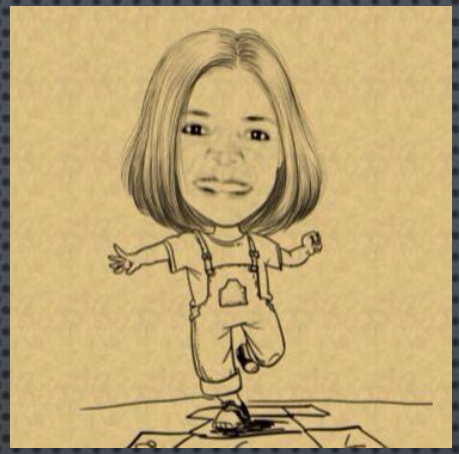
VACCINATION AS AN APPROACH TO REDUCING ANTIMICROBIAL RESISTANCE



HELLO!

I AM MARÍA L. AVILA-AGUERO
PEDIATRIC INFECTIOUS DISEASES
COSTA RICA

ANTIBIOTIC RESISTANCE: KEY FACTS

- Antibiotic resistance is one of the biggest threats to global health, food security, and development today.
- Antibiotic resistance can affect anyone, of any age, in any country.
- Antibiotic resistance occurs naturally, but misuse of antibiotics in humans and animals is accelerating the process.
- A growing number of infections – such as pneumonia, tuberculosis, gonorrhoea, and salmonellosis – are becoming harder to treat as the antibiotics used to treat them become less effective.
- Antibiotic resistance leads to longer hospital stays, higher medical costs and increased mortality.

National Action Plan for Combating Antibiotic-Resistant Bacteria

CAUSES OF ANTIBIOTIC RESISTANCE

HANDLE ANTIBIOTICS WITH CARE

Antibiotic resistance happens when bacteria change and become resistant to the antibiotics used to treat the infections they cause.

Over-prescribing of antibiotics

Patients not finishing their treatment

Over-use of antibiotics in livestock and fish farming

Poor infection control in hospitals and clinics

Lack of hygiene and poor sanitation

Lack of new antibiotics being developed

www.who.int/drugresistance

#AntibioticResistance

World Health Organization

MRSA is the leading cause of **healthcare-associated** infections.

Treatment failures of last resort drugs for gonorrhea have been reported from 10 countries.

Antimicrobial resistance is a

global problem.

AMR infections cause **8 million hospital days** and **$30 billion** cost to U.S. health care system per year.

No new major antibiotics have been discovered for **25 years**.

The major reason for resistance development is **inappropriate use** of antimicrobial drugs.

1.2 million infections and **$96 million** cost are caused by resistant *Streptococcus pneumoniae* in the U.S. per year.

Multi-drug resistant tuberculosis strains caused **450 000 infections** worldwide in 2012.

The WHO predicts a **post-antibiotic era**.

WHO-PAHO

Table 2

Dynamics of antibiotic resistance acquisition in bacteria (the table reports some of the most significant examples and it is not meant to be comprehensive). Most of the nosocomial pathogens listed herein harbor multiple resistances (e.g. *S. aureus* for all of them)

Antibiotic	Discovery	Clinical use	Emergence of resistant bacteria	Nosocomial pathogen with the resistance	References
β-Lactams					
Penicillin	1928	1940	1942	*S. aureus*, *Enterococcus spp.*, *C. difficile*, *P. aeruginosa*, *Acinetobacter spp.*, *H. influenzae*, *K. pneumoniae*, *E. coli*	[34]
Methicillin	1959	1960	1961	*S. aureus*	[34]
Aminoglycosides					
Streptomycin	1943	1946	1946	*S. aureus*, *Enterococcus spp.*, *P. aeruginosa*, *Acinetobacter spp.*, *E. coli*, *K. pneumoniae*	[41]
Gentamicin	1963	1971	1974	*S. aureus*, *Enterococcus spp.*, *P. aeruginosa*, *Acinetobacter spp.*, *H. influenzae*, *K. pneumoniae*, *E. coli*	[42]
Tetracyclines					
Tetracycline	1948	1948	1949	*S. aureus*, *Enterococcus spp.*, *C. difficile*, *P. aeruginosa*, *Acinetobacter spp.*, *H. influenzae*, *K. pneumoniae*, *E. coli*	[43]
Macrolide					
Erythromycin	1949	1952	1952	*S. aureus*, *Enterococcus spp.*, *C. difficile*, *H. influenzae*, *E. coli*	[44]
Glycopeptides					
Vancomycin	1953	1972	1988	*S. aureus*, *Enterococcus spp.*, *C. difficile*	[45]
Quinolones					
Fluoroquinolones	1978	1982	1985	*S. aureus*, *Enterococcus spp.*, *C. difficile*, *P. aeruginosa*, *H. influenzae*, *Acinetobacter spp.*, *E. coli*	[46]
Lipopeptide					
Daptomycin	1980	2003	2005	*S. aureus*, *Enterococcus spp.*	[36]
Oxazolidinone					
Linezolid	1987	1999	1999	*S. aureus*, *Enterococcus spp.*	[47]

Current Opinion in Microbiology 2012, 15:596–602

THE USE OF VACCINES TO REDUCE ANTIBIOTIC RESISTANCE

- Vaccines are a key component in the fight against antibiotic resistance both directly and indirectly.
- By targeting bacterial pathogens, vaccines directly reduce the need for the use of antibiotics.
- Vaccines can have an indirect effect on pathogenic bacteria by reducing complications associated to *super-infections* that routinely require antibiotic use.
- Vaccines also contribute to the reduction of antibiotic usage through the establishment of herd immunity
- The use of pneumococcal conjugate vaccine (PCV) that targets the most virulent, serotypes linked to invasive pneumococcal disease (IPD) and that are associated with antibiotic resistance

Even vaccines with relatively low efficacy may be useful tools against antimicrobial resistance

- The growing prevalence of antimicrobial resistance in major pathogens is outpacing discovery of new antimicrobial classes
- Vaccines mitigate the effect of antimicrobial resistance by reducing the need for treatment, but vaccines for many drug-resistant pathogens remain undiscovered or have limited efficacy, in part because some vaccines selectively favor pathogen strains that escape vaccine-induced immunity
- A strain with even a modest advantage in vaccinated hosts can have high fitness in a population with high vaccine coverage, which can offset a strong selection pressure such as antimicrobial use that occurs in a small fraction of hosts

EVEN VACCINES WITH RELATIVELY LOW EFFICACY MAY BE USEFUL TOOLS AGAINST ANTIMICROBIAL RESISTANCE

- Joice and Lipsitch propose a strategy to target vaccines against drug-resistant pathogens, by using resistance-conferring proteins as antigens in multicomponent vaccines
- Resistance determinants may be weakly immunogenic, offering only modest specific protection against resistant strains
- Therefore, if such vaccines confer even slightly higher protection (additional efficacy between 1% and 8%) against resistant variants than sensitive ones, they may be an effective tool in controlling the rise of resistant strains, given current levels of use for many antimicrobial agents

