The value that vaccines bring in the AMR fight and why new-generation antibiotics alone cannot resolve the AMR crisis

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14th December 2023

Aims

Introduce BactiVac

Risk of infection in the context of age and “immune function/status”

Interventions to control infection

The differences between antimicrobial and vaccine use and the concept of resistance

The evidence that vaccines reduce antimicrobial use in children and adults

Gaps and needs

Open for discussion

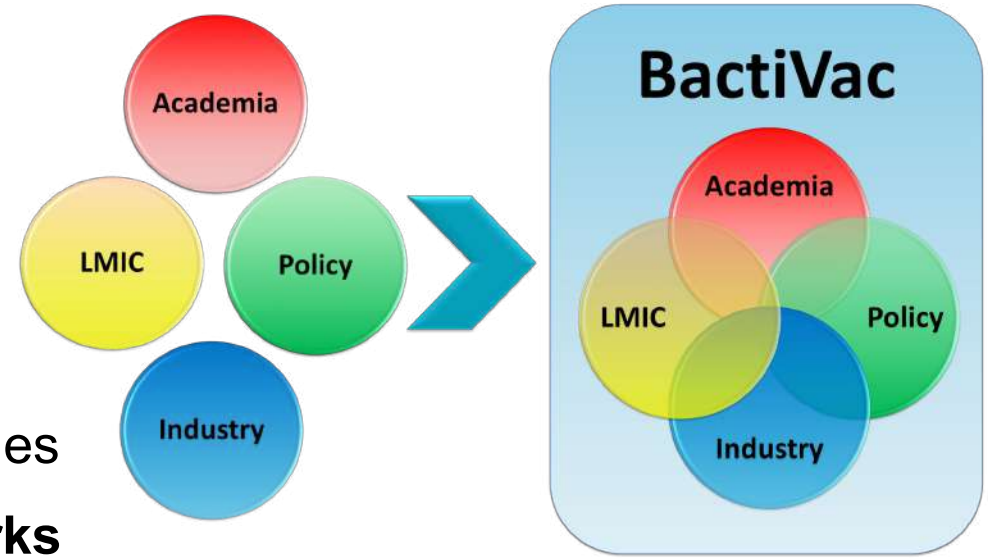
The evidence for this is taken from EU, UK, US and other global sources

BactiVac: what is our mission?

Accelerating the development of vaccines

against bacterial infections relevant to Low Middle Income Countries

- >8 million deaths yearly from bacterial infections
- Focus on bacterial vaccines - >1700 members
- Catalyst project and training funding
- Attract investment/leverage funding
- Advocacy for the development of bacterial vaccines
- **Partnership & collaboration with other networks**
- **Engagement & interaction with industry**



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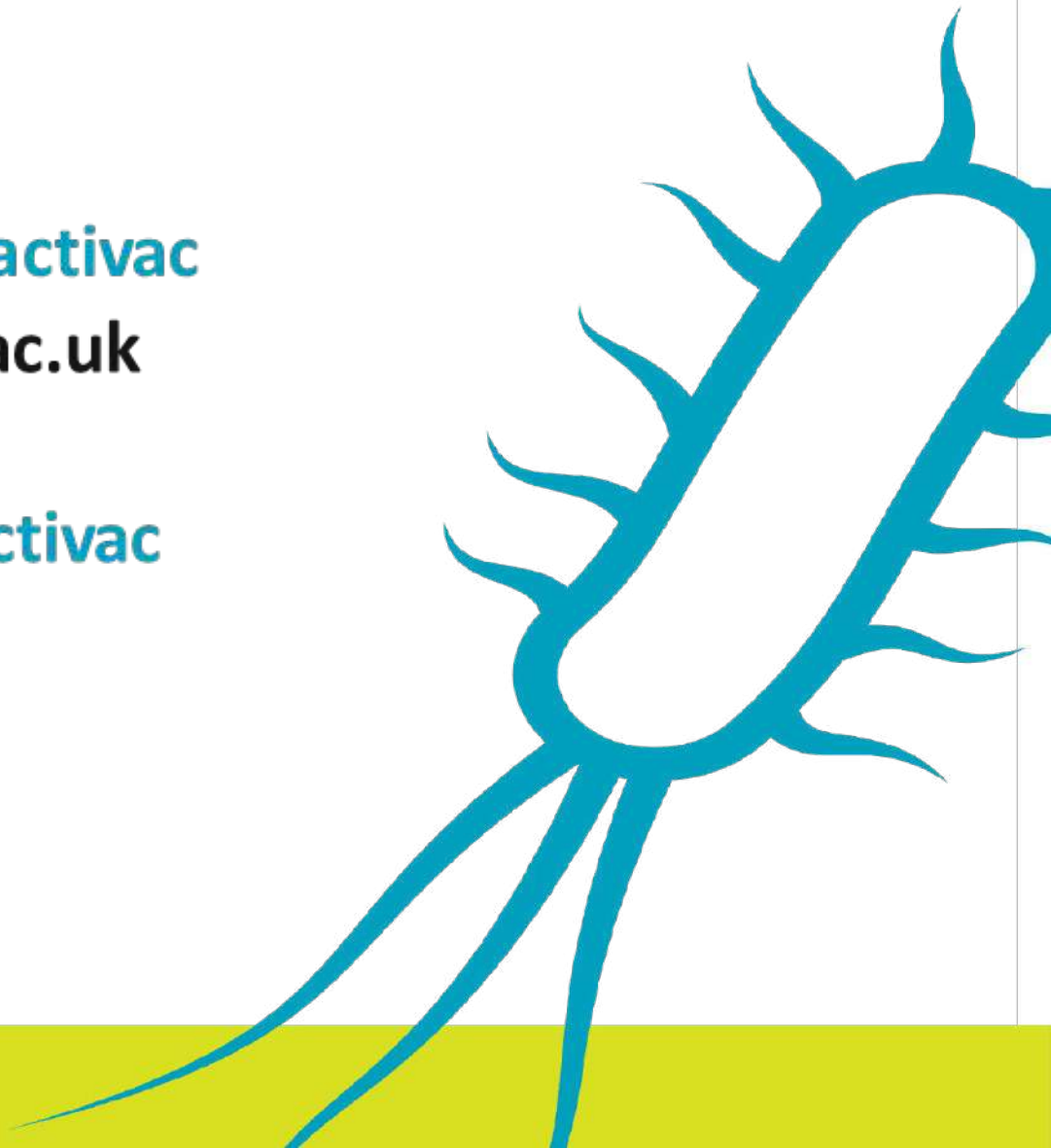


Infectious disease was a major contributor to total deaths during wars until recently

TABLE 2.—*Deaths from disease and battle deaths in principal wars, foreign armies and U. S. Army, 1846–1945*

War	Date	Deaths from-		Ratio of deaths from disease to deaths from battle injuries and wounds
			Battle injuries and wounds [1]	
Mexican War (United States)	25 Apr. 1846–5 July 1848.	11, 155	1, 721	6. 48:1
Crimean War (French)	1854–56	70, 000	7, 500	9. 33:1
Civil War (North)	15 Apr. 1861–1 Aug. 1865.	[3] 199, 720	138, 154	1. 45:1
Danish War	1864			
German		310	738	. 42:1
Danish		[illegible]	[illegible]	[illegible]
German War (German)	1866	5, 219	4, 008	1. 30:1
Franco-Prussian War (German)	1870–71	14, 904	17, 225	. 86:1
Russo-Turkish War	1877–78	80, 000	20, 000	4. 00:1
Sino-Japanese War (Japanese)	1894–95	15, 850	1, 311	12. 09:1
Spanish-American War	1 May 1898–31 Aug. 1898	1, 939	369	5. 25:1
Philippine Insurrection	[illegible]	[illegible]	[illegible]	[illegible]
	cember 1902.			
Boer War (British)	1899–1901	11, 377	6, 425	1. 77:1
War in Southwest Africa (German)	1904–7	689	802	. 86:1
Russo-Japanese War	1904–5			
Japanese		[illegible]	[illegible]	[illegible]
Russian, less Port Arthur		[illegible]	[illegible]	[illegible]
World War I	1 Apr. 1917–31 Dec. 1918.			
Total United States Army		51, 447	[4] 50, 510	1. 02:1
American Expeditionary Forces.		[illegible]	[illegible]	[illegible]
World War II	7 Dec. 1941–31 Dec. 1945.			
Total United States Army		15, 779	234, 874	. 07:1
United States Army in Europe		1, 779	135, 576	. 01:1

