidrug-resistant strains



S. pneumoniae Antibiotic Resistance in US



PCV: Psychological Impact on Prescribers

↓ FOMO

= fear of missing occult infection

2

Influenza virus

Impact of Influenza Vaccination

- Multinational randomized-controlled trial in children 6-35 month of age (n=12,018)
- Randomization to either inactivated quadrivalent influenza vaccine (IIV) or control during 5 influenza seasons
- Surveillance from 14 days post-vaccination until end of the influenza season

Impact of Influenza Vaccination

**Flu-associated
medical visits**

47% risk reduction

with IIV

**Flu-associated ED
visits**

79% risk reduction

with IIV

**Flu-associated
missed daycare**

54% risk reduction

with IIV

**Flu-associated
missed work**

54% risk reduction

with IIV

**What about flu-associated antibiotic
prescriptions?**

Flu-associated antibiotic use



50% risk reduction

with IIV

Impact of Universal Influenza Immunization

- Canadian Province of Ontario introduced universal influenza immunization in 2000
- Other provinces continued to target high-risk groups and their contacts
- Ecological study comparing pre- and post-intervention with concurrent controls

Impact of Universal Influenza Immunization

Vaccine uptake	1996-97	Post-2000
Ontario	18%	38%
Other Provinces	13%	24%

Impact of Universal Influenza Immunization

Flu-associated mortality

39% greater decrease
in Ontario

Flu-associated hospitalizations

42% greater decrease
in Ontario

Flu-associated ED use

55% greater decrease
in Ontario

Flu-associated MD Office Visits

59% greater decrease
in Ontario

What about respiratory antibiotic prescriptions?

Impact of Universal Influenza Immunization

Respiratory antibiotic prescription rate (Rx per 1000 people)	1996-97	Post-2000
Ontario	17.6	6.4
Other Provinces	8.3	8.2



64% greater reduction

in respiratory antibiotic prescriptions in Ontario compared with other provinces



~144,000

Respiratory antibiotic prescriptions prevented annually

3

Gonorrhea

(Neisseria gonorrhoeae)

