Imperial College London

Global burden of bacterial infections: The role of vaccines in reducing AMR

E. David G. McIntosh AM

MBBS MPH LLM PhD FAFPHM FRACP FRCP&CH FFPM DRCOG DCH Dip Pharm Med

Honorary Clinical Senior Lecturer, Imperial College, London UK

Declaration of Interest

- Dr McIntosh is an employee of Takeda Pharmaceuticals International AG, which is developing vaccines against dengue, norovirus, Zika virus, poliomyelitis virus and influenza
- The views expressed herein are the views of Dr McIntosh and do not necessarily reflect the views of Imperial College or Takeda

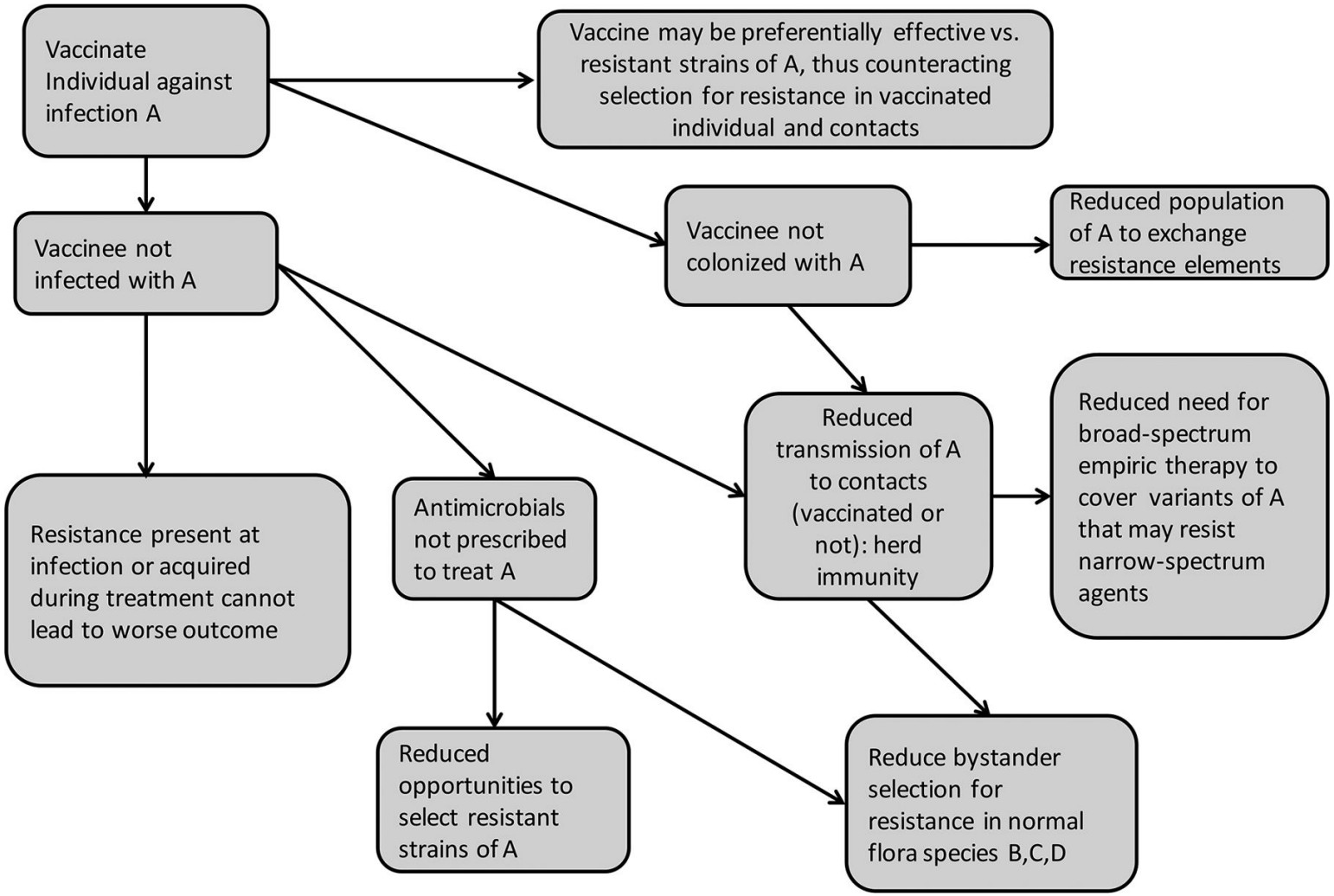
Vaccination is an approach to reducing antimicrobial resistance

“Superbugs”

- Bacteria, viruses, parasites and fungi that are resistant to drugs cause 700,000 deaths each year
- By 2050, such ‘superbugs’, inured to treatments, could cause up to 10 million deaths annually and cost the global economy US$100 trillion

Rappuoli, Bloom, Black. Deploy vaccines to fight superbugs. Nature 2017; 552: 163-167.
http://www.nature.com/articles/d41586-017-08323-0
And Wellcome Trust

Mechanisms by which vaccines can contribute to reducing the prevalence and impact of antimicrobial resistance.



Marc Lipsitch, and George R. Siber mBio 2016; doi: 10.1128/mBio.00428-16

Agenda

- Global burden of bacterial/mycobacterial infections
  - Selected examples
- Prevention versus cure
  - Major features of antibiotics and vaccines
- Vaccines to reduce antibiotic resistance
  - The example of pneumococcal conjugate vaccine
- Even vaccines with relatively low efficacy may be useful
  - *Staphylococcus aureus*
- Viral vaccines also have a role
  - Influenza
- Future approaches

Common clinical conditions for which antibiotic therapy reduces the risk of mortality

Woolhouse *et al*. J Global Health 2016; 6(1): 010306

Category	Condition
Communicable diseases	Tuberculosis
	Sexually-transmitted bacterial infections
	Respiratory bacterial infections (esp. lower respiratory tract)
	Bacterial diarrhoea for which antibiotics are indicated
	Healthcare-associated bacterial infections
Endogenous infections	Urinary tract infections
	Skin and soft tissue infections
	Infective endocarditis
	Sepsis
Prevention of infections	Burns, wounds
	Caesarian Section
	Joint replacements
	Cancer therapy
	Organ transplants