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0068940

Table 1

Major features of antibiotics and vaccines

Relevant features	Antibiotics	Vaccines	Reference
Therapeutic/prophylactic	Mostly therapeutic	Mostly prophylactic	See text
Coverage and specificity (different bacterial species)	Broad, indiscriminate	Narrow, very specific	See text
Resistance emergence	Common	Not observed	See text
Selective pressure	High	Low	Figure 1
Time to develop resistant strains	Short (emergence of resistance during therapy)	Not observed	Table 2
Durability	Restricted to the time of treatment	Duration of protection persists from several months to life-long	[15,16]
Treatment/prevention of viral infections	No	Yes	See text
Herd or community effect	No	Yes	See text
Prevention of perinatal infections	Yes	Yes (maternal immunity)	[17]
Prevention of cancer	No	Yes (prevention of HBV and HPV associated cancers)	[18]
Prevention of infections in cancer patients	Yes (e.g. lymphomas)	No	See text
Prevention of infections in immune compromised patients	Yes (e.g. neutropenia)	Yes (by herd immunity)	See text
Prevention of surgical-associated infections	Yes	No	See text
Cost	From few $ to thousands $ (for one therapy, depends on the length of the therapy)	From few $ to <200 $ (1 or few immunizations can be sufficient for lifelong protection)	[http://www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htm]

INCREASING COVERAGE OF VACCINES CAN REDUCE ANTIBIOTIC USE

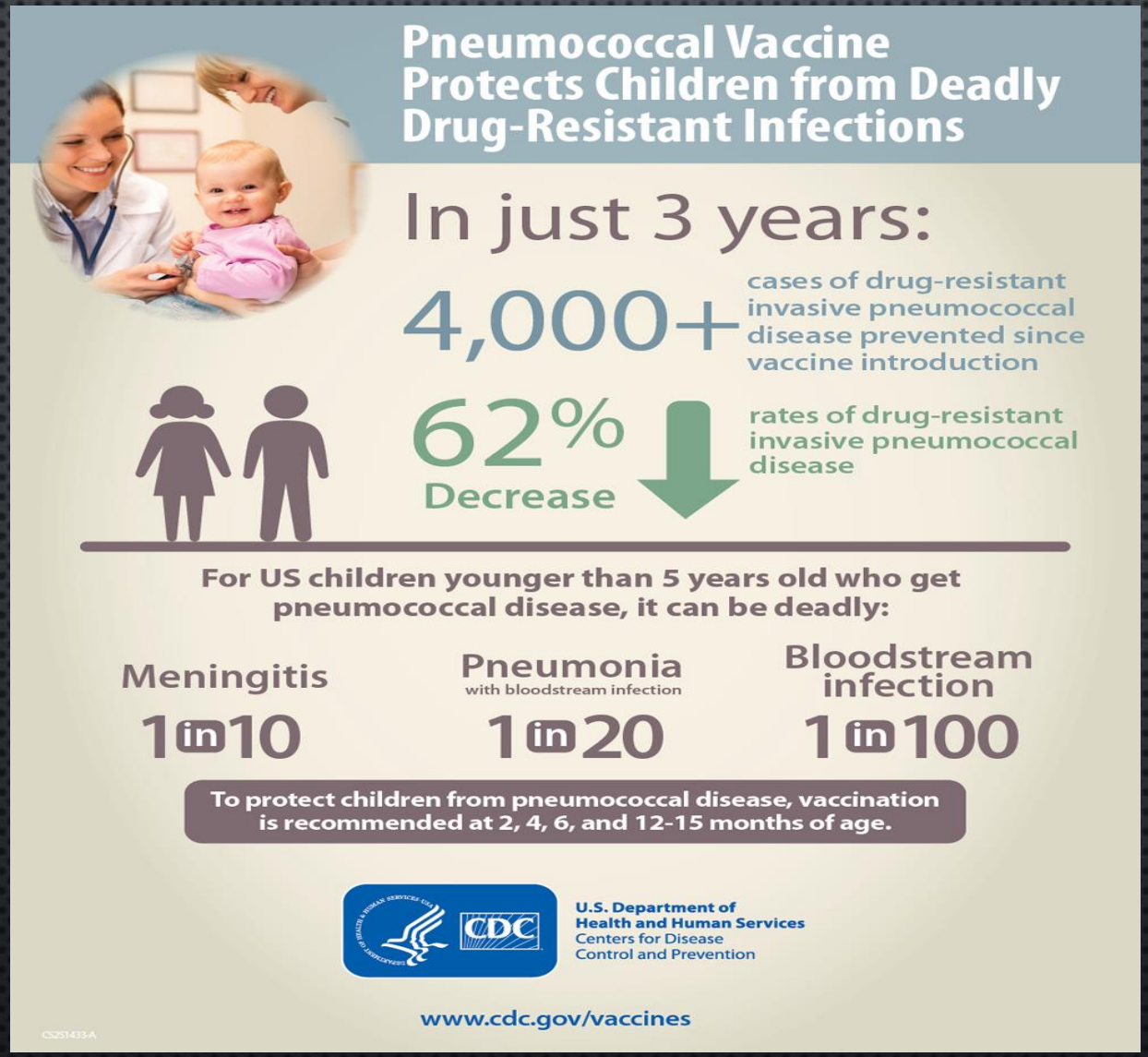
Universal coverage by a pneumococcal conjugate vaccine could potentially avert 11.4 million days of antibiotic use per year in children younger than five, roughly a 47% reduction in the amount of antibiotics used for pneumonia cases caused by *S. pneumoniae*.