Disease 70 000 Fighting 7 500

Disease 199 000 Fighting 138 000

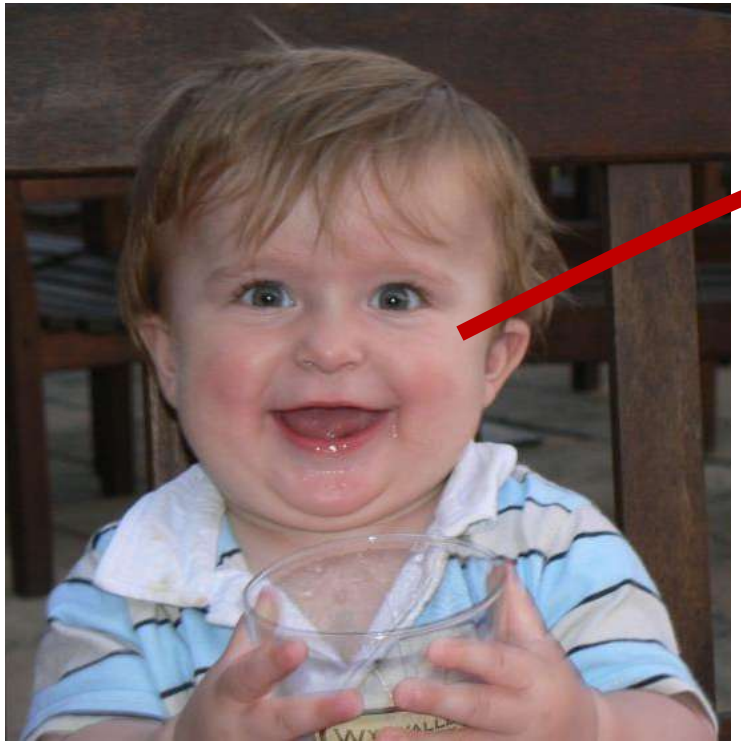
Disease 15 000 Fighting 17 000

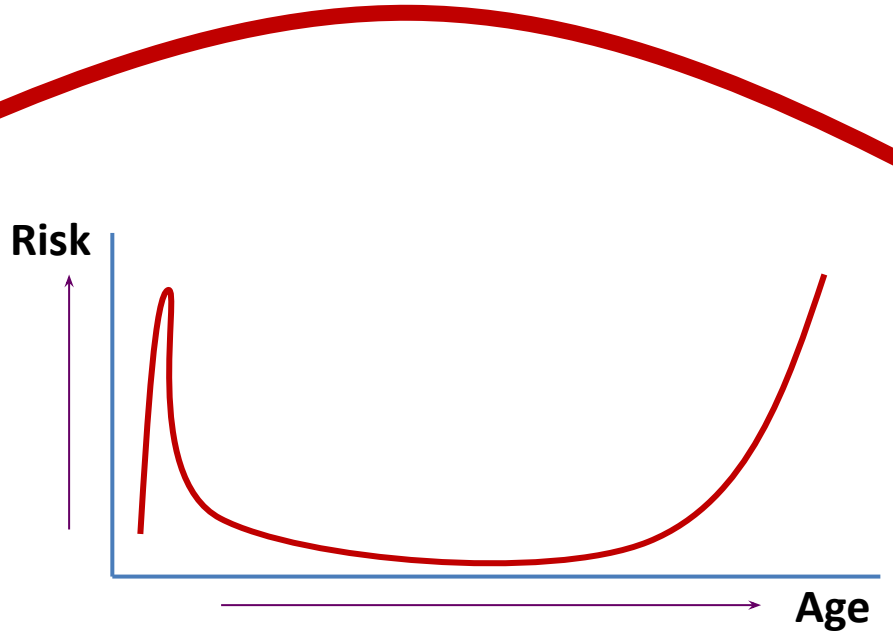
Disease 16 000 Fighting 1 000

Disease 51 000 Fighting 50 000

Disease 16 000 Fighting 235 000

The extremes of age are when we are most at risk from infection





‘Blank canvas’

‘Immunologically experienced’

Bacterial infections are a leading cause of death

Antimicrobial Resistance (AMR) and a lack of vaccines, and their use, contribute to this

7.7 million deaths associated with 33 bacterial pathogens
1 in 7 of all deaths globally
2nd leading cause of death globally in 2019

Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019

*GBD 2019 Antimicrobial Resistance Collaborators**

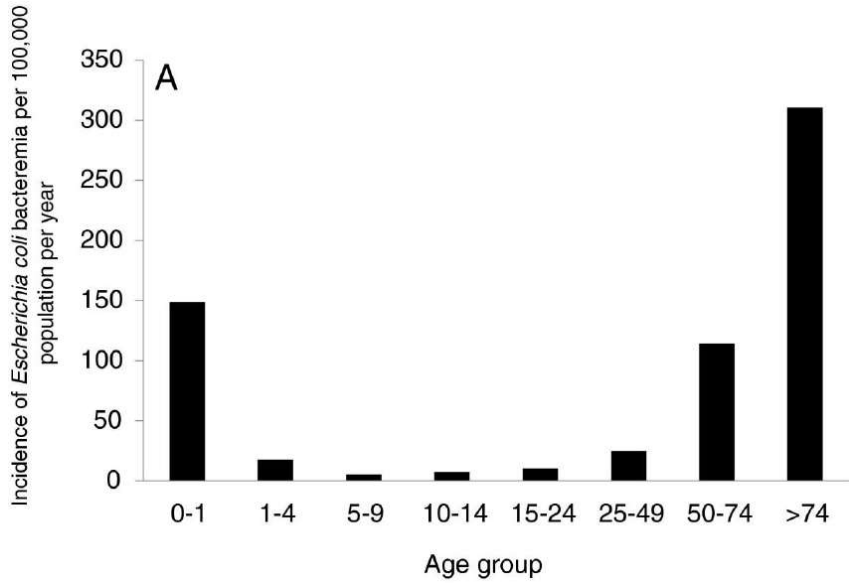
4.95 million deaths associated with AMR
1.27 million deaths attributable to AMR

Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis

*Antimicrobial Resistance Collaborators**

Age and poorer health (co-morbidities) can combine to amplify risk

Incidence of *Escherichia coli* bloodstream infection by age



Auckland District Health Board, New Zealand, 2005 – 2011.
Williamson DA et al. BMC Infect Dis 13, 385 (2013). https://doi.org/10.1186/1471-2334-13-385

Approximate Relative risk

	Type 1 Diabetes	Type 2 Diabetes
Bone/joint infections	22	5
Endocarditis (Heart)	7	2
Meningitis	6	2
Pneumonia	3	2
Sepsis	6	2
Death from infections	8	2

Adapted from Iain Carey et al Diabetes Care 2018

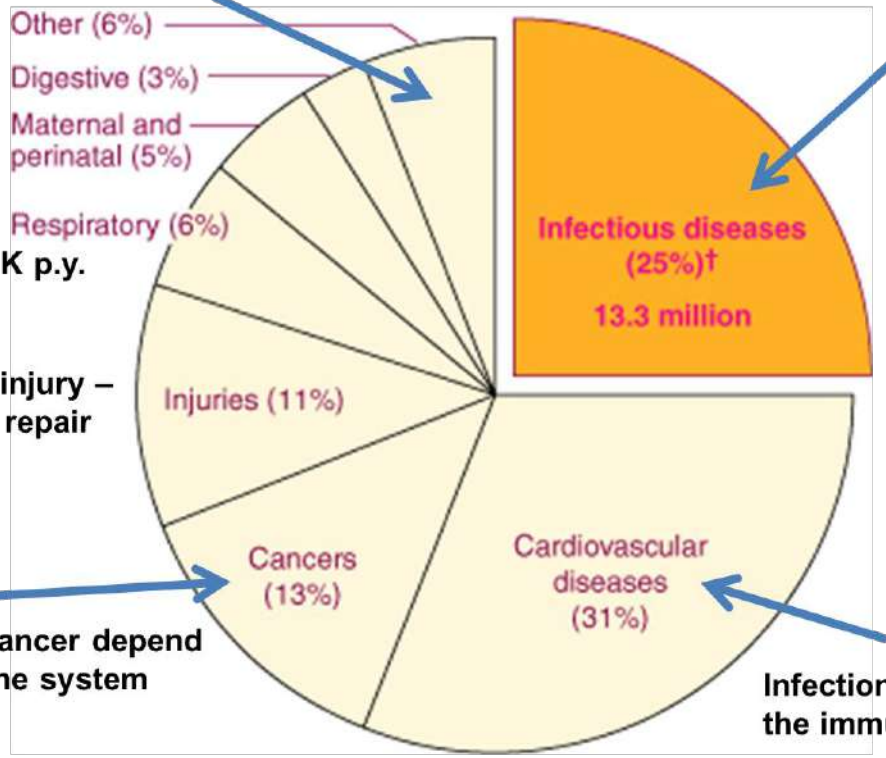
COVID-19 (USA)
75% deaths in >65 years old
<1% deaths in <30 years old

Increased risk with other co-morbidities – chronic kidney disease, cancer (+/- treatment), some autoimmune diseases (+/- treatment)…

Infections cross-cut nearly all diseases

e.g. Autoimmunity and its consequences - arthritis

Young and elderly – until recently 1 in 2 dead by age 20 – Black Death killed >60% of people



e.g. Asthma - >1000 deaths in UK p.y.