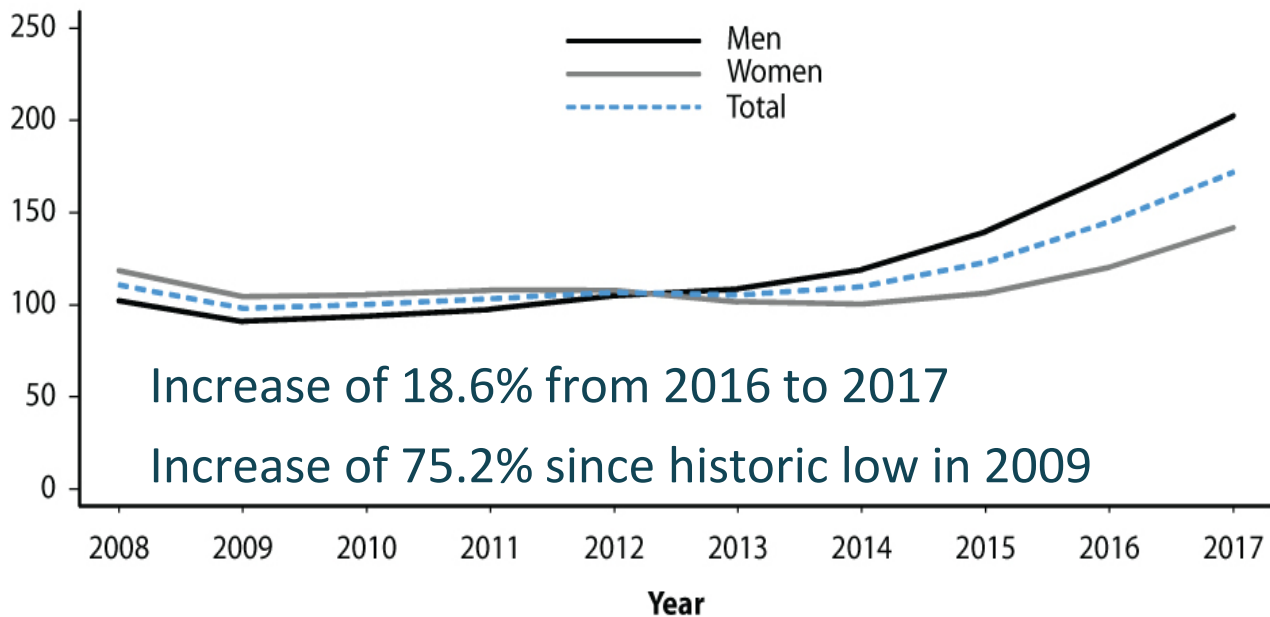
Neisseria gonorrhoeae: Background

- Major global public health concern with ~100 million cases worldwide each year
- Significant morbidity: pelvic inflammatory disease, infertility, and chronic pain
- Antimicrobial resistance has grown steadily and extensively drug-resistant strains have emerged

Neisseria gonorrhoeae: Incidence in US



Rate (per 100,000 population)



<https://www.cdc.gov/std/stats17/gonorrhea.htm>

Neisseria gonorrhoeae: An URGENT threat

Antibiotic-Resistant Gonorrhea



Gonorrhea is developing resistance to the antibiotics we use to treat it.



There are about **820,000** new gonorrhea infections each year in the U.S.



Gonorrhea is the **2nd** most commonly reported infectious disease



We are down to **1** recommended effective class of antibiotics to treat it

***Neisseria gonorrhoeae*:** **An URGENT threat**

Antibiotic development

- At least 3 new agents at various stages of clinical development
- How long before resistance develops?

Vaccine development

- Only 4 vaccine candidates have progressed to clinical trials (all before 1990)
- None have provided any protection against gonorrhea

Petousis-Harris H et al. *Lancet* 2017;390:1603-10.
Seib KL. *Lancet* 2017;390:1567-8.
Edwards JL et al. *Curr Op ID* 2018;31:246-50.

Neisseria gonorrhoeae: **Lessons from *N. meningitidis***

- Very different disease manifestations
- 80-90% genetic homology
- Most virulence factors in one have an equivalent in the other

Petousis-Harris H et al. *Lancet* 2017;390:1603-10.
Seib KL. *Lancet* 2017;390:1567-8.

Effectiveness of group B meningococcal vaccine against gonorrhea

- Outer membrane vesicle (OMV) meningococcal B vaccine was given to ~1 million people in New Zealand between 2004 and 2008 in response to a serogroup B meningococcal epidemic
- Retrospective case-control study on patients at a sexual health clinic aged 15-30 years
- Odds of having received OMV vaccine compared between cases (gonorrhea only) and controls (chlamydia only)

Petousis-Harris H et al. *Lancet* 2017;390:1603-10.
Seib KL. *Lancet* 2017;390:1567-8.