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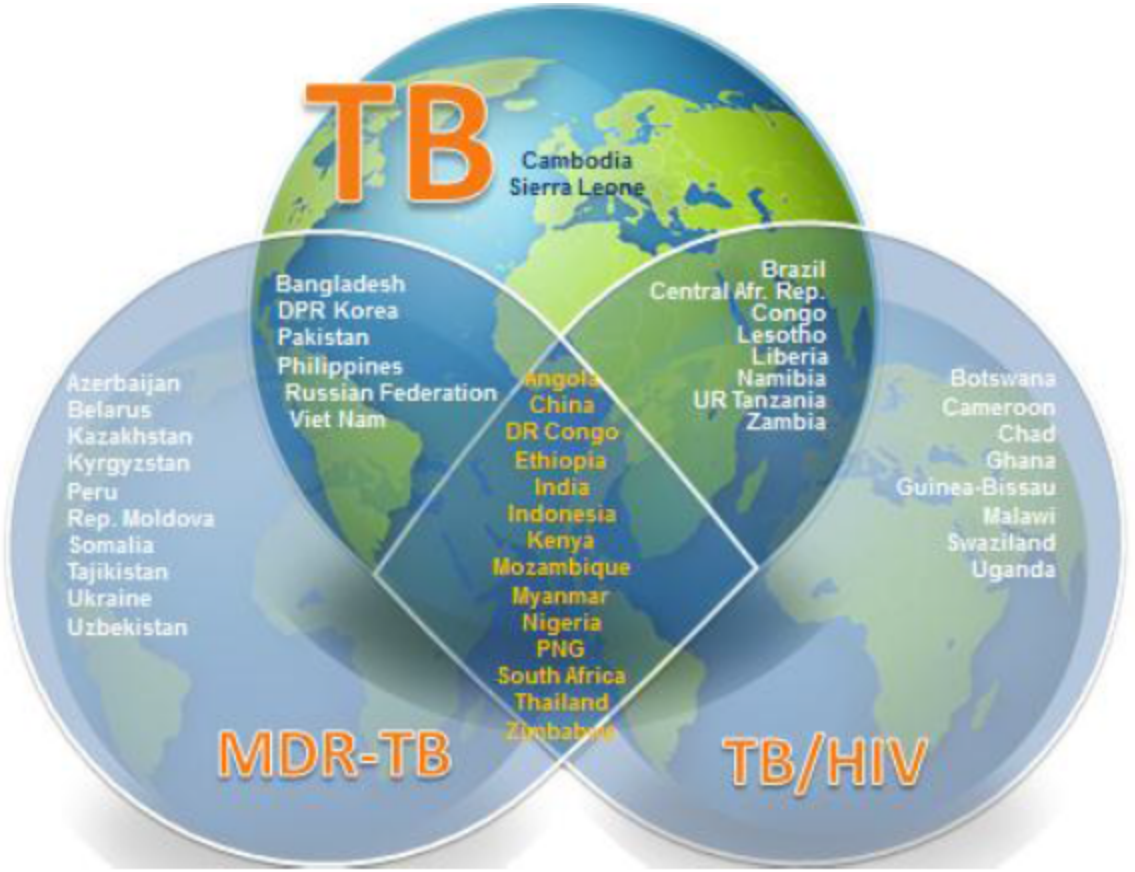
Tuberculosis High Burden Countries (WHO 2016-2020):

10,000 cases per yr of TB; 100 per yr of TB/HIV and MDR-TB



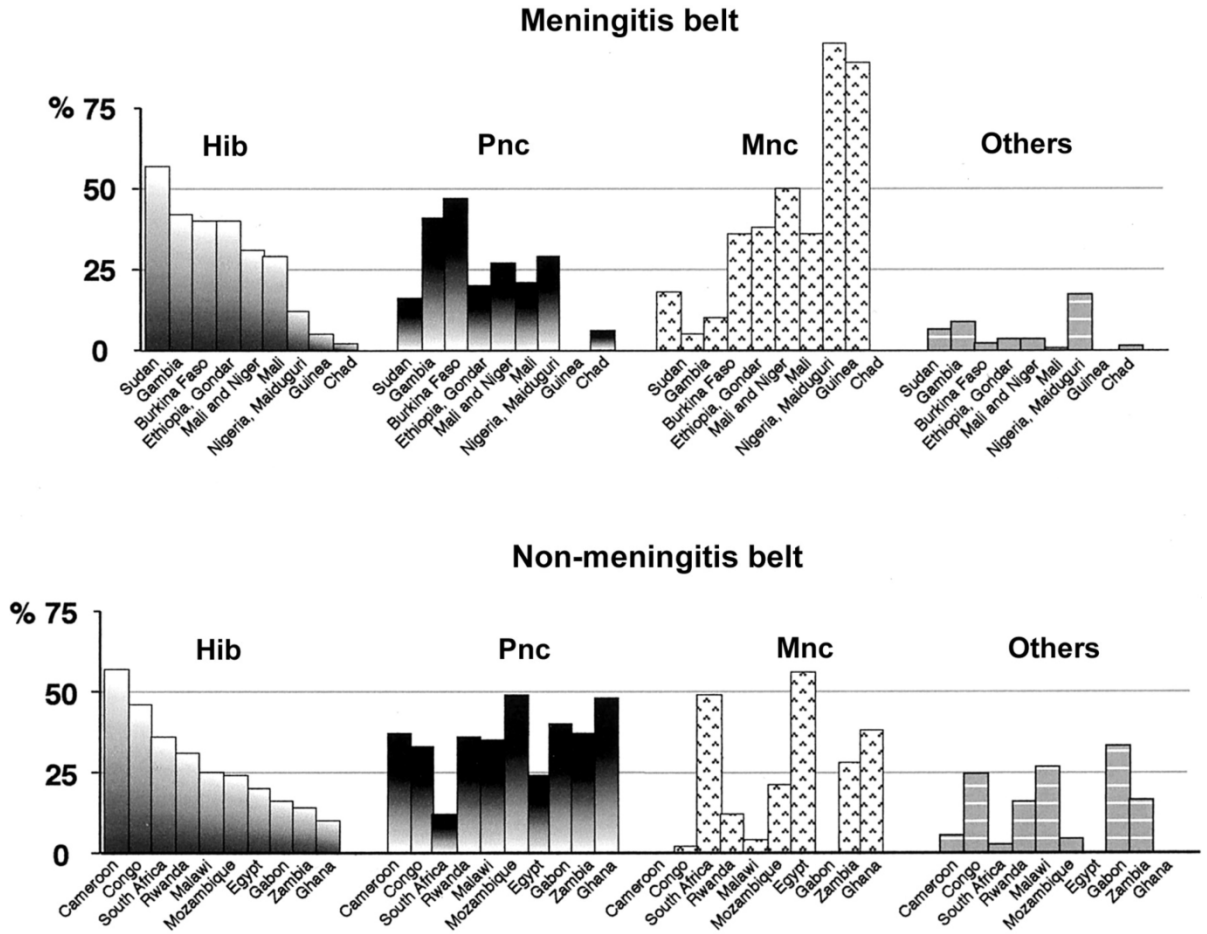
http://www.who.int/tb/publications/global_report/en/

Estimates of the global, regional, and national morbidity, mortality, and aetiologies of *lower respiratory tract infections* in 195 countries: Systematic analysis for the Global Burden of Disease Study 2015 Lancet ID 2017; 17(11): 1133-1161

- Lower respiratory tract infections (LRIs) in 2015 are estimated to have caused:
  - 2·74 million deaths (95% uncertainty interval [UI] 2·50 million to 2·86 million) and
  - 103·0 million DALYs (95% UI 96·1 million to 109·1 million) in 2015
- LRIs have a disproportionate effect on children younger than 5 years, responsible for:
  - 704 000 deaths (95% UI 651 000 to 763 000) and
  - 60.6 million DALYs (95% UI 56·0 to 65·6)
- Between 2005 and 2015, the number of deaths due to LRI decreased by:
  - 36·9% (95% UI 31·6 to 42·0) in children younger than 5 years, and by
  - 3·2% (95% UI −0·4 to 6·9) in all ages
- Pneumococcal pneumonia caused 55·4% of LRI deaths in all ages
  - This equals 1,517,388 deaths (95% UI 857,940 to 2,183,791)

http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(17)30396-1/fulltext

Role of *Haemophilus influenzae*(Hib) , pneumococcus (Pnc) , meningococcus (Mnc) , and other causative agents in childhood meningitis in Africa, among cases of proven etiology



From: Burden of Meningitis and Other Severe Bacterial Infections of Children in Africa: Implications for Prevention. Clin Infect Dis 2001;32(1):64-75. doi:10.1086/317534. Clin Infect Dis © 2001 Infectious Diseases Soc of America
https://academic.oup.com/cid/article/32/1/64/310637

Estimates of global, regional, and national morbidity, mortality, and aetiologies of *diarrhoeal diseases*: Systematic analysis for the Global Burden of Disease Study 2015