Infection can kill after injury – immune system helps repair

ENDEMIC INFECTIONS

VS

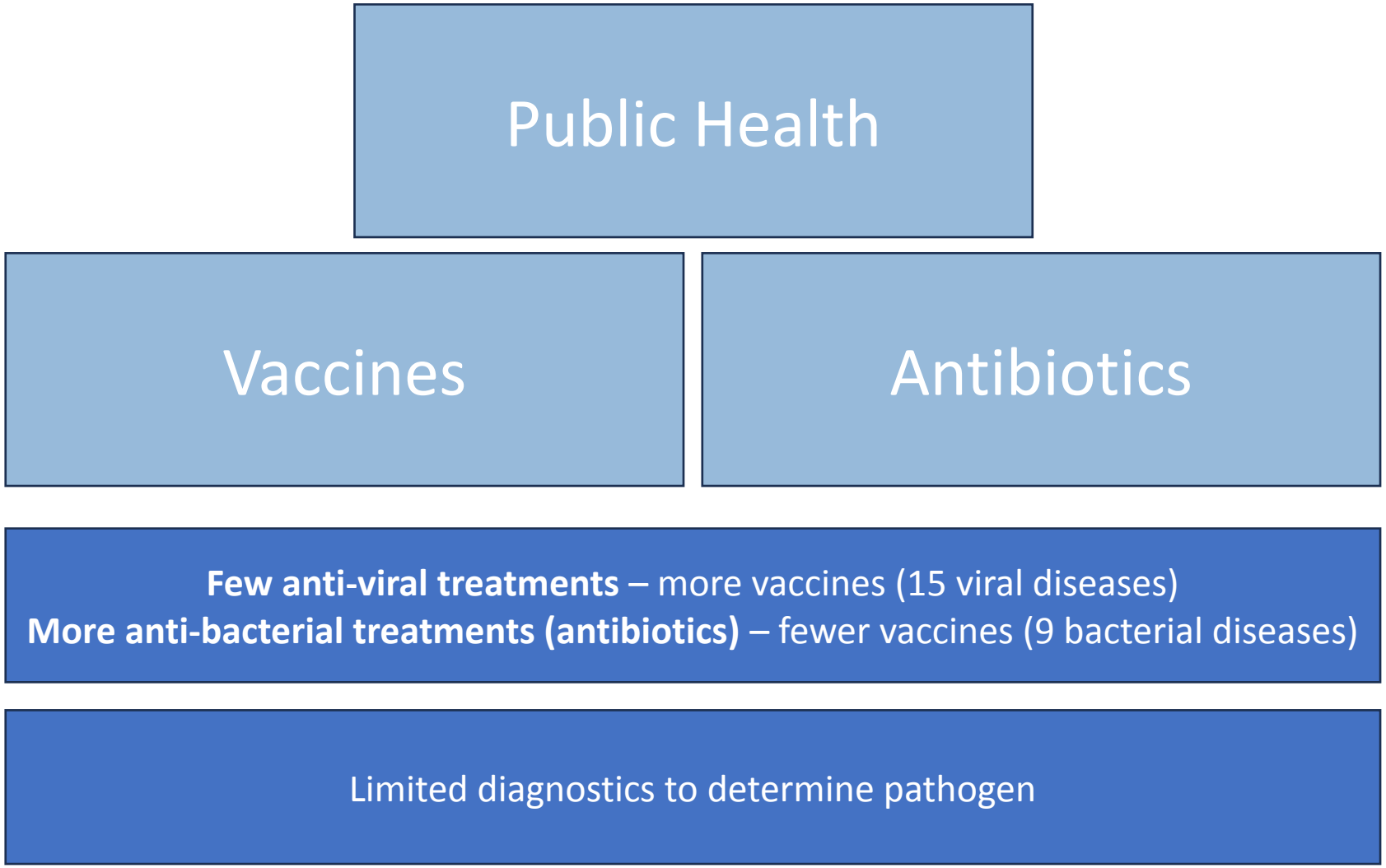
EPIDEMIC INFECTIONS

Cause and control of cancer depend on infection and immune system

Infection can cause heart disease and the immune system can exacerbate this

COVID-19 shows what happens in the absence of effective interventions (AMR and vaccines)

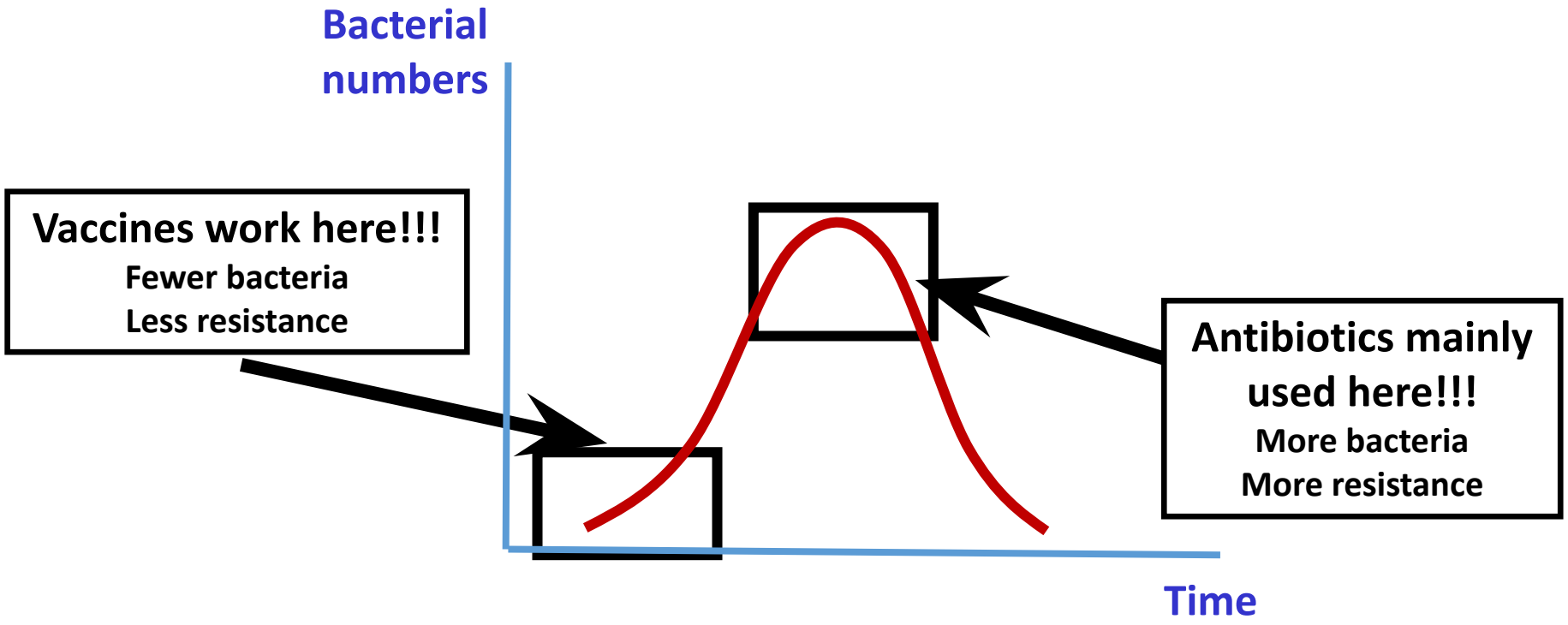
There are three major ways to control infection



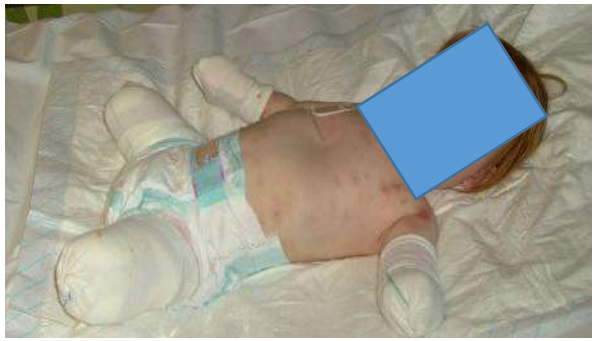
Remember, the key point is reducing disease burdens, AMR should be considered in this context!!