47%
reduction in antibiotic use

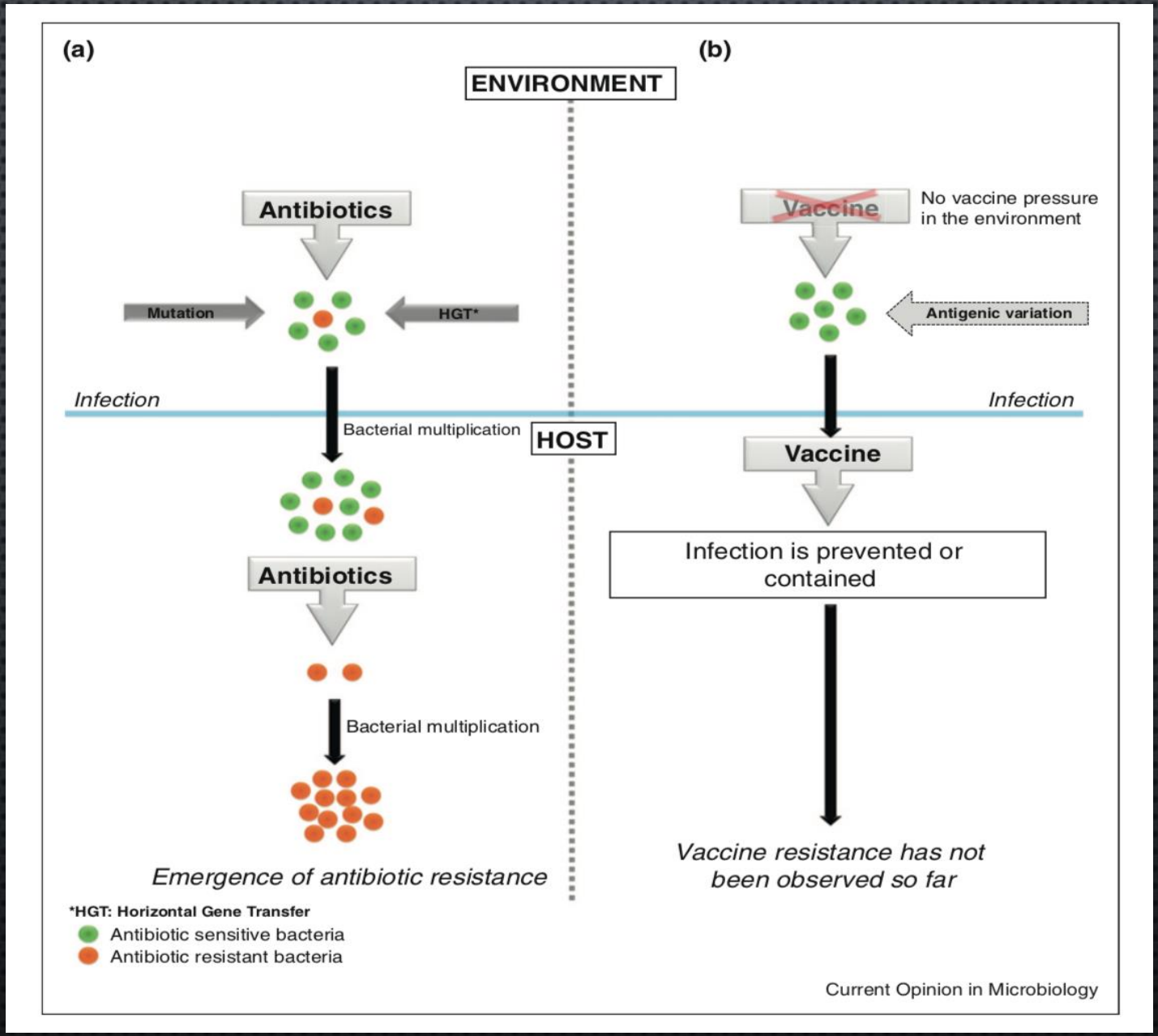
Source: Laxminarayan R, Matsoso P, Pant S, Brower C, Røttingen J, Klugman K, Davies S, Access to effective antimicrobials: A worldwide challenge, Antimicrobials: access and sustainable effectiveness, *Lancet*, 2016, 387: 168–75.

Review on Antimicrobial Resistance

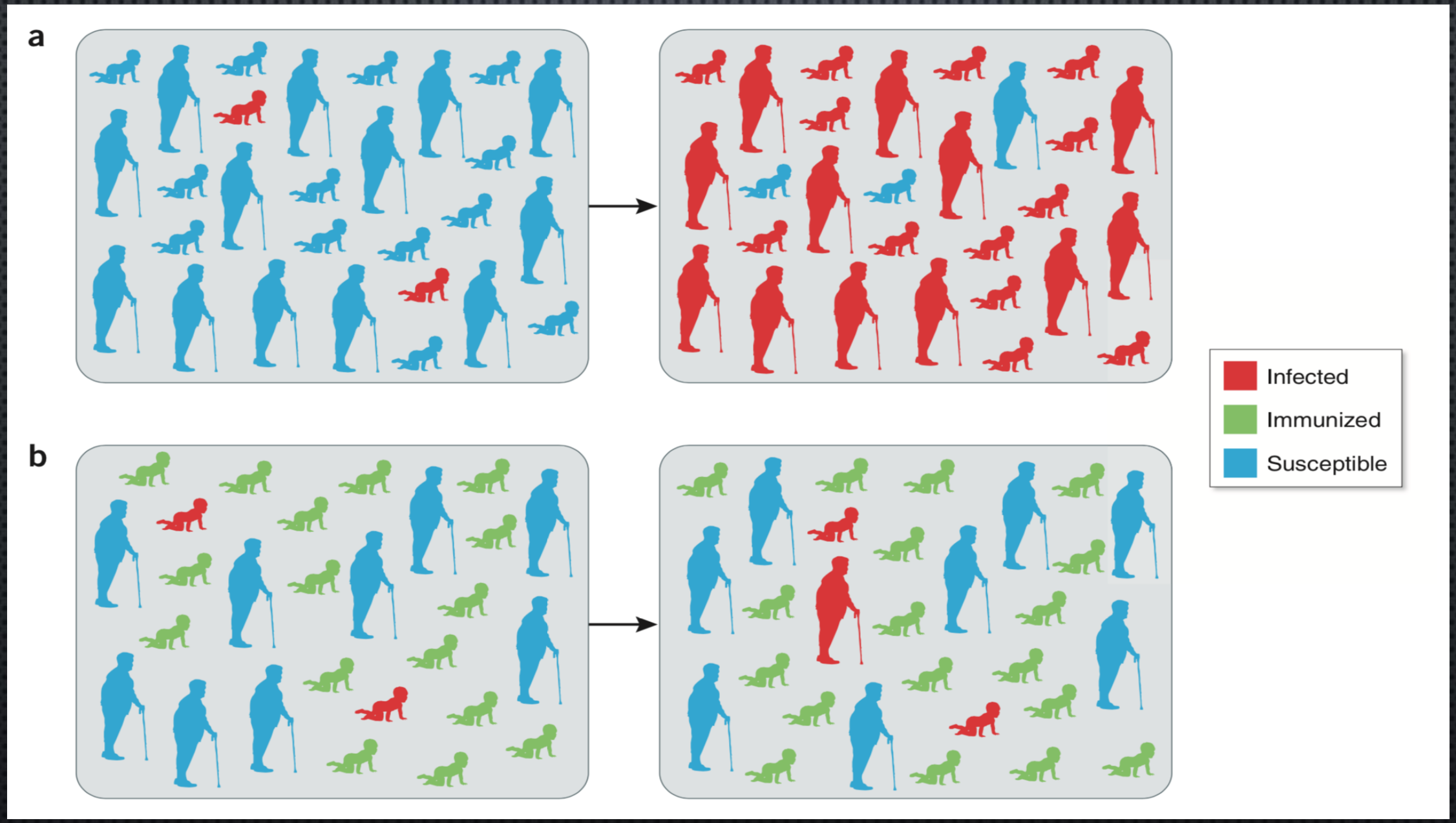
BIG CONCEPT


Pneumococcal Vaccine Protects Children from Deadly Drug-Resistant Infections
In just 3 years:
4,000+
cases of drug-resistant invasive pneumococcal disease prevented since vaccine introduction
62%
Decrease
rates of drug-resistant invasive pneumococcal disease
For US children younger than 5 years old who get pneumococcal disease, it can be deadly:
Meningitis
1 in 10
Pneumonia
with bloodstream infection
1 in 20
Bloodstream infection
1 in 100
To protect children from pneumococcal disease, vaccination is recommended at 2, 4, 6, and 12-15 months of age.
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention
www.cdc.gov/vaccines