- Diarrhoea was estimated to be a leading cause of death among all ages in 2015:
  - 1·31 million deaths (95% uncertainty interval [95% UI] 1·23 million to 1·39 million)
- Also a leading cause of DALYs because of its disproportionate impact on young children
  - 71·59 million DALYs (95% UI 66·44 million to 77·21 million)
- Diarrhoea was a common cause of death among children under 5 years old
  - 499 000 deaths (95% UI 447 000 to 558 000)
  - The number of deaths due to diarrhoea decreased by an estimated 20·8% (95% UI 15·4 to 26·1) from 2005 to 2015
- Leading causes of diarrhoea deaths:
  - Rotavirus (199 000, 95% UI 165 000 to 241 000)
  - *Shigella* spp (164 300, 95% UI 85 000 to 278 700)
  - *Salmonella* spp (90 300, 95% UI 34 100 to 183 100)
- Among children under 5 years old, the three aetiologies responsible for the most deaths were rotavirus, *Cryptosporidium* spp, and *Shigella* spp

http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(17)30276-1/fulltext

Common types of healthcare-associated infections

	Incidence	Notes
Central line-associated bloodstream infections	Death in 12% to 25%	Estimated 30,100 occur in ICU and acute facility wards in the USA each year
Surgical site infections	2% to 5% of surgical patients, but may be as high as 20%	Commonly caused by *Staphylococcus aureus*
Ventilator associated pneumonia	9% to 27% of those on mechanical ventilation	86% of nosocomial pneumonia is associated with ventilation

Khan *et al*. Nosocomial infections: epidemiology, prevention, control and surveillance. Asian Pacific Journal of Tropical Biomedicine 2017; 7(5): 478-482. https://www.sciencedirect.com/science/article/pii/S2221169116309509

Common bacterial pathogens causing healthcare-associated infections

	Notes
Acinetobacter spp.	Accounts for 80% of reported infections in ICU
Bacteroides fragilis	Causes infection when combined with other bacteria
Clostridium difficile	Transmitted from an infected patient to others
Enterobacteriaceae such as *Klebsiella* spp. and *Escherichia coli*	High resistance towards carbapenems
Methicillin-resistant *Staphylococcus aureus*	Causes sepsis, pneumonia, and skin and soft tissue infections

Khan *et al*. Nosocomial infections: epidemiology, prevention, control and surveillance. Asian Pacific Journal of Tropical Biomedicine 2017; 7(5): 478-482. https://www.sciencedirect.com/science/article/pii/S2221169116309509

Major features of antibiotics and vaccines

Relevant Feature	Antibiotics	Vaccines
Therapeutic/prophylactic	Mostly *therapeutic*	Mostly *prophylactic*
Coverage and specificity	Broad, indiscriminate	Narrow, specific
Resistance emergence	Common	Not observed
Selective pressure	High	Low
Time to develop resistant strains	Short	Not observed
Durability	Restricted to the time of treatment	Duration of protection persists from several months to life-long
Treatment/prevention of viral infections	No	Yes
Herd or community effect	No	Yes
Prevention of perinatal infections	Yes	Yes (maternal immunity)
Prevention of cancer	No	Yes (HBV, HPV)
Cost	Few $s to $1000s	Few $s to <$200

Mishra *et al*. Vaccines and antibiotic resistance. Current Opinion in Microbiology 2012; 15 (5): 596 - 602

The use of vaccines to reduce antibiotic resistance

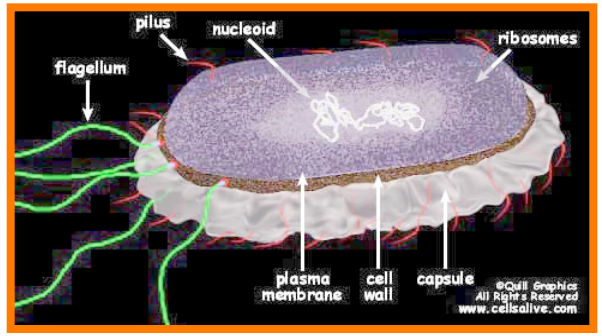
- Vaccines are a key component in the fight against antibiotic resistance both directly and indirectly
- By targeting bacterial pathogens, vaccines directly reduce the need for the use of antibiotics
- However, even vaccines created against non-bacterial pathogens can also have an indirect effect on 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
- One of the best documented examples of this effect is the use of pneumococcal conjugate vaccine (PCV) that targets the most virulent, serotypes linked to invasive pneumococcal disease (IPD) and that are also associated with antibiotic resistance

Streptococcus pneumoniae

Pneumococcal vaccine development

Vaccine development takes more than a few years – technology is not the only bottle neck

R & D Goes on



2009 – 10-valent/13-valent conjugate vaccine

2001

1983 – 7-valent PS conjugate vaccine licensed

1977 – 23-valent plain PS vaccine licensed

1946 – 14-valent plain PS vaccine licensed

1930 – 6-valent plain PS vaccine licensed, withdrawn within a few years because penicillin treatment was preferred