Vaccines democratise opportunity across the life course

There are limited options to treat active infections



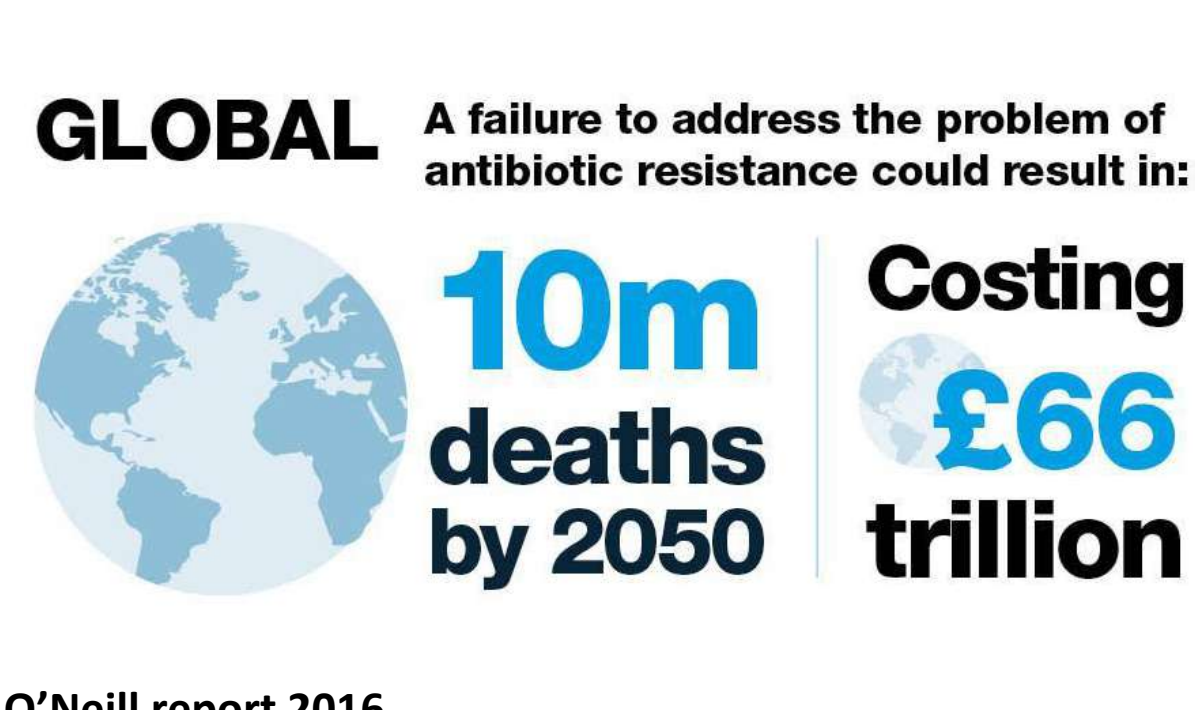
Vaccines save lives

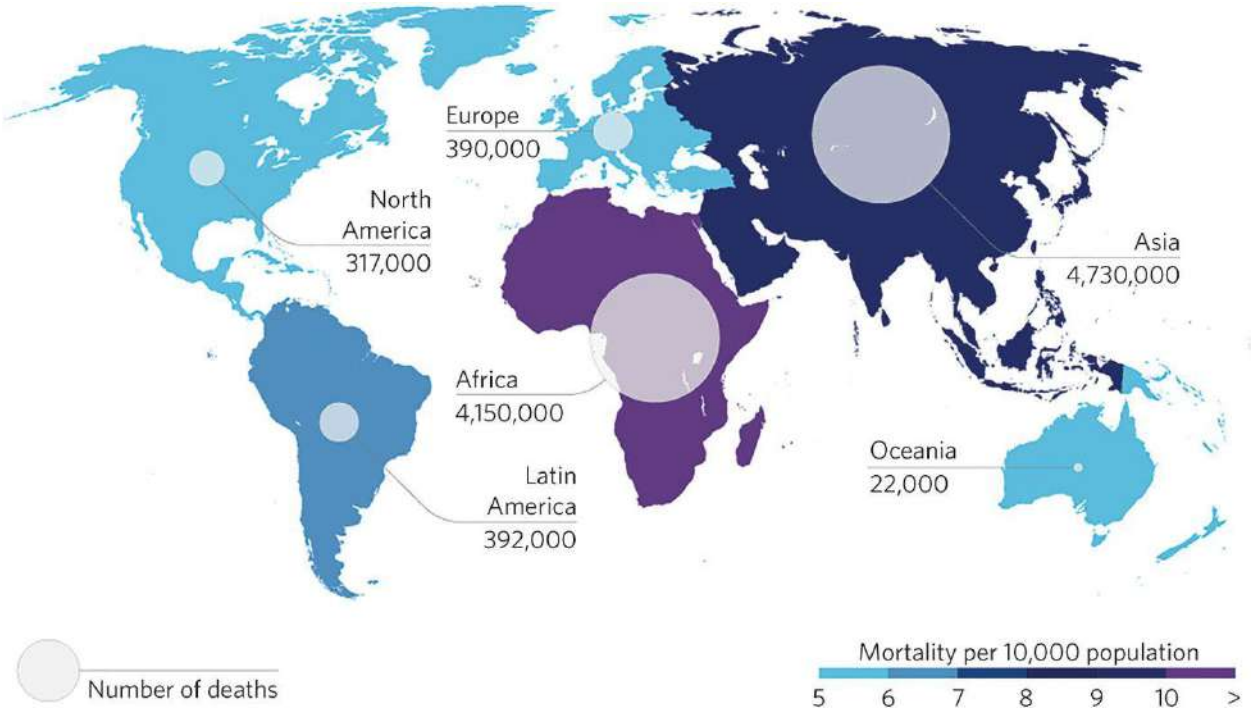


Antibiotics save lives

The success of vaccines (we rarely know when they have saved our life) can make selling their importance more difficult *cf* antibiotics

AMR can and is changing the landscape of medicine





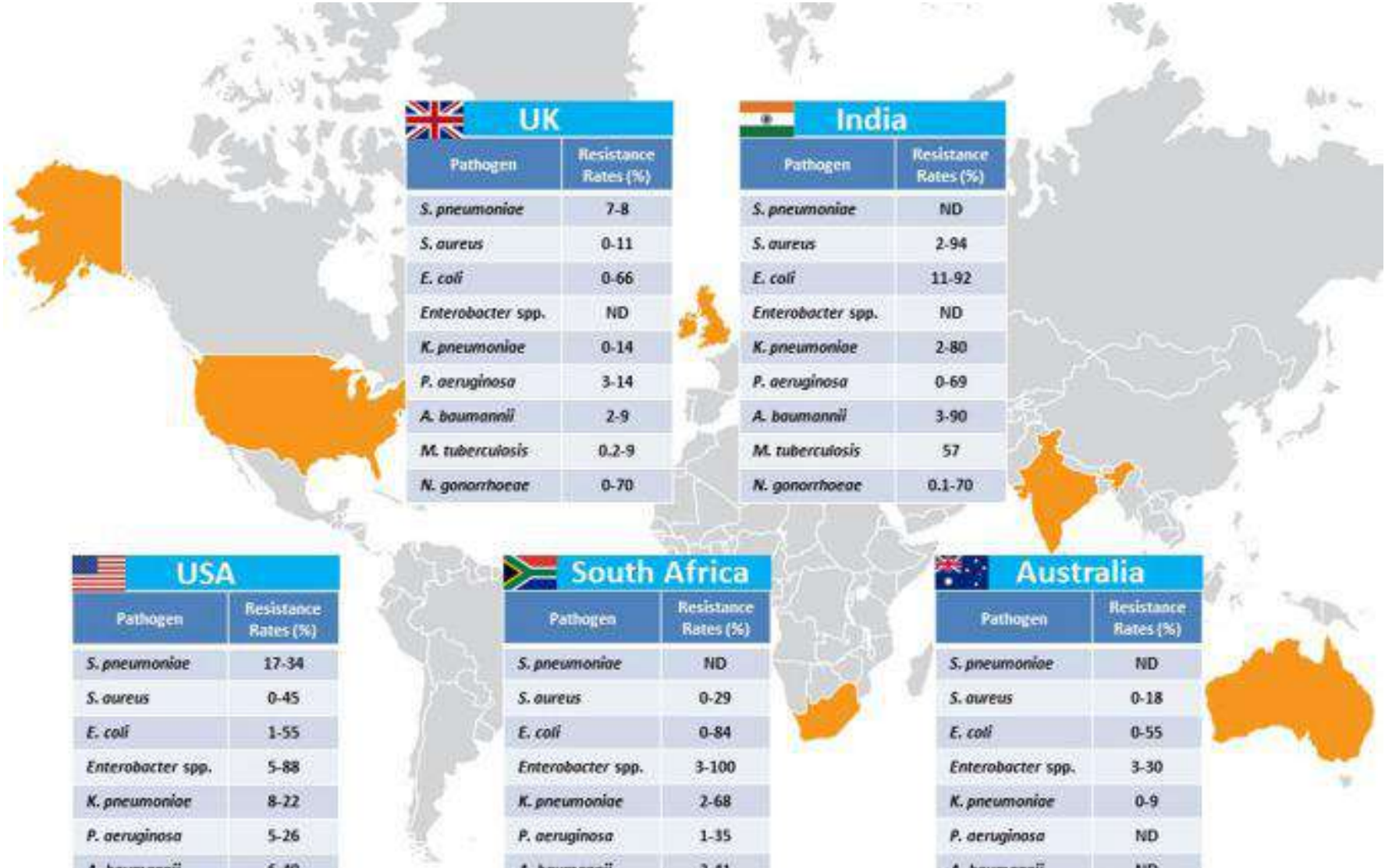
O'Neill report 2016

AMR can develop rapidly once an antibiotic is introduced

Antibiotic use continuous and not reducing - 60% of use in veterinary settings

Routine medicine (eg AMR could cause 1000s deaths after hip and colorectal surgery)