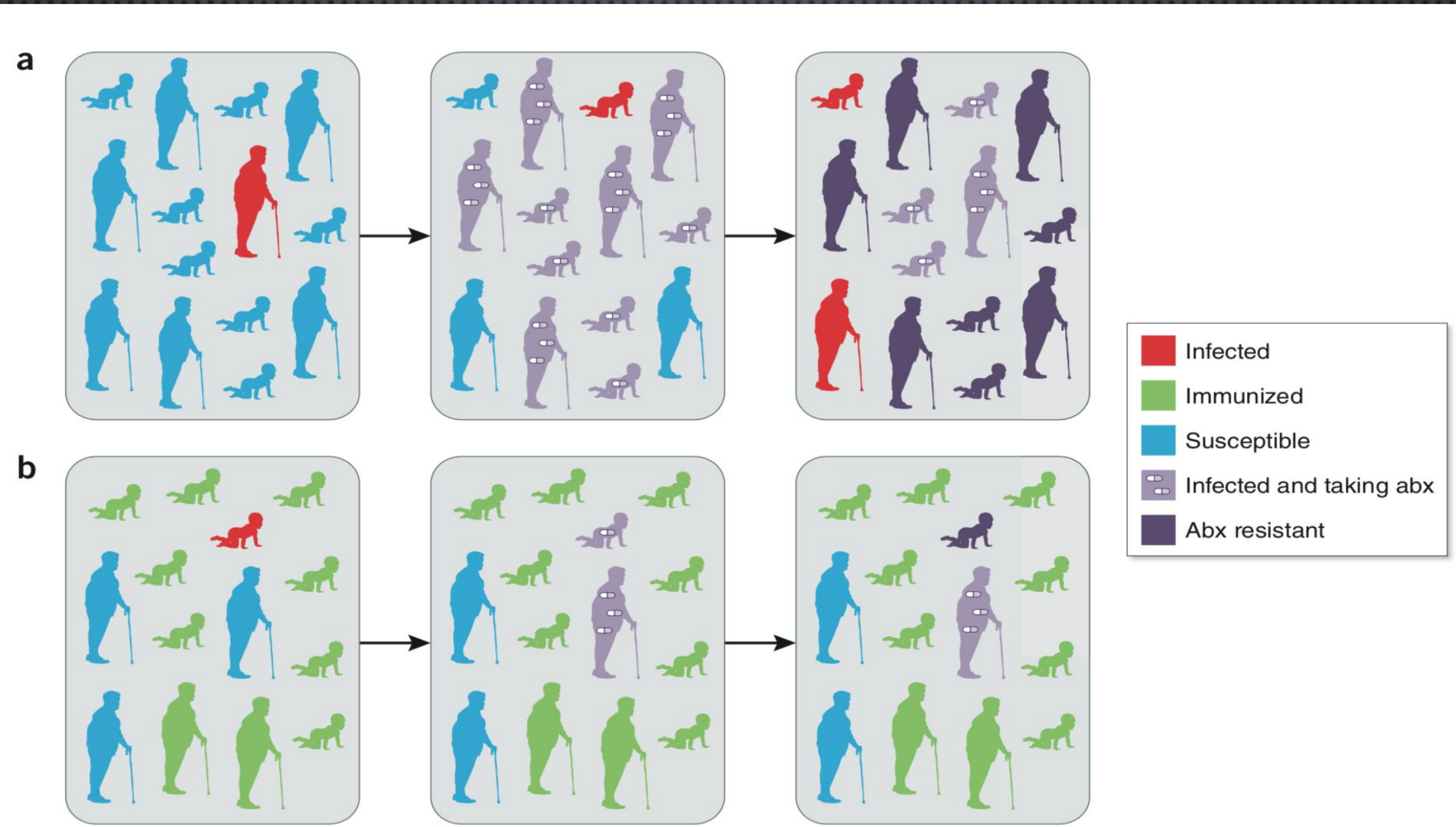
BIG CONCEPT



Mishra RPN *et al* Current Opinion in Microbiology 2012, 15:596–602



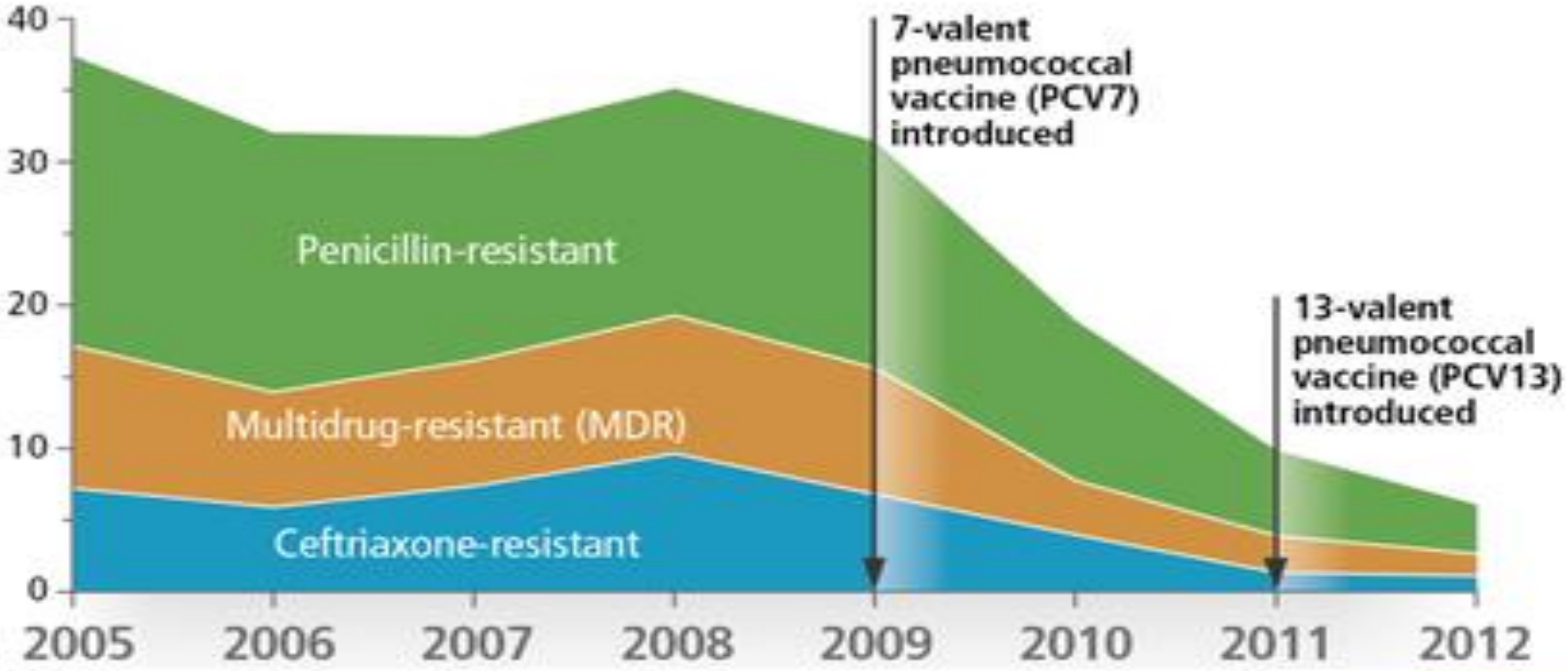
Nat Med. 2018 Jan 9;24(1):10-19



Nat Med. 2018 Jan 9;24(1):10-19

VACCINES REDUCE ANTIBIOTIC RESISTANCE