1887 – Purified capsular polysaccharides (PS) shown to be immunogenic in humans

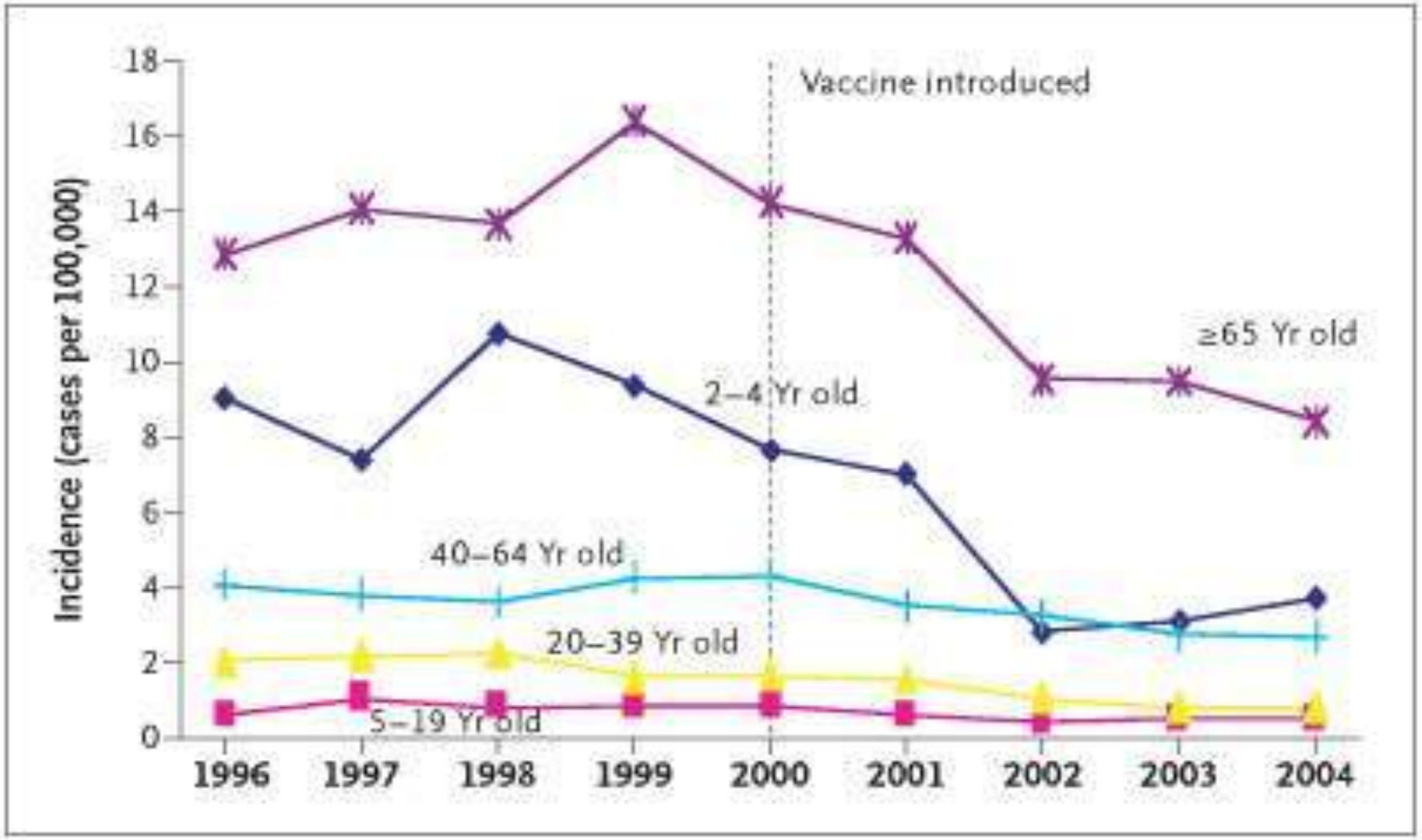
1881 – Distinct serotypes demonstrated

Diplococcus pneumoniae first isolated and grown in vitro

Pneumococcal vaccines

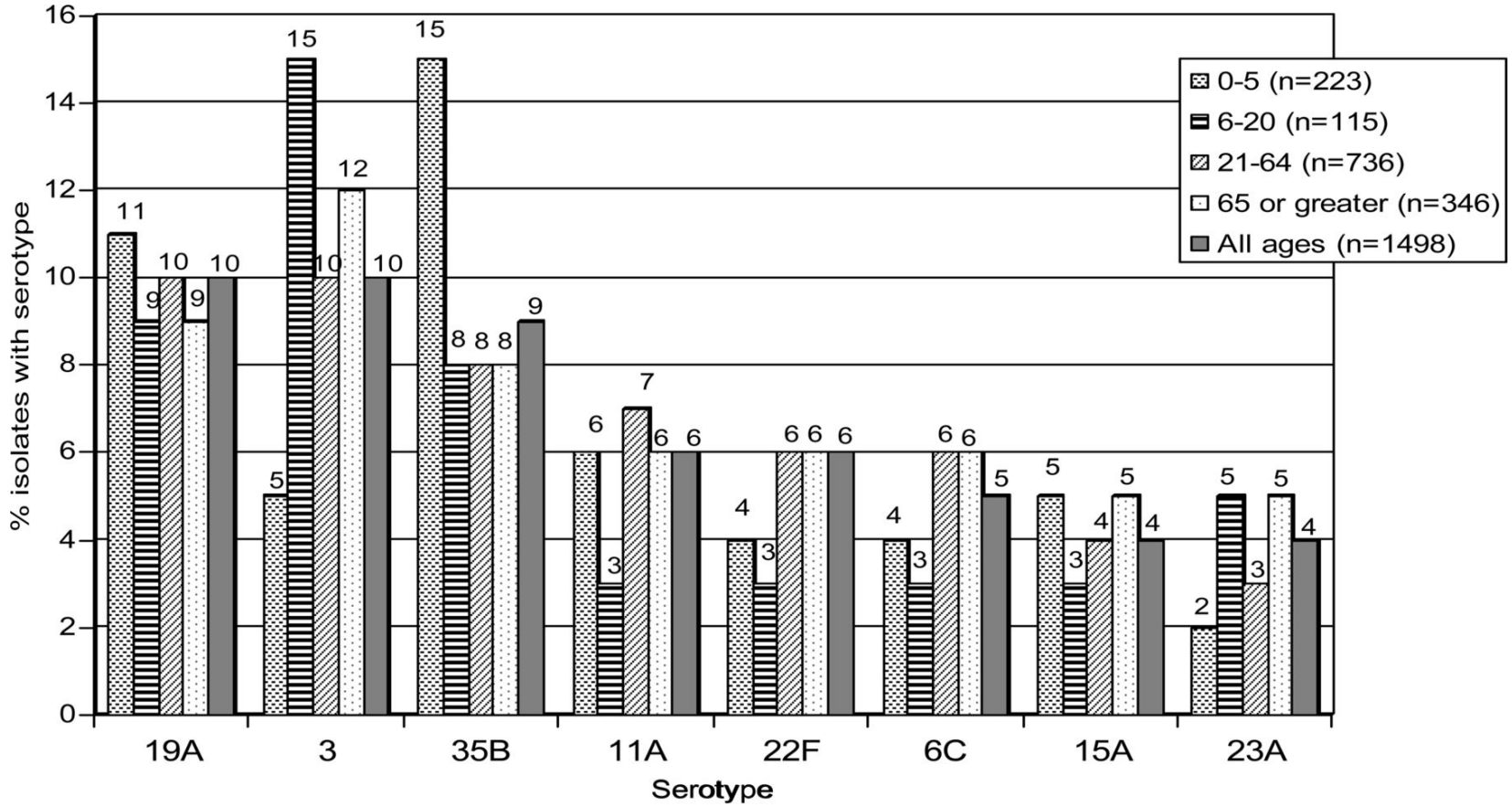
- Plain pneumococcal polysaccharide vaccine
  - First U.S. vaccine in 1946 (hexavalent)
  - 23-valent version introduced in 1983 with good efficacy in prevention of invasive pneumococcal disease but inconsistent data relating to efficacy against pneumococcal pneumonia
- Pneumococcal conjugate vaccines (PCV)
  - 7-valent PCV introduced in 2000-2001 for infants/children
  - 10-valent PCV licensed in 2008 in Europe and elsewhere
  - 13-valent PCV introduced in 2010 in infants/children

Penicillin resistance children *over* two *and adults*
Impact of pneumococcal conjugate vaccine



Kyaw *et al*, NEJM 2006; 354:1455-63

Distribution of predominant serotypes by patient age for 1,498 pneumococcal isolates recovered in 2012-13 in the USA



The change in prevalence of PCV13 serotypes (43.4 to 27.1%) was primarily due to a decrease in serotype 19A strains, i.e., 22% of all strains in 2008-09 to 10% of all strains in 2012-13.

Sandra S. Richter et al. Antimicrob. Agents Chemother. 2014;58:6484-6489

Antimicrobial Agents and Chemotherapy

Antimicrobial susceptibility data of pneumococcal isolates from Cambodia according to vaccine coverage of serotypes