Antibiotic resistance is pervasive and global



UK

Pathogen	Resistance Rates (%)
S. pneumoniae	7-8
S. aureus	0-11
E. coli	0-66
Enterobacter spp.	ND
K. pneumoniae	0-14
P. aeruginosa	3-14
A. baumannii	2-9
M. tuberculosis	0.2-9
N. gonorrhoeae	0-70

India

Pathogen	Resistance Rates (%)
S. pneumoniae	ND
S. aureus	2-94
E. coli	11-92
Enterobacter spp.	ND
K. pneumoniae	2-80
P. aeruginosa	0-69
A. baumannii	3-90
M. tuberculosis	57
N. gonorrhoeae	0.1-70

USA

Pathogen	Resistance Rates (%)
S. pneumoniae	17-34
S. aureus	0-45
E. coli	1-55
Enterobacter spp.	5-88
K. pneumoniae	8-22
P. aeruginosa	5-26
A. baumannii	6-49
M. tuberculosis	0-3
N. gonorrhoeae	0.1-30

South Africa

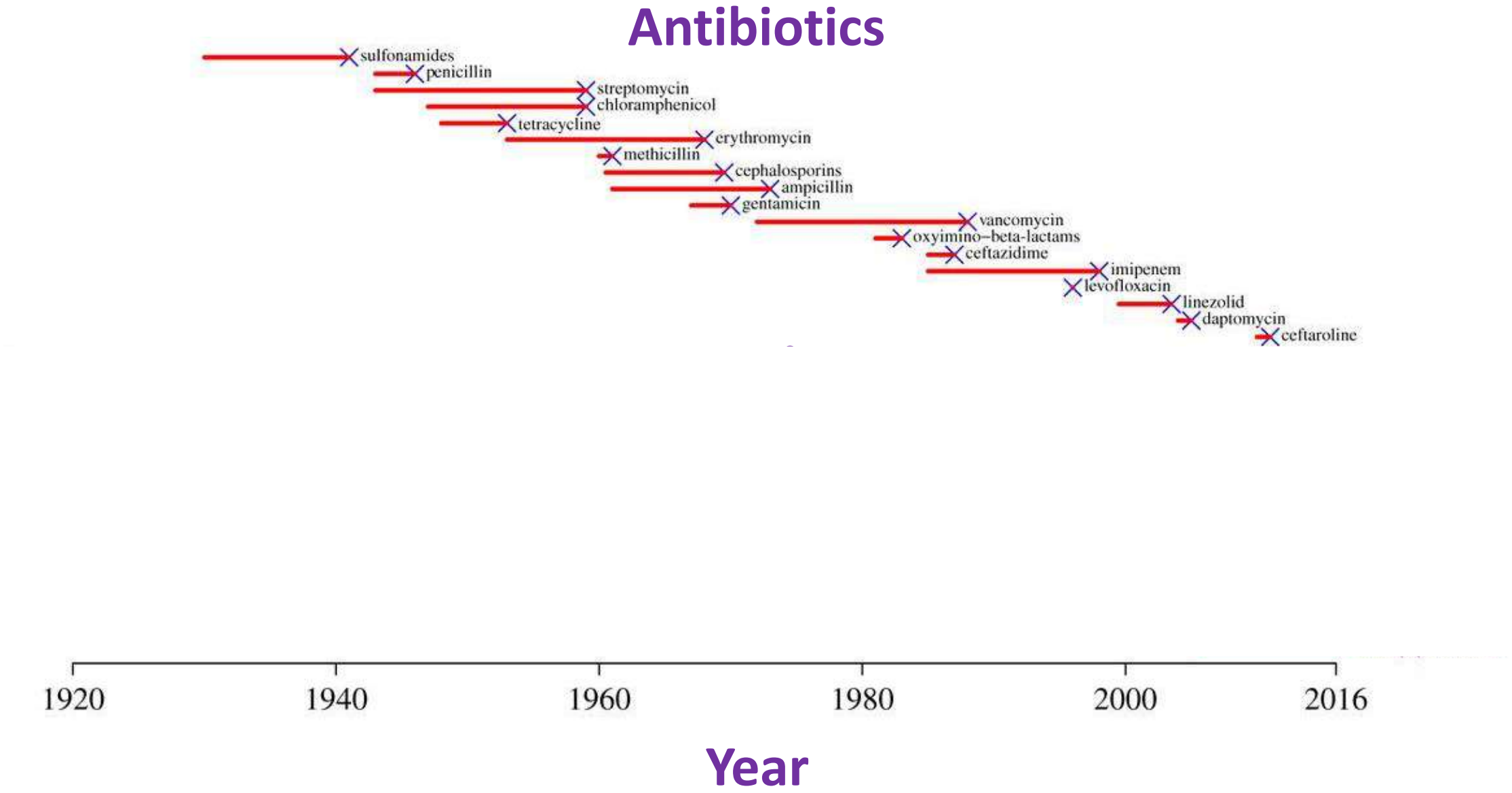
Pathogen	Resistance Rates (%)
S. pneumoniae	ND
S. aureus	0-29
E. coli	0-84
Enterobacter spp.	3-100
K. pneumoniae	2-68
P. aeruginosa	1-35
A. baumannii	2-41
M. tuberculosis	100
N. gonorrhoeae	0.1-70

Australia

Pathogen	Resistance Rates (%)
S. pneumoniae	ND
S. aureus	0-18
E. coli	0-55
Enterobacter spp.	3-30
K. pneumoniae	0-9
P. aeruginosa	ND
A. baumannii	ND
M. tuberculosis	0-2.9
N. gonorrhoeae	0.1-70

Jansen, K.U., *et al. Environ Chem Lett* **19**, 4031–4062 (2021).

Resistance to antibiotics develops soon after their introduction – but not to vaccines



Kennedy & Read Proc. R. Soc. B 2017;284:20162562

What does success look like for a bacterial vaccine?

Vaccines prevent infections from establishing

Vaccines stop infections from developing into disease

Vaccines reduce the severity of disease if it occurs

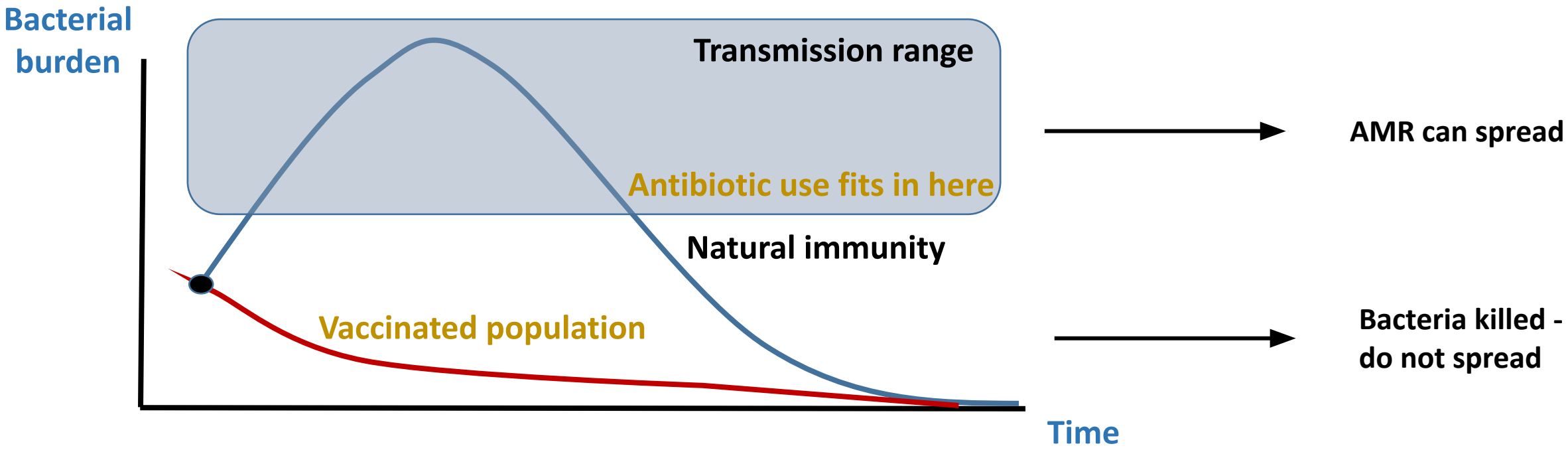
Persistence - Time from vaccination to pathogen encounter