Incidence of antibiotic-resistant invasive pneumococcal disease in children < 2 years, South Africa (cases per 100,000 person-years)

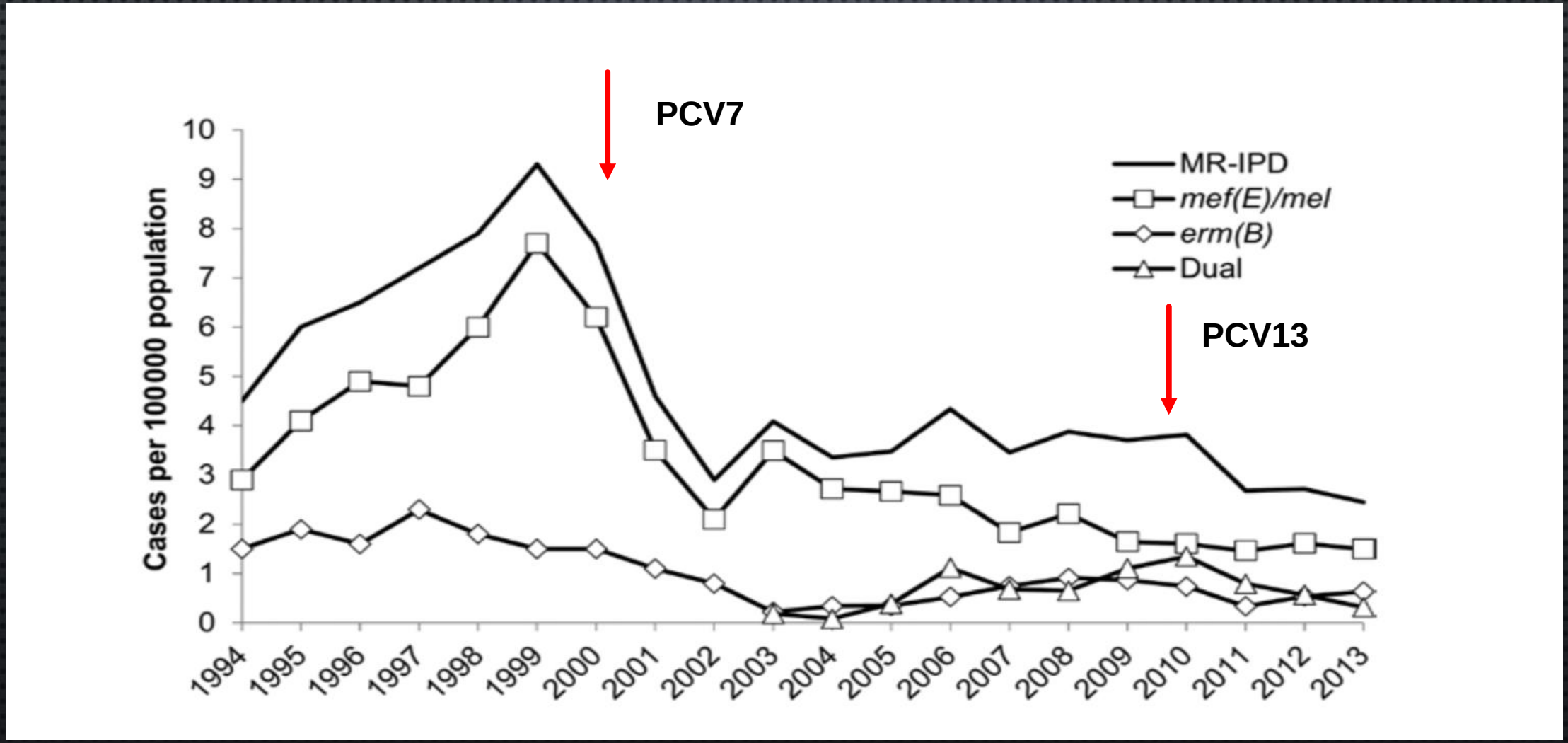


Source: A von Gottberg et al, for GERMS-SA. Publication submitted April 2014.