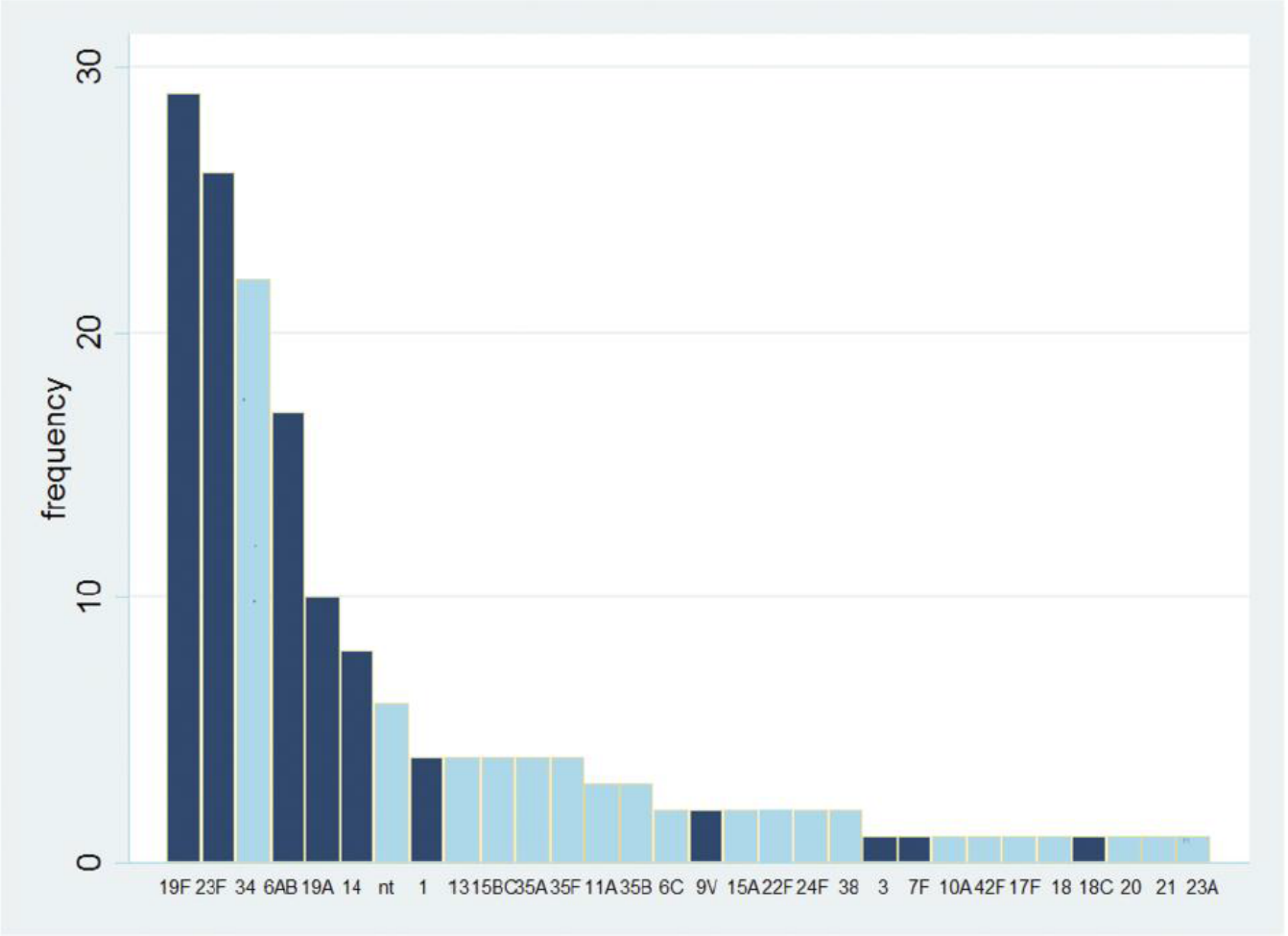
	Overall *N* (%)	PCV13 isolates *N* (%)	Non-vaccine isolates *N* (%)	*P* value
Penicillin G*				0.02
Susceptible	95 (58)	50 (51)	45 (68)	
Amoxicillin†				0.31
Susceptible	127 (93)	68 (91)	59 (95)	
Ceftriaxone‡				0.10
Susceptible	149 (94)	87 (93)	62 (98)	
Cotrimoxazole§				0.005
Susceptible	15 (9)	4 (4)	11 (17)	
Erythromycin‖				0.006
Susceptible	81 (49)	40 (40)	41 (62)	

22% of study subjects 0 to 15 yrs; 61% 16 to 65 yrs; 17% >65 yrs

Inghammar *et al*. Serotype distribution of clinical *Streptococcus pneumoniae* isolates before the introduction of the 13-valent pneumococcal conjugate vaccine (PCV13) in Cambodia. Am J Tropical Medicine and Hygiene Jan 2018.

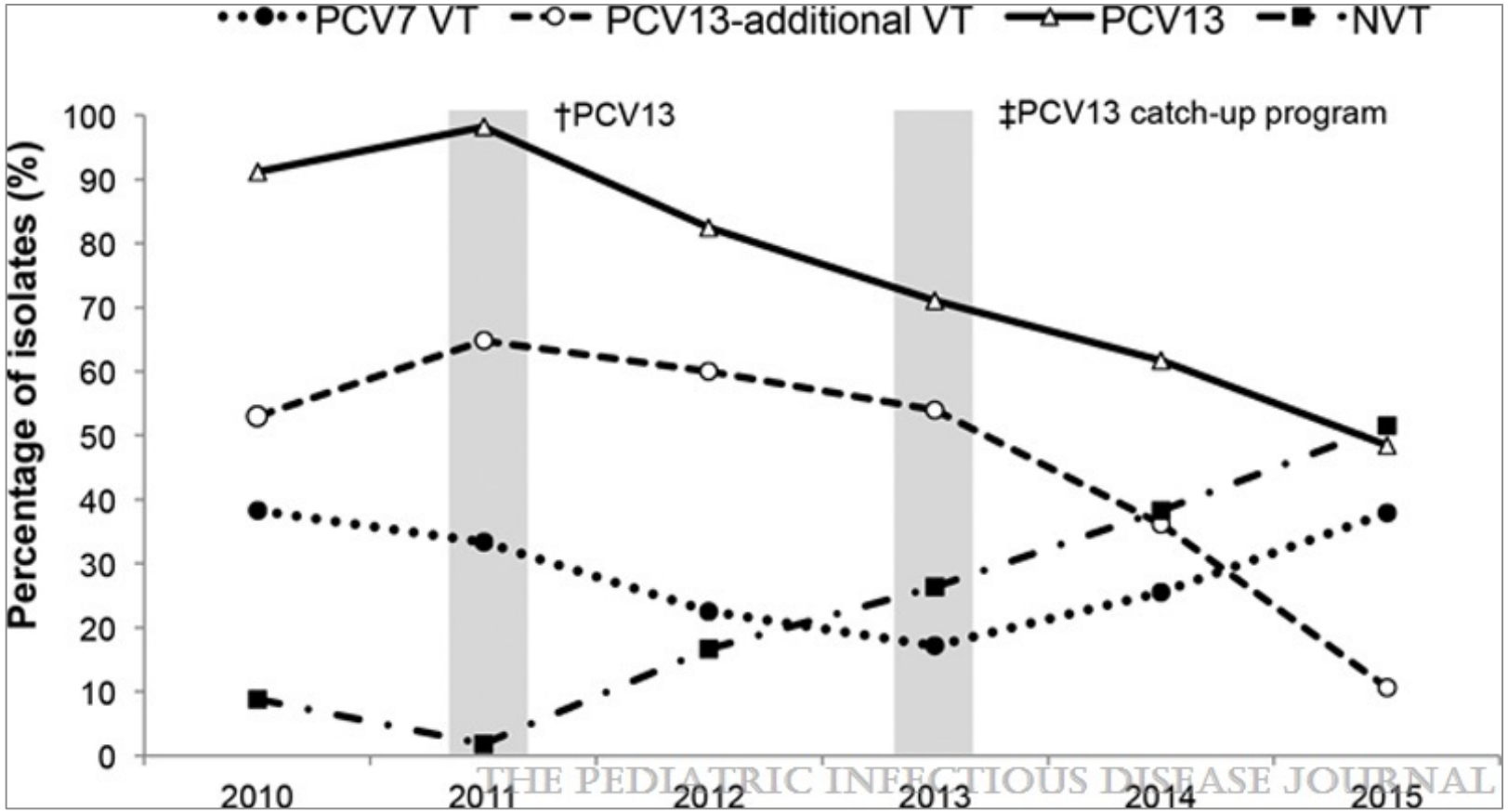
Serotype distribution of 166 isolates cultured from samples collected from 2006 to 2014 in Cambodia.