Vaccination has a massive impact on disease rates

Disease	Pre-vaccine Era	2000	% change
Diphtheria	31,054	1	>99
Measles	390,852	86	>99
Mumps	21,342	338	>98
Pertussis	117,998	7,867	>93
Polio (wild)	54,953	0	100
Tetanus	1,314	35	-97
Invasive HiB Disease	24,856	112	-99
Total	**566,706**	**8,624**	**-98**
All Vaccine Adverse Events	0	<13 500	

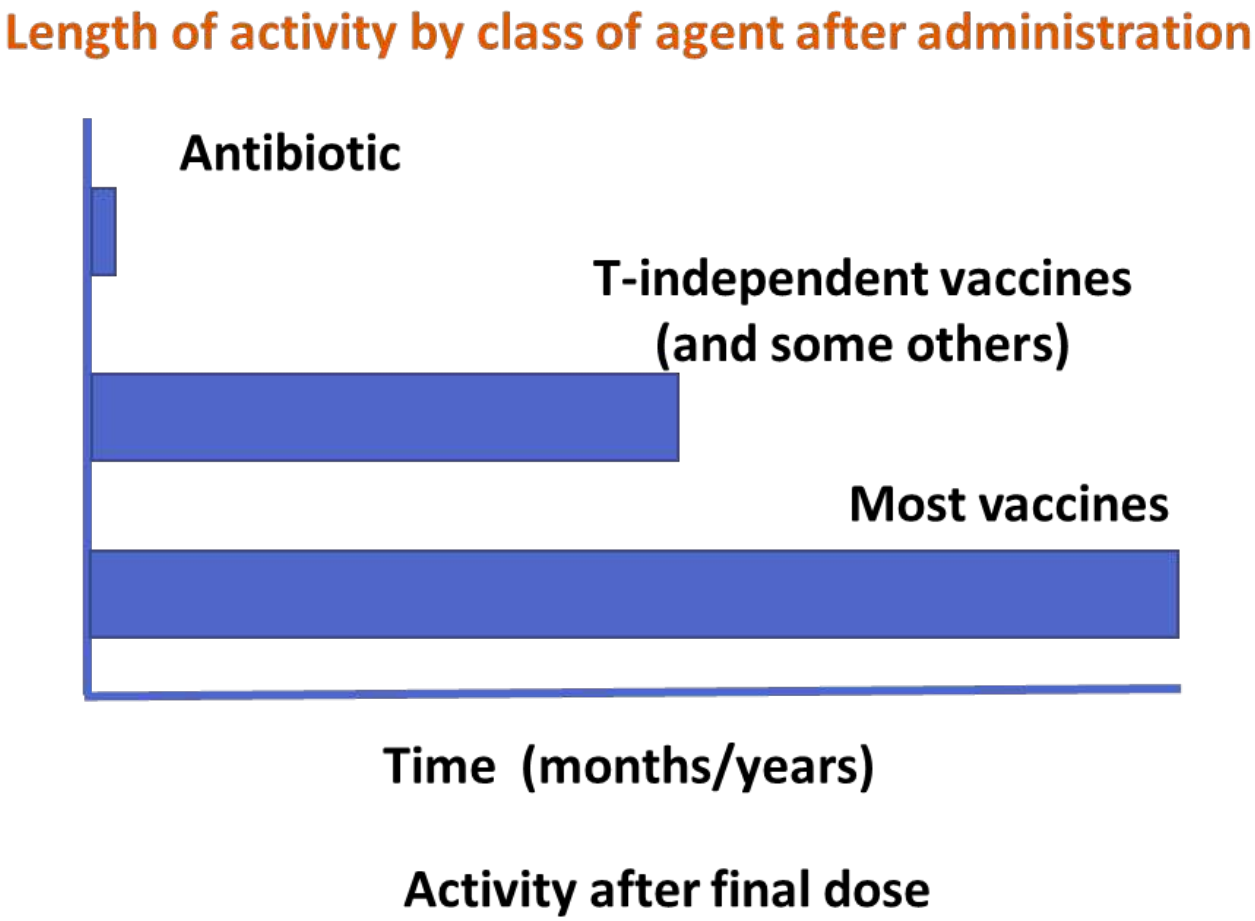
Vaccines save up to 10 million lives / year (young & old)

Vaccination prevents pathogen numbers getting sufficiently high to spread



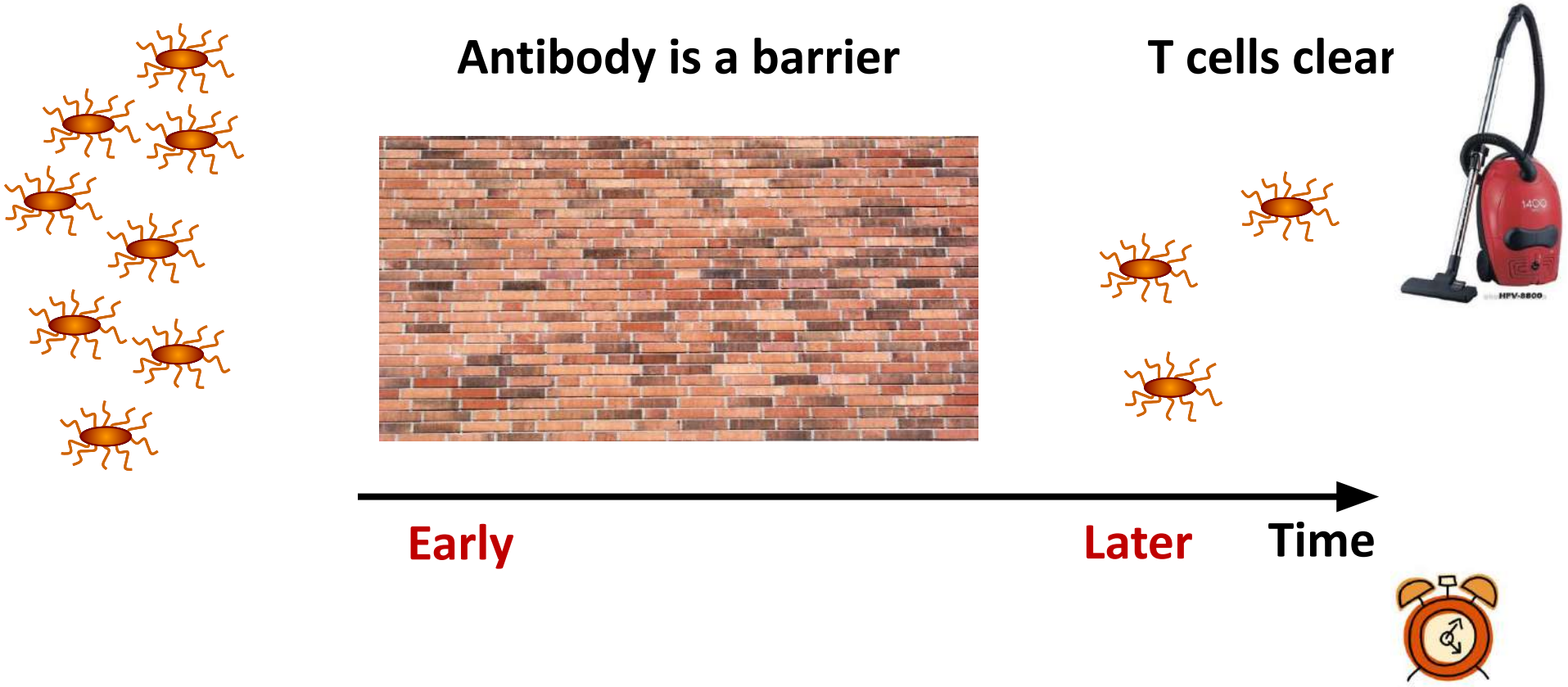
Vaccines offer sustained protection against specific pathogens, whilst antibiotics offer (broader but) short-term activity

Persistence of responses and lack of acquisition of **resistance** help make vaccines effective



Vaccines are effective because they work before disease becomes established

Vaccines have helped protect within hours after infection



Why is resistance common against antibiotics but not vaccines?