#vaccineswork

Gavi

PCV-13 IMPACT ON MACROLIDE RESISTANCE

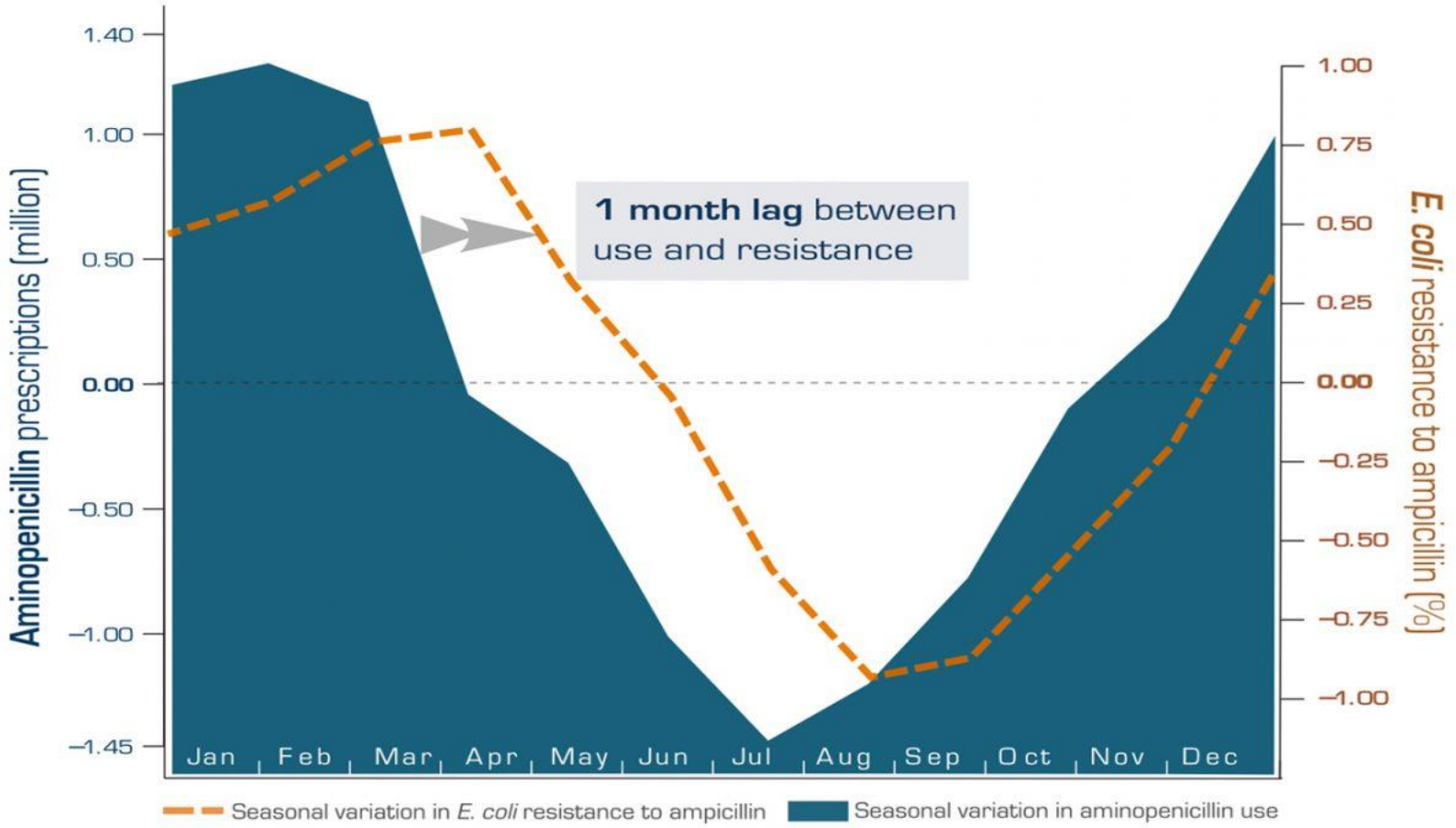


CID 2017

FLU AND BACTERIAL SUPER-INFECTIONS

- FLU IS KNOWN TO PLAY A RISK-AGGRAVATING ROLE IN BACTERIAL SUPER- INFECTIONS.
- THE IMPORTANCE OF VIRAL-BACTERIAL SYNERGY IN INFECTIONS BY INFLUENZA IS PROBABLY UNDERESTIMATED. VACCINATION AGAINST INFLUENZA MAY OFFER AN ATTRACTIVE STRATEGY TO LIMIT THE DEVELOPMENT OF SECONDARY BACTERIAL DISEASE.
- THE FINELLY STUDY OBSERVED DURING THREE STUDY SEASONS BACTERIAL INFECTION IN 6, 15 AND 34% OF CASES.
- VIRAL-BACTERIAL
- SYNERGY IS CERTAINLY AN IMPORTANT MORTALITY FACTOR.

Annual fluctuations in drug resistance are linked to seasonal antibiotic use



Data source:
Seasonality and Temporal Correlation between Community Antibiotic Use and Resistance in the United States
Lova Sun; Eili Y. Klein; Ramanan Laxminarayan
Clinical Infectious Diseases 2012; doi: 10.1093/cid/cis509

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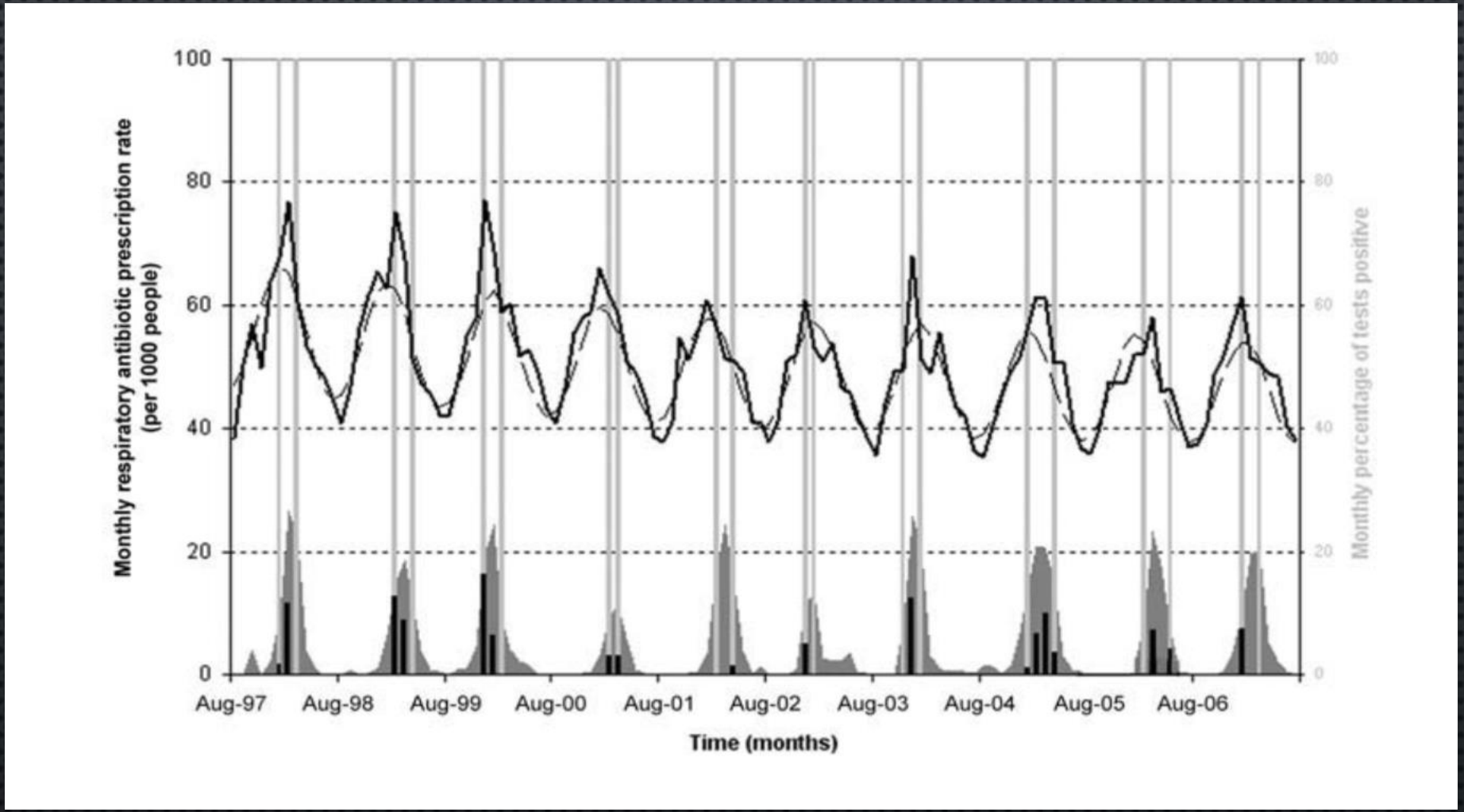