Serotypes included in PCV13 are shaded in dark



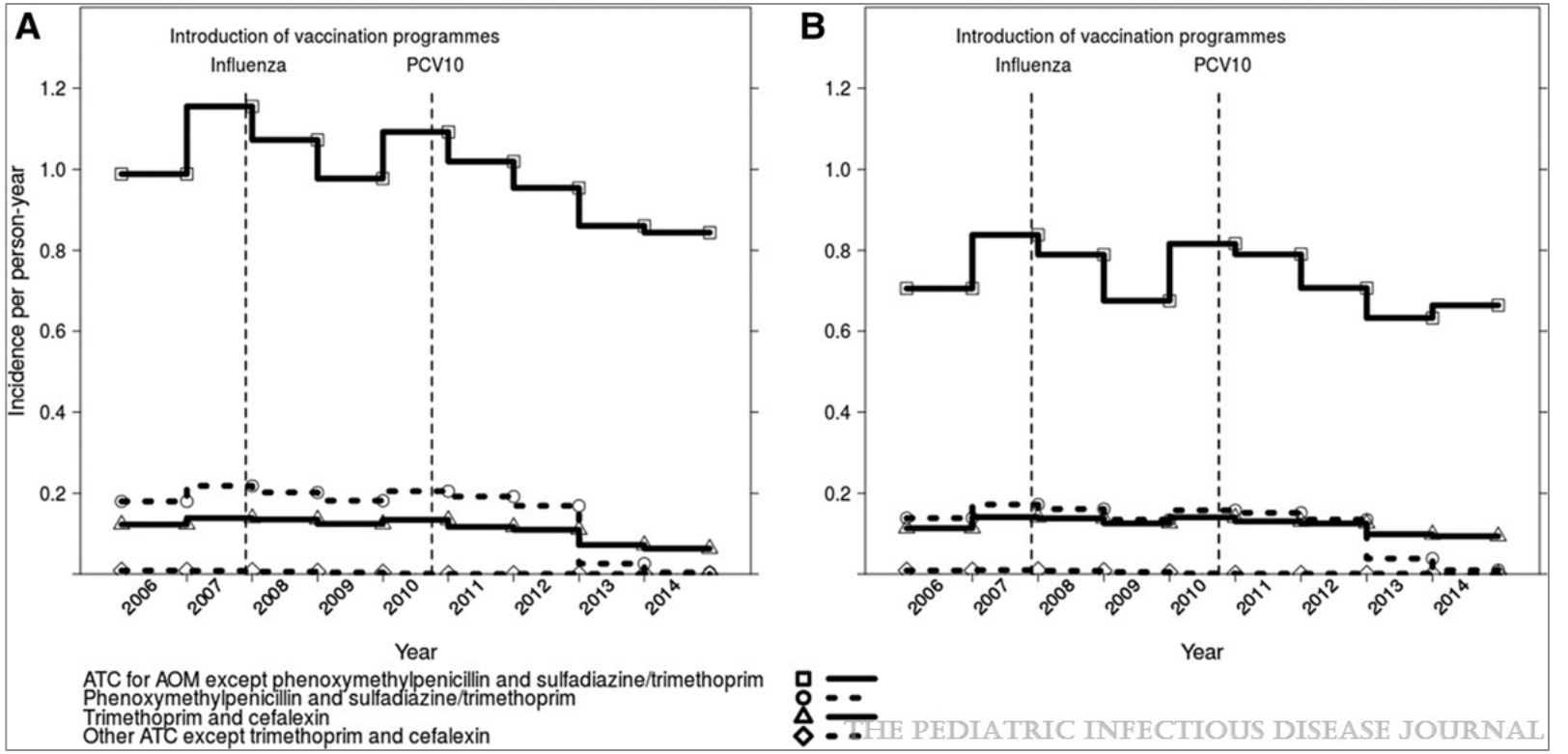
Inghammar *et al*. Serotype distribution of clinical *Streptococcus pneumoniae* isolates before the introduction of the 13-valent pneumococcal conjugate vaccine (PCV13) in Cambodia. Am J Tropical Medicine and Hygiene Jan 2018.

Proportion of serotypes belonging to either PCV7 vaccine serotypes (VT), PCV13 VT or NVT. †PCV13 was introduced in the private market in April 2011
‡PCV13 catch-up program was started in March 2013



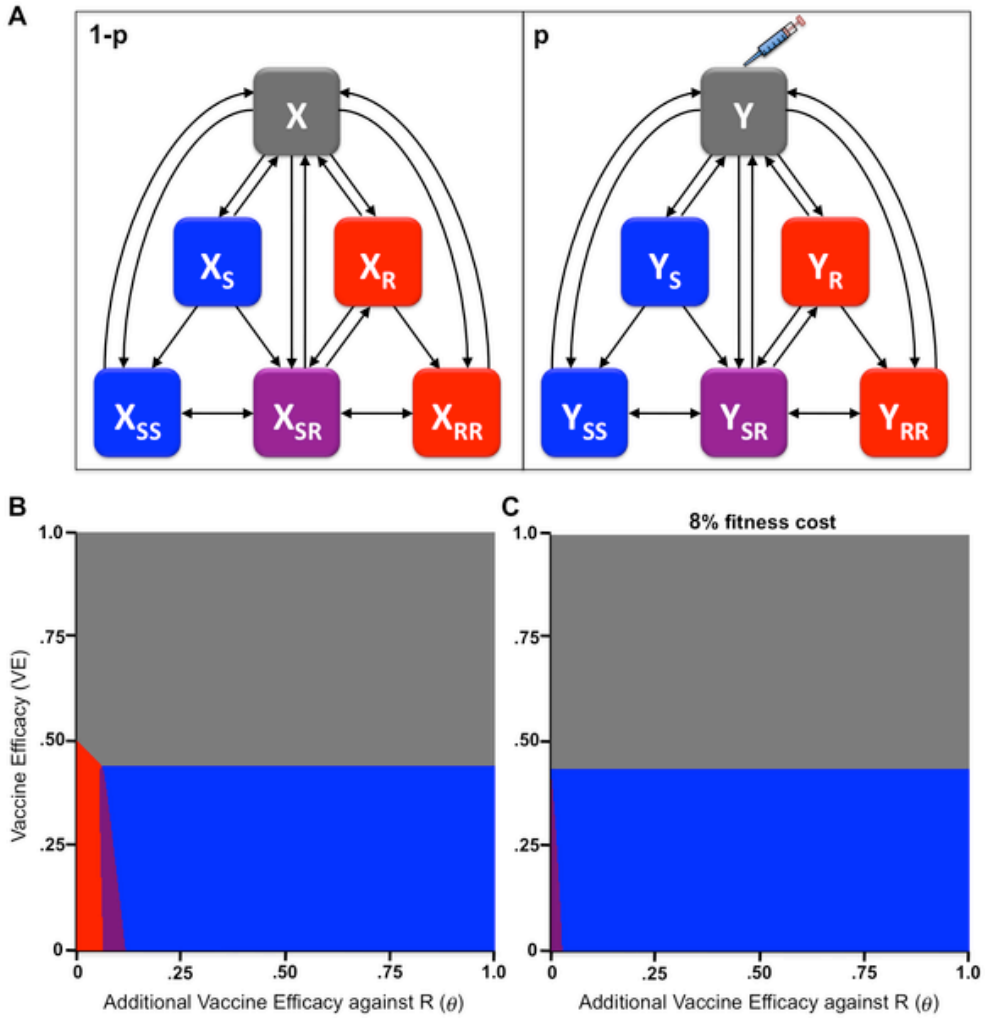
Cho *et al*. Redistribution of *Streptococcus pneumoniae* serotypes after nationwide 13-valent PCV programme in Children in Northern Taiwan. Pediatr Infect Dis J 2017; 36(12): e334-e340. December 2017

Marked decrease in incidence rates of outpatient antimicrobial purchases among all children per calendar years 2006 through 2014 (A) and 2- to 4-year old children (B). ATC codes with cessation of reimbursement 2013–2014 are shown separately. The line widths correspond to the 95% CIs.



Palmu *et al*. Impact of national ten-valent pneumococcal conjugate vaccine program on reducing antimicrobial use and tympanostomy tube placements in Finland. Pediatr Infect Dis J 2018; 37(1): 97-102

Modeling a vaccine with increased efficacy against drug-resistance determinants for an endemic colonizing pathogen (*S. pneumoniae*).