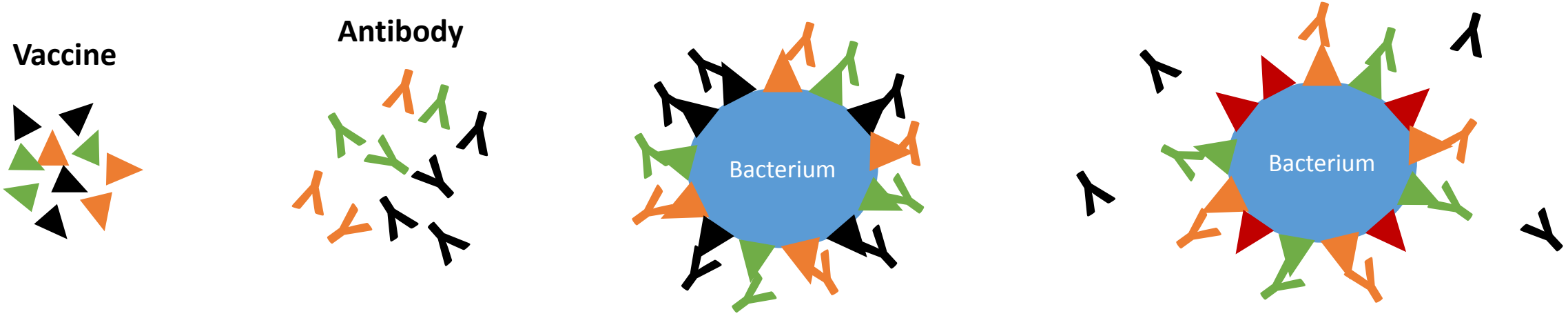
Antibiotics typically have only one target

Bacteria can resist antibiotics through multiple routes – (efflux, antibiotic inactivating enzymes (eg β-lactamases), target modification (loss of binding), cell surface alterations, direct modification of target)

Resistance mechanisms can be spread quickly through genetic mechanisms

Vaccines target multiple epitopes/antigens, this redundancy in targets is important

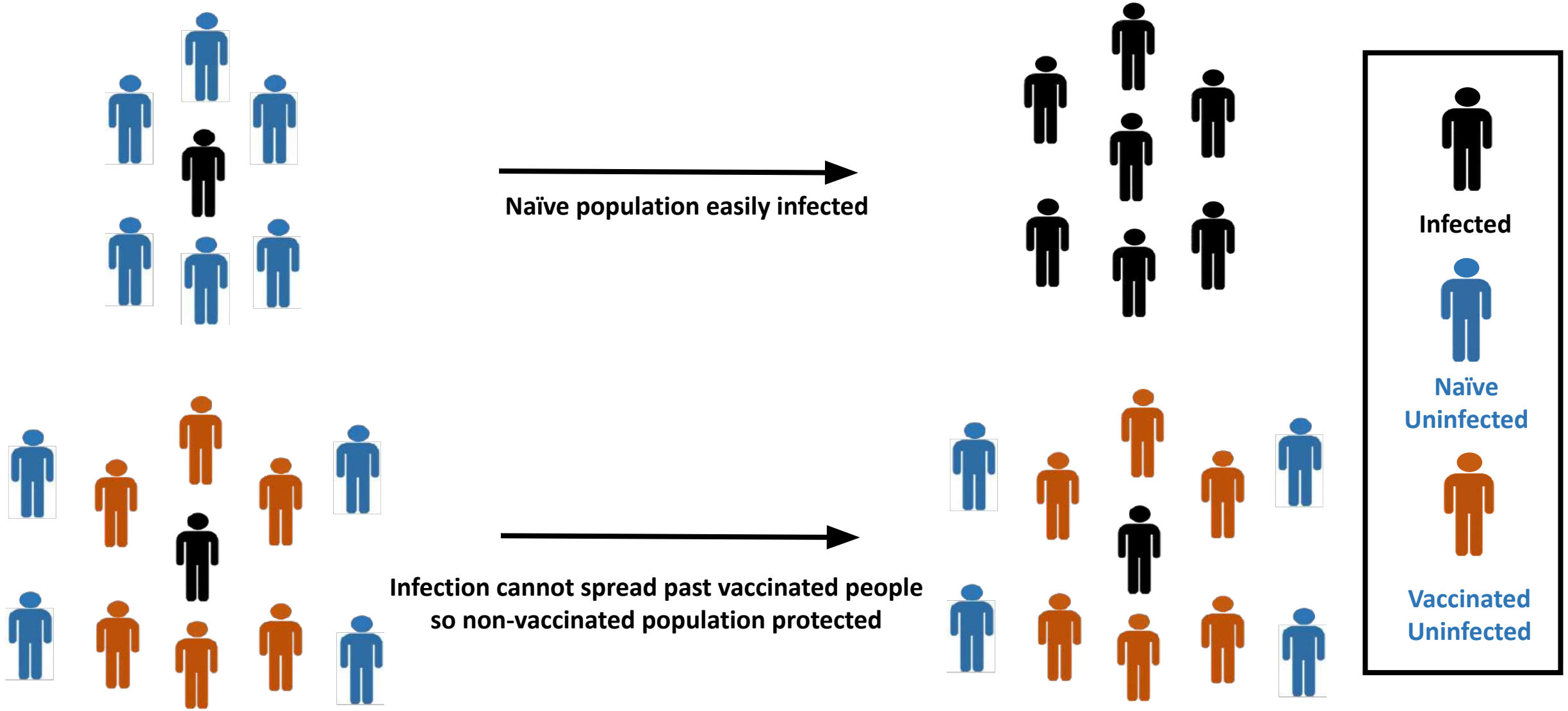
Therefore, multiple mutations needed for evasion – difficult to achieve and spread



Vaccine induces antibody that recognises multiple bacterial targets

Even 'mutant' bacteria still recognised because multiple antigens targeted

Herd immunity decreases transmission risk and potentially the level of circulating pathogen



How can vaccines help reduce AMR?

Vaccines can help directly and indirectly – prevent infection, block transmission

Direct –

Reducing antibiotic use for mild infections

Reduce development of resistance – Tetanus, pertussis and diphtheria

Reduce burden of infections with existing AMR – *Haemophilus influenzae* B, pneumococcus, *Neisseria* spp

Reduce bacterial transmission – Herd immunity

Reduce opportunity for genetic exchange by bacteria in shared niches

Indirect –

Block transmission – target "similar" pathogens (Bexsero and gonococcus)

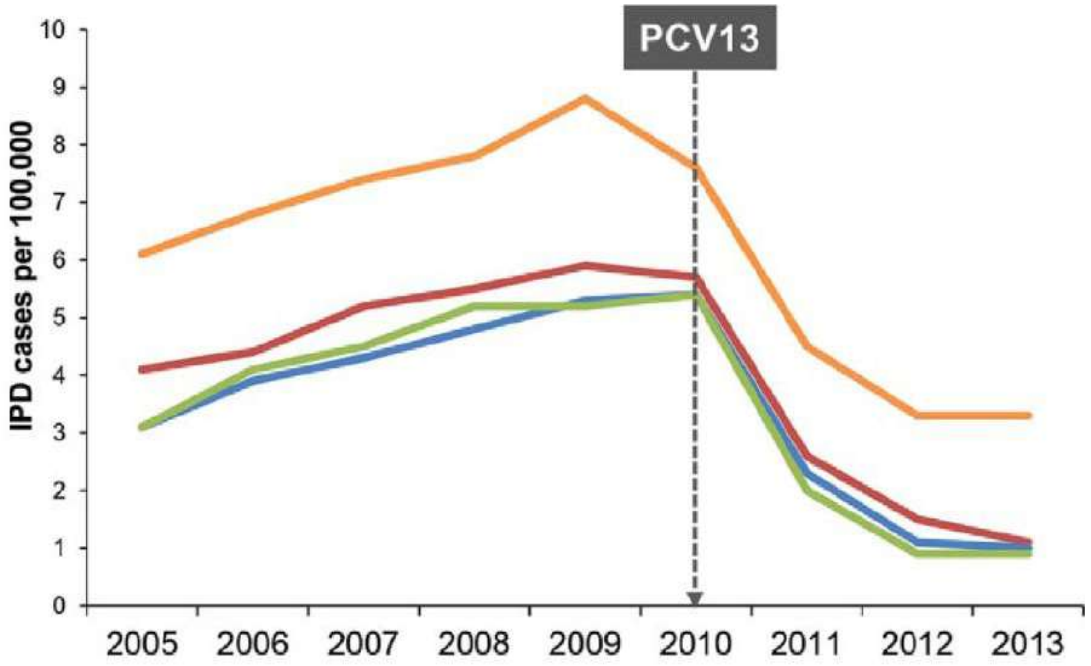
50% antibiotic use inappropriate – flu season correlates with antibiotic use - diagnostics

Flu vaccine reduces secondary bacterial infections and antibiotic treatments

Vaccinating different age groups - children

Most vaccines designed to protect the young

Clear evidence vaccines reduces antimicrobial use and are effective against AMR pathogens (HiB and typhoid)



Antibiotic % Change 2009 vs 2013	
63%	Macrolides
81%	Cephalosporins
81%	Tetracyclines
83%	Penicillins

Full use of pneumococcal PCV-13 vaccine would mean 11 million less days of antibiotic use each year

A vaccine against Group A Streptococcus would mean 6 billion less antibiotic doses given yearly

MINI-REVIEW

The role of vaccines in fighting antimicrobial resistance (AMR)

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2018, VOL. 14, NO. 9, 2142–2149
https://doi.org/10.1080/21645515.2018.1476814

Kathrin U. Jansen and Annaliesa S. Anderson

Pfizer Vaccine Research and Development, Pearl River, NY, USA

Vaccinating different age groups - adults

Fewer vaccines given routinely to adults – so less evidence on full impact on antimicrobial use

Key impacts made for use of pneumococcal and flu vaccines and mostly for over 65s

Evidence mirrors what is seen for vaccinating children – childhood vaccines can reduce disease in adults

Strong evidence that vaccine-mediated protection is independent of antibiotic sensitivity of the pathogen

Pneumococcal conjugate vaccine can reduce AMR strains by up to 80% in adults (Kyaw 2006)

This means controlling AMR bacteria can be helped by being vaccinated – individual vs population

Vaccinating against viral and bacterial infections can both help!!