From: The Effect of Universal Influenza Immunization on Antibiotic Prescriptions: An Ecological Study
Clin Infect Dis. 2009;49(5):750-756. doi:10.1086/605087

THE EFFECT OF UNIVERSAL INFLUENZA IMMUNIZATION ON ANTIBIOTIC PRESCRIPTIONS: AN ECOLOGICAL STUDY

- The results of this study have public health and clinical relevance, indicating the potential for universal influenza immunization to reduce influenza-associated antibiotic utilization by 64% more than targeted immunization.
- Although the impact of universal influenza immunization on the incidence of antibiotic-resistant organisms remains uncertain, jurisdictions wishing to decrease antibiotic use might consider programs to increase influenza vaccination.

Kwong JC *et al* Clinical Infectious Diseases 2009;49:750–6

FLU AND BACTERIAL SUPER-INFECTIONS

TAKE HOME MESSAGES

- Bacterial-viral co-infection is common during severe acute lower respiratory infection by influenza.
- Infections by influenza modulate the antibacterial response in multiple ways and lead to increased pneumococcal replication in the upper respiratory tract.
- Increases in upper respiratory tract pneumococcal load are associated with increased severity of pneumococcal disease and with inter-individual spread.
- Vaccination against influenza virus may offer an attractive strategy to limit the development of secondary bacterial disease.

Tackling Antimicrobial Resistance in 9 Steps

Public awareness

Sanitation and hygiene

Antibiotics in agriculture and the environment

Vaccines and alternatives

Surveillance

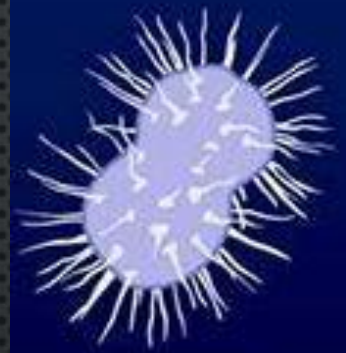
Rapid diagnostics

Human capital

Drugs

Global Innovation Fund

TEN MOST DANGEROUS ANTIBIOTIC RESISTANT BACTERIA



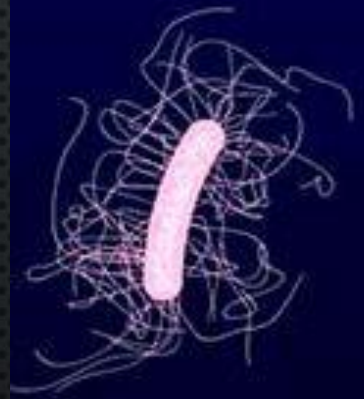
NEISSERIA GONORRHOEAE

ACINETOBACTER BAUMANNII

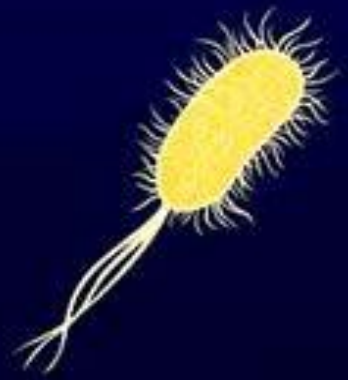
STAPHYLOCOCCUS AUREUS (MRSA)

BURKHOLDERIA CEPACIA

PSEUDOMONAS AERUGINOSA



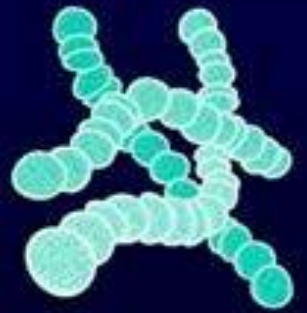
CLOSTRIDIUM DIFFICILE



ESCHERICHIA COLI (E.COLI)

MYCOBACTERIUM TUBERCULOSIS

KLEBSIELLA PNEUMONIAE



STREPTOCOCCUS PYOGENES

Table 2 Vaccine candidates in clinical development with the potential to prevent diseases caused by pathogens highlighted in this review

Vaccine	Composition	Latest trials
C. difficile		
PF-06425090 (Pfizer)[58]	Genetically/chemically inactivated *C. difficile* toxins A and B ClinicalTrials.gov identifier NCT03090191	Phase 3
ACAM-CDIFF (Sanofi)[86]	Formalin-inactivated wild-type toxoid (A and B) ClinicalTrials.gov identifier NCT01887912	Phase 3
VLA84 (Valneva)[87]	Recombinant fusion protein consisting of truncated toxin A and B ClinicalTrials.gov identifier NCT02316470	Phase 2
S. aureus		
SA4Ag (Pfizer)[88]	CP5/CP8-CRM_{197}, P-Y variant ClfA, MntC ClinicalTrials.gov identifier NCT02388165	Phase 2b
4C-Staph (GSK)[89]	Csa1A (Sur2), FhuD2, EsxA/EsxB, HlAH35L ClinicalTrials.gov identifier NCT01160172	Phase 1
Group B *Streptococcus*		
Trivalent GBS vaccine (GSK)[90]	Capsular epitopes of GBS serotypes Ia, Ib and III conjugated to CRM197 ClinicalTrials.gov identifier NCT02270944	Phase 2
Bivalent GBS protein vaccine (Minervax)[91]	N-terminal domains of the Rib and alpha C surface proteins	Phase 1
E. coli		
EcoXyn-4V (GlycoVaxyn)[92]	*E. coli* bioconjugate vaccine ClinicalTrials.gov identifier NCT02289794	Phase 1
FimH adhesin vax[93] (Sequoia)	Protein-based vaccine	Phase 1
JNJ63871860 (Janssen)[94]	*E. coli* bioconjugate vaccine	Phase 2
M. tuberculosis		
Multiple vaccines	http://www.aeras.org/pages/global-portfolio	Phases 1–3
RSV		
Multiple vaccines	http://who.int/immunization/research/vaccine_pipeline_tracker_spreadsheet/en/	Phases 1–3