Joice R, Lipsitch M (2013) Targeting Imperfect Vaccines against Drug-Resistance Determinants: A Strategy for Countering the Rise of Drug Resistance. PLoS ONE 8(7): e68940. doi:10.1371/journal.pone.0068940
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0068940

PLOS | ONE

Jauneikaite *et al*. Nosocomial outbreak of drug-resistant *Streptococcus pneumoniae* serotype 9V in an adult respiratory medicine ward (in the UK)
J Clin Microbiol 2017; 55(3): 776-782

- *Streptococcus pneumoniae* infections arising in hospitalized patients are often assumed to be sporadic and linked to community acquisition. Here, whole-genome sequencing was used to demonstrate nosocomial acquisition of antimicrobial-resistant sequence type 156 (ST156) serotype 9V *S. pneumoniae* in 3 respiratory patients that resulted in two bacteremias and one lower respiratory tract infection
- Two of the cases arose in patients who had recently been discharged from the hospital and were readmitted from the community
- Nosocomial spread was suspected solely because of the highly unusual resistance pattern and case presentations within 24 h of one another. The outbreak highlights the potential for rapid transmission and the short incubation period in the respiratory ward setting
- Note: serotype 9V covered by 13-valent PCV

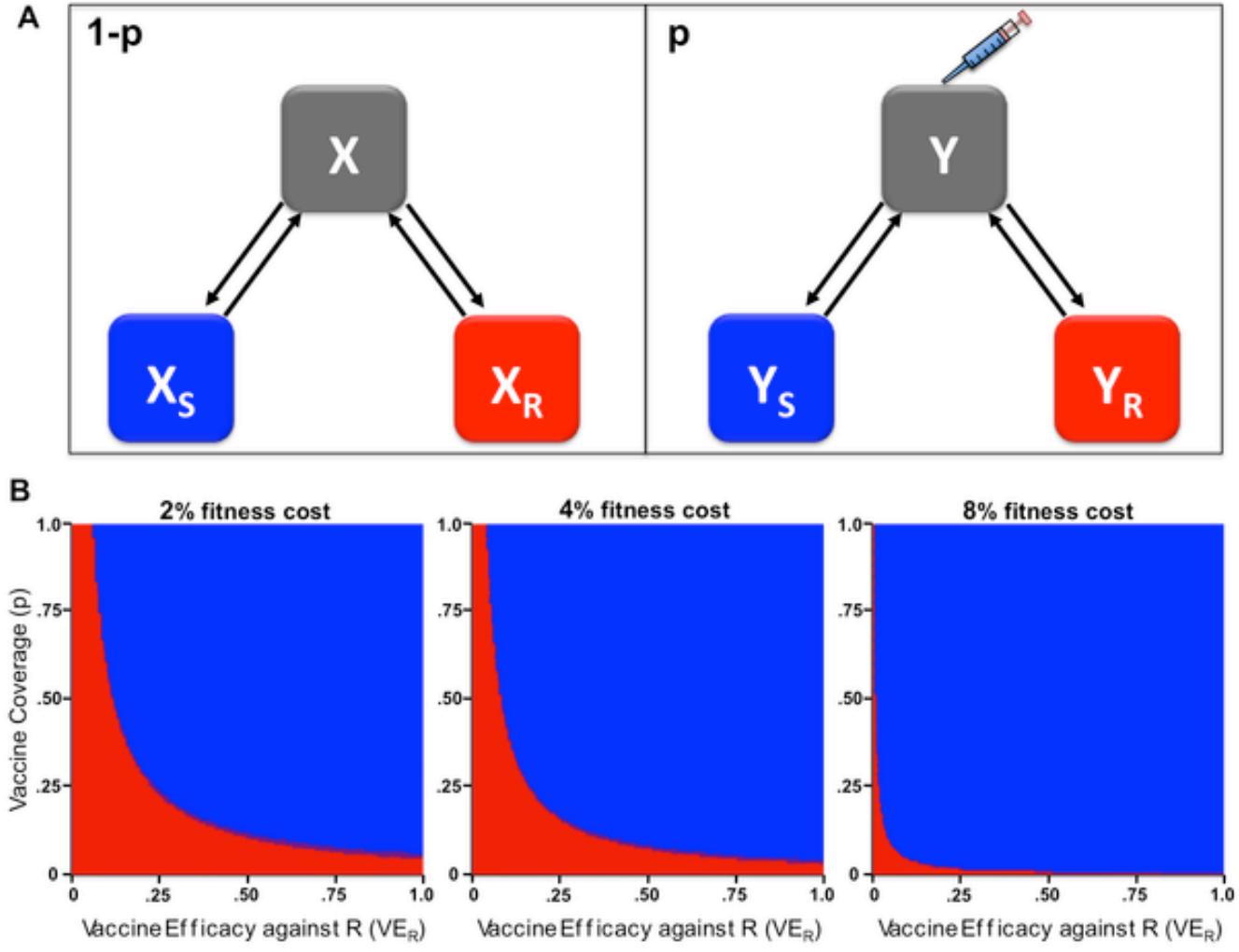
Staphylococcus aureus

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
- 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

Modeling a vaccine against drug-resistance determinants for an endemic colonizing pathogen for which no vaccine currently exists (*S. aureus*).



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

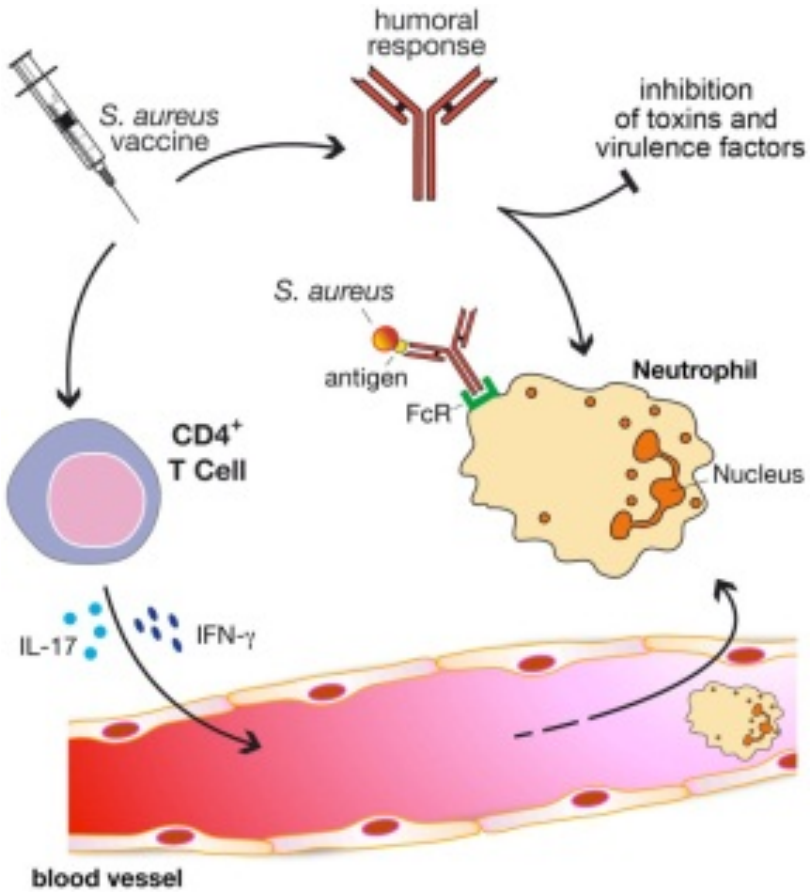
PLOS | ONE

Bagnoli *et al*. Inferring reasons for the failure of *S. aureus* vaccines in clinical trials. Cell Infect Microbiol 2012