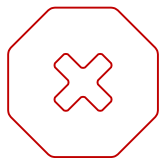
31%

Estimated vaccine effectiveness against gonorrhea



First time

A vaccine has shown any protection against gonorrhea



But OMV vaccine no longer available

N. meningitidis: **Available vaccines**

Serogroup ACWY vaccines

Conjugate vaccines

Menveo: 2 mo to 55 yr of age

Menactra: 9 mo to 55 yr of age

Serogroup B vaccines

Licensed for ages 10 & above

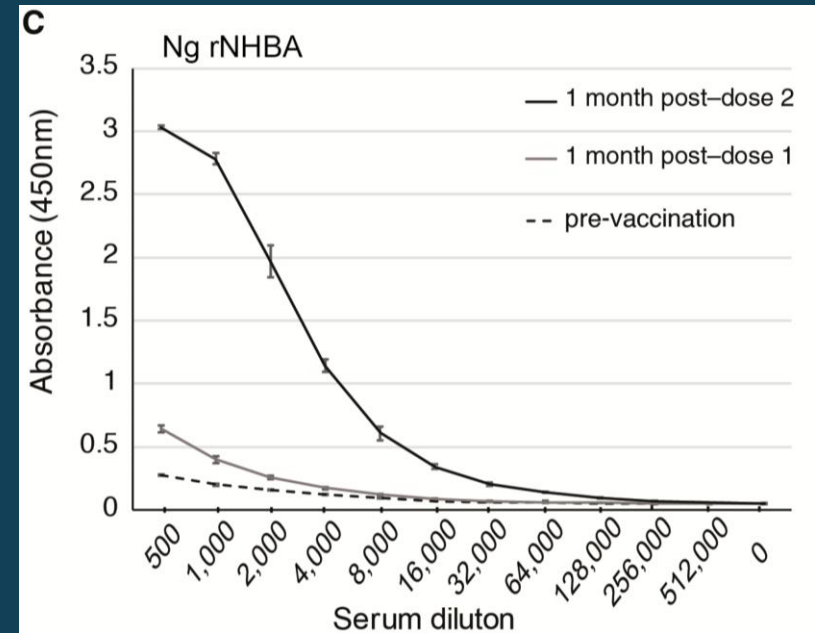
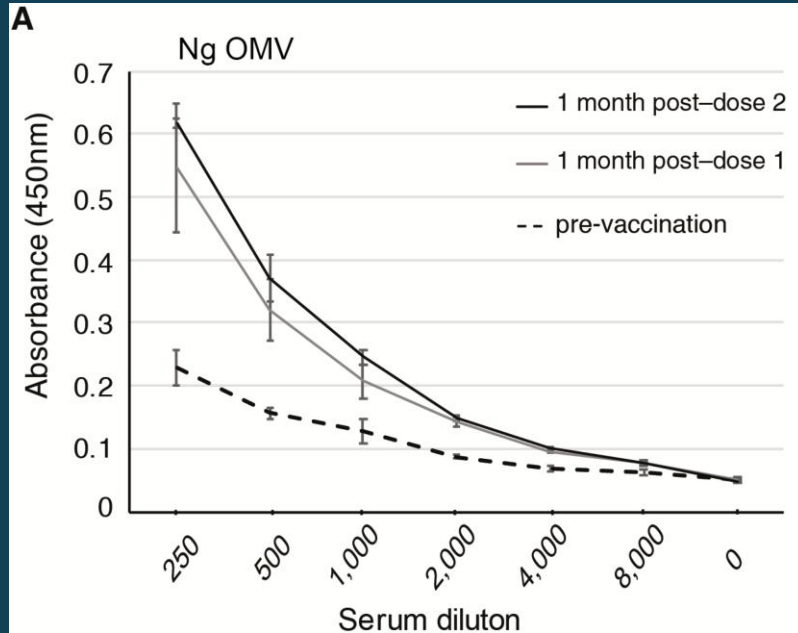
Trumenba (MenB-FHbp):
factor H binding protein

Bexero (MenB-4C):

FHbp, NadA, NHBA, OMV

Bexero induces antibodies to *Neisseria gonorrhoeae*

- Bexero (MenB-4C) contains OMV (same as vaccine in New Zealand) plus 3 recombinant antigens (FHbp, NadA, NHBA)
- Study examined whether vaccine induces antibodies that recognize *Neisseria gonorrhoeae*



Bexero induces antibodies in humans that recognize gonococcal proteins (OMV and NHBA) and may provide cross-protection against gonorrhea

Summary

- Vaccines are a vital but under-recognized tool in combating antibiotic resistance
 - Economics aligns with public health interests
 - Efficacy more sustained than antibiotics
 - Promotion of herd immunity rather than herd dysbiosis
- Reducing the burden of disease can decrease
 - Excess antibiotic use (both appropriate & inappropriate)
 - Incidence of AMR infections
 - FOMO (which impacts prescribing behavior)

World Health Organization: Ten Threats to Global Health in 2019

1. Air pollution & climate change
2. Noncommunicable diseases
3. Global influenza pandemic
4. Fragile & vulnerable settings
5. **Antimicrobial resistance**
6. Ebola & other high-threat pathogens
7. Weak primary health care
8. **Vaccine hesitancy**
9. Dengue
10. HIV

THANKS!

Any questions?

You can contact me at blee@mail.cho.org