Surprisingly, flu vaccination in adults may be more beneficial than vaccinating against pneumococcus for AMR

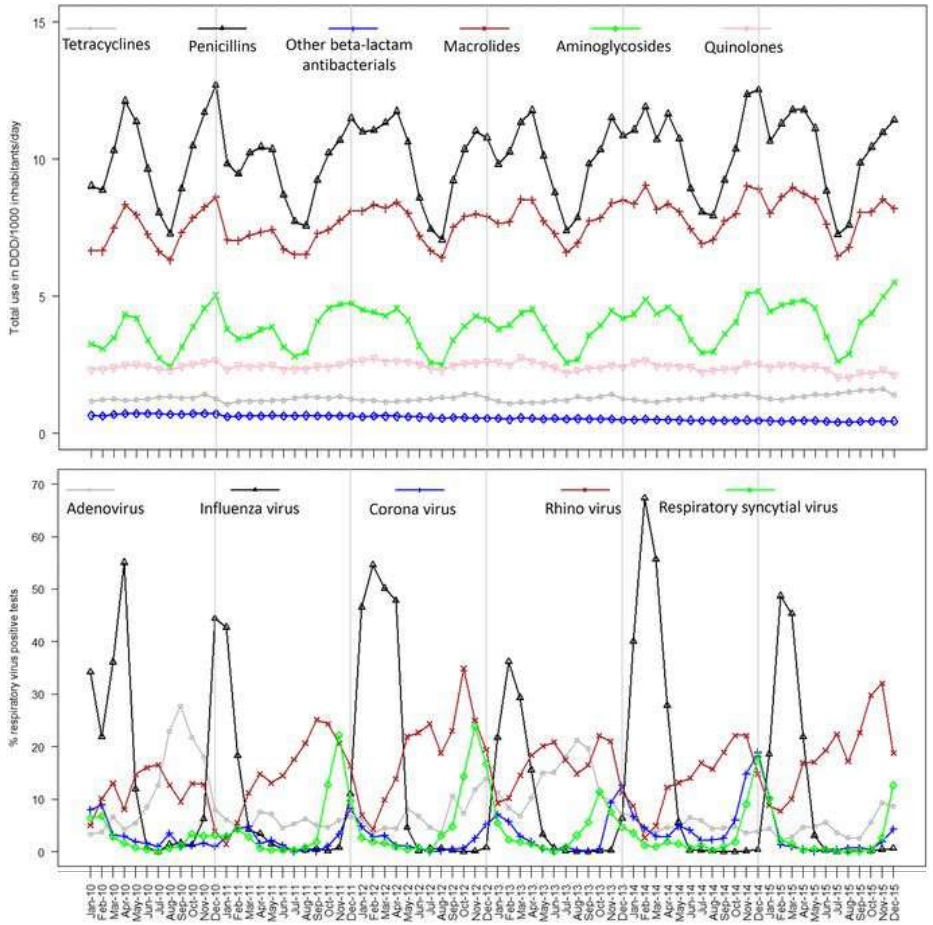
Vaccinating against pneumococcus reduces risk of some viral lower respiratory tract infections and pneumonia

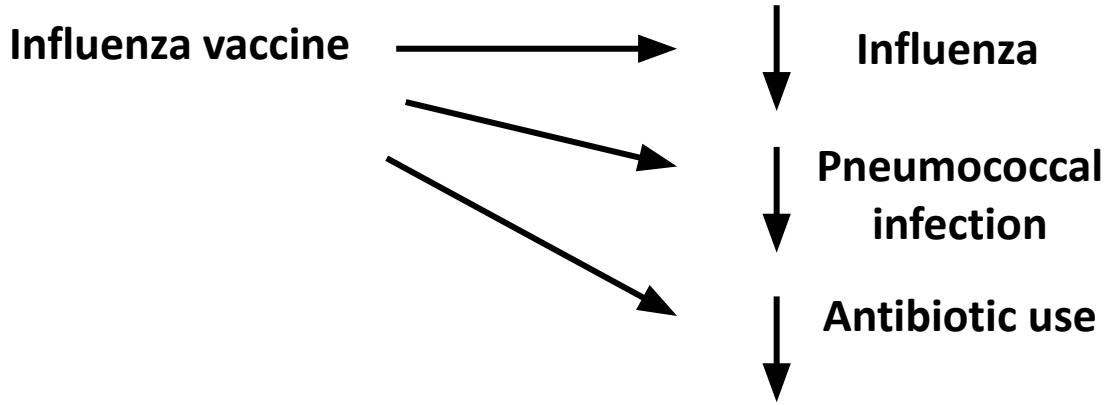
Why?

Influenza virus can cause pathology directly or result in susceptibility to a secondary bacterial infection

Viral infection can increase susceptibility to pneumococcus, *Staphylococcus aureus*, *Haemophilus influenzae* B

This relationship with pneumococcus the key reason Spanish flu of 1918 so devastating





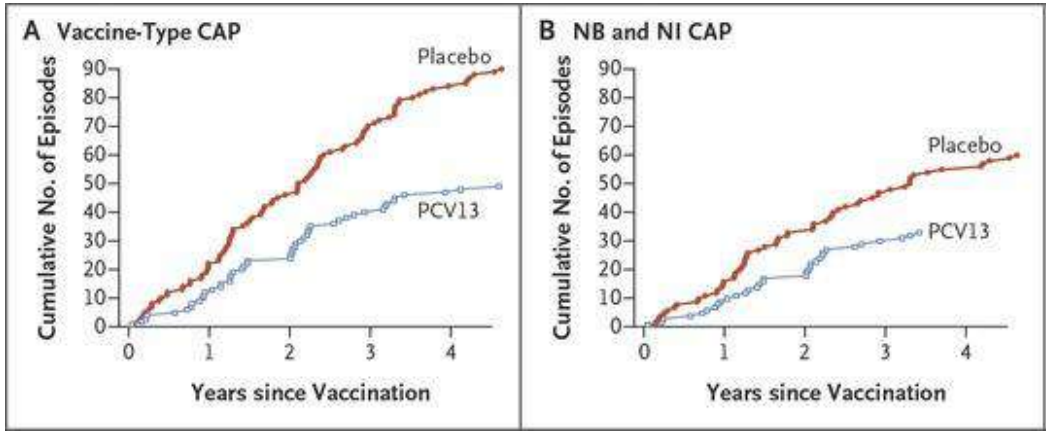
Vaccinating against flu reduces antibiotic use for viral infection

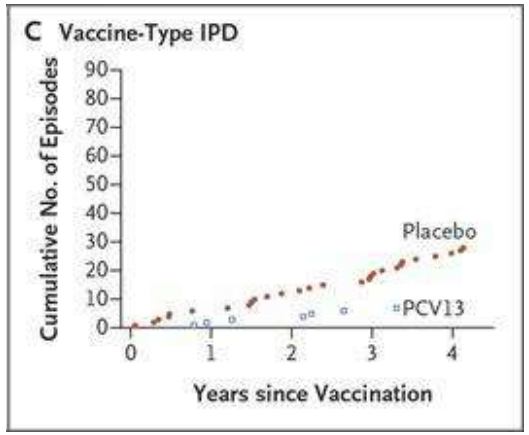
Vaccinating against flu reduces secondary pneumococcal+ infections

Vaccinating against influenza can reduce antimicrobial use in adults by up to 64% among adults and may reduce selection for AMR

Ryu, S., *et al.* *Antimicrob Resist Infect Control* **7**, 56 (2018). https://doi.org/10.1186/s13756-018-

Pneumococcal vaccination reduces invasive pneumococcal disease at both ends of the age spectrum