- There are several potential reasons behind the disappointing results of *S. aureus* vaccine clinical trials. Some, which are common to all the trials, determined their downfall
  - First of all, preclinical results obtained with antigens tested in clinical trials were likely overestimated by vaccine manufacturers
  - Furthermore, vaccines tested in humans to date, since they all targeted single antigens, were probably disproportionate to the complex pathogenic mechanisms of the bacterium
  - In addition, the lack of known correlates of protection in humans has severely limited the ability to interpret both preclinical and clinical data
  - Finally, the vaccines did not contain new generation adjuvants, which may be critical in augmenting antibody production and steering the T-cell response toward the proper profile of cytokine production

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3417391/

A model to generate protective immunity against *S. aureus* infections through vaccination (Bagnoli *et al*. 2012)



Protective vaccines should be able to elicit three major immune responses:
(i) antibodies to directly inhibit bacterial viability and/or toxicity;
(ii) antibodies to mediate opsonophagocytosis; and
(iii) cell-mediated immunity to stimulate recruitment of phagocytes (eg neutrophils) at site of infection

Staphylococcus aureus antigens tested in clinical trials

Antigen	Vaccine	Sponsor	Clinical phase
Toxins			
LukS-PV	*S. aureus* Toxoids	USUHS[a]	I
α-hemolysin	4C-Staph, GSK2392, *S. aureus* Toxoids	USUHS, Novartis, GSK	I
Enterotoxin B	STEBvax	NIAID[b]	I
Adhesion factors			
ClfA	SA3Ag, SA4Ag, GSK2392	Pfizer, GSK	I, II, IIb
Als3	NDV-3	NovaDigm	I
Nutrient-scavenging factors			
IsdB	V710	Merck	I, II, III
MntC	SA4Ag	Pfizer	I, II, IIb
FhuD2	4C-Staph	Novartis	I
Capsular polysaccharides			
CP5 and CP8	SA3Ag, SA4Ag, GSK2392, StaphVAX	Pfizer, GSK, NABI	I, II, III
Antigens with other/unknown function			
EsxA and EsxB	4C-Staph	Novartis	I
Csa1A	4C-Staph	Novartis	I

LukS-PV Panton–Valentine leukocidin component *S*; *ClfA* clumping factor A; *Als3* agglutinin-like sequence protein 3 (from Candida albicans); *IsdB* iron-regulated surface determinant protein B; *MntC* manganese transport protein C; *FhuD2* ferric hydroxamate uptake D2; *CP* capsular polysaccharide; *Esx* ess extracellular; *CSA* conserved staphylococcal antigen

[a]Uniformed Services University of the Health Sciences

[b]National Institute of Allergy and Infectious Diseases

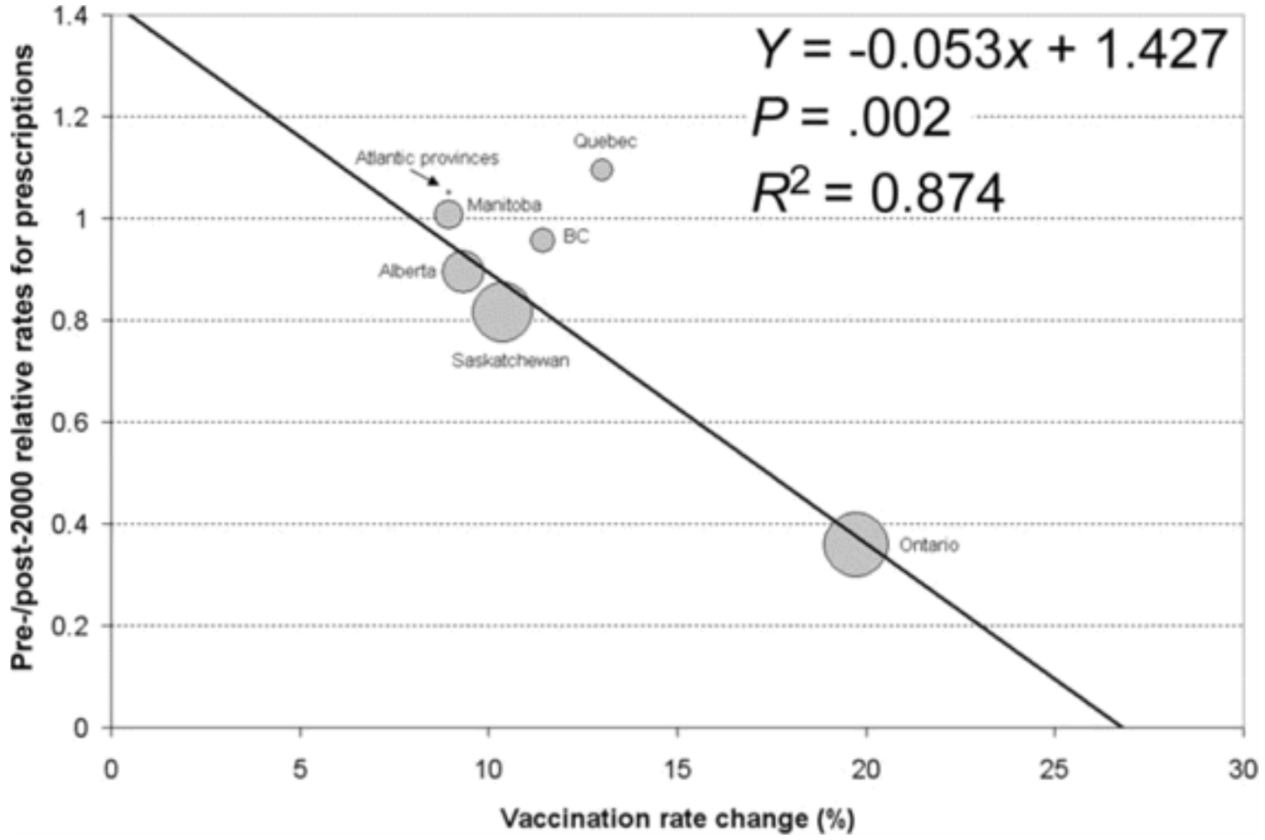
Influenza

Influenza vaccination

- Influenza results in ~200,000 hospitalisations/yr in the USA
- By preventing some of these, influenza vaccines reduce both appropriate and inappropriate antimicrobial prescribing
- It is estimated that in the USA, one third of antibiotic prescriptions in ambulatory care are *inappropriate*, with a large proportion of inappropriate prescribing attributable to acute respiratory infections, some of which are likely to have been caused by influenza of other viruses
- Moreover, influenza vaccination can also prevent cases of influenza that would have otherwise led to secondary bacterial infections requiring (appropriate) antibiotic treatment

Lipsitch and Siber 2017. http://mbio.asm.org/content/7/3/e00428-16.full

Dose-response relationship between change in respiratory antibiotic prescriptions and influenza vaccination rate in Canada. Vertical axis: respiratory antibiotic prescriptions; horizontal axis: absolute change in influenza vaccination rate for the household population aged ⩽12 years from 1996–1997 to the mean during the post-2000 period



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

Future vaccination to target

- Healthcare-associated infections
  - For example: *Clostridium difficile*
- Antimicrobial resistant organisms
  - For example: *K. pneumoniae*, *E. coli*, MRSA and *A. baumannii*
- Viral vaccines
  - For example: respiratory syncytial virus

Conclusions

- Antibiotics differ from vaccines in many ways
- Evidence that vaccines have contributed in a positive way to antibiotic prescribing and to antimicrobial resistance
- Even vaccines with relatively low efficacy may be useful
- New approaches needed, such as a better understanding of immune responses, adjuvants and reverse vaccinology