Nat Med. 2018 Jan 9;24(1):10-19

VACCINES CAN REDUCE ANTIBIOTIC USE IN HUMANS

Reduce the number of bacterial infections that need antibiotics

Reduce the number of drug-resistant infections

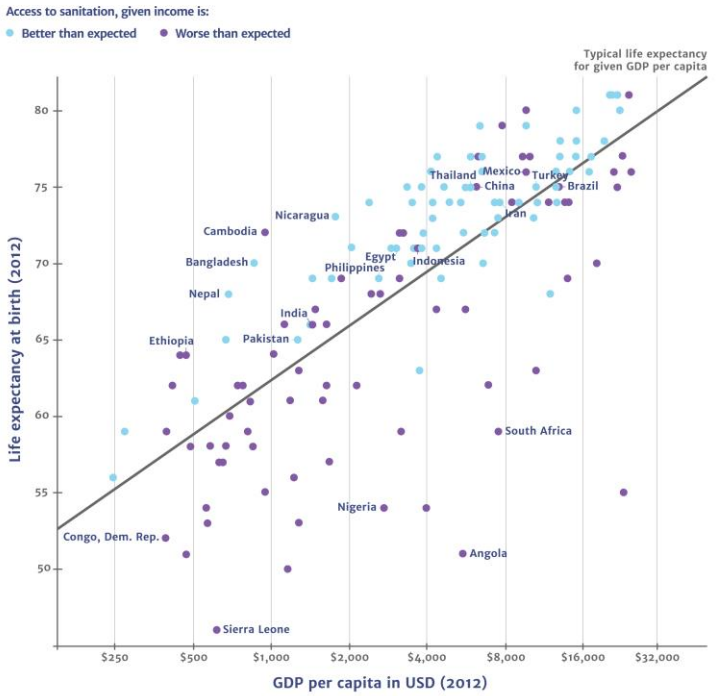
Reduce the number a of viral infections for which antibiotics are unnecessarily given

Proportion of reduction shown is only for illustrative purposes

Review on Antimicrobial Resistance

LIFE EXPECTANCY IS LONGER WHERE THERE IS BETTER SANITATION

Controlling for income, increasing access to sanitation in a country by 50% is correlated with more than nine years of additional life expectancy.



Graph includes all countries with a GDP per capita of less than $25000 for which data was available, high-income countries were excluded as almost all have close to 100% sanitation rates. Sanitation and life expectancy data are from the World Health Organization, income data is from the World Bank and the calculations are the Review's own. Results are statistically significant at 1%, T-value-5.33, p-value- 0.000.

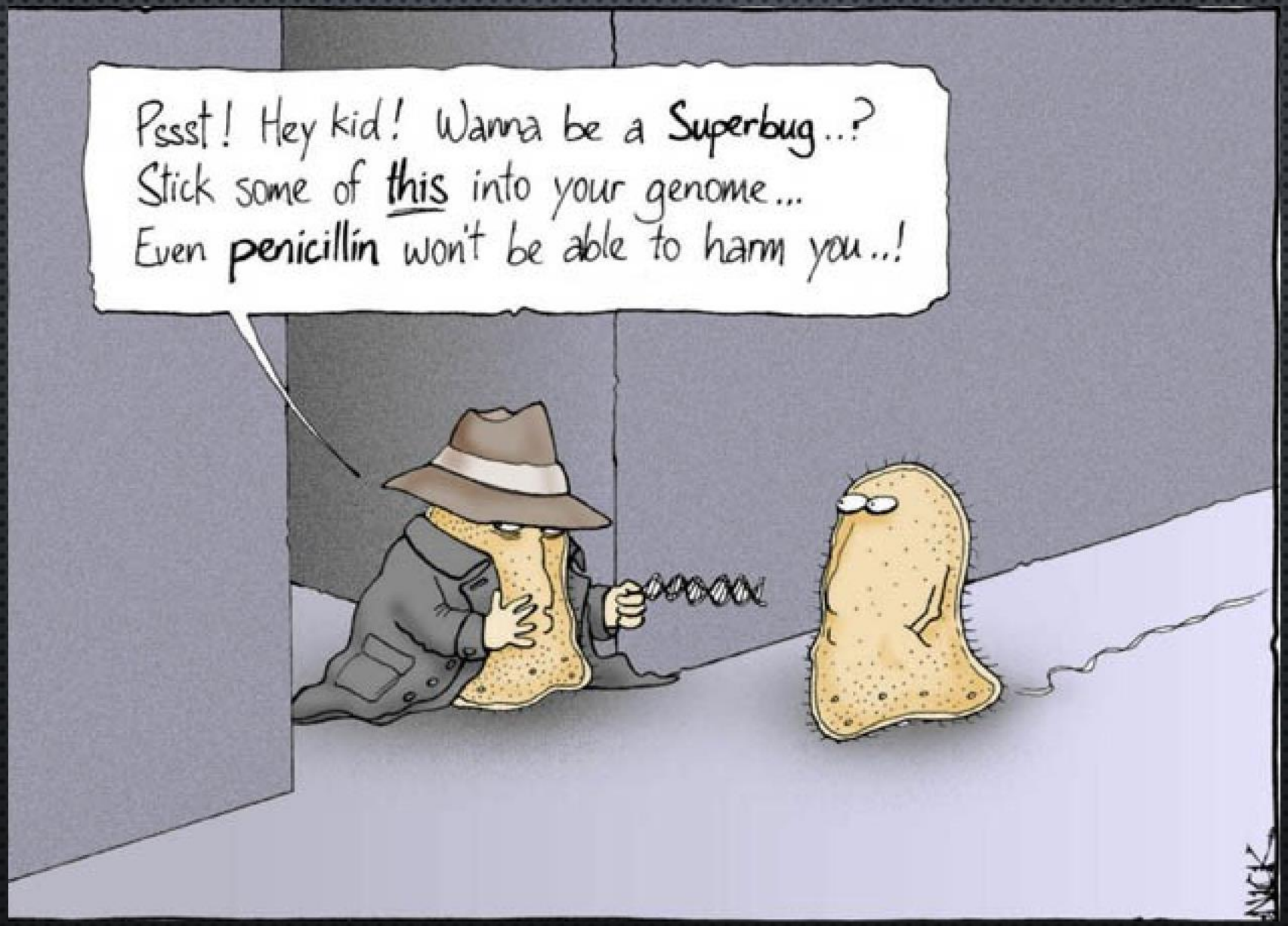
Review on Antimicrobial Resistance

CONCLUSIONS

- At the very least new and potential future AMR initiatives should consider vaccine projects on the same basis as proposals for new antibiotics or diagnostics.
- There should be regular reviews of progress in vaccine development and promotion such that the '***vaccine AMR value***' concept is prominent whenever strategies for combatting AMR are being considered. And there needs to be a similar initiative in livestock production, to consider measures necessary to reduce antibiotic use, including enhanced use of vaccination.

CONCLUSIONS

- Policy makers at national and international level need to be presented with more evidence, underpinned by economic modelling, on the value of vaccines in combatting AMR so that the latter's development and use are encouraged and supported.
- Those responsible for vaccine research, international organisations that support vaccine research and vaccination, and national govern- ments need to be persuaded that investment in vaccines will play a significant role in the reduction of AMR. Researchers and manufacturers need to be offered appropriate incentives, in particular for vaccines that could have a high impact on AMR but where the commercial market prospects are uncertain.


Pssst! Hey kid! Wanna be a Superbug..?
Stick some of this into your genome...
Even penicillin won't be able to harm you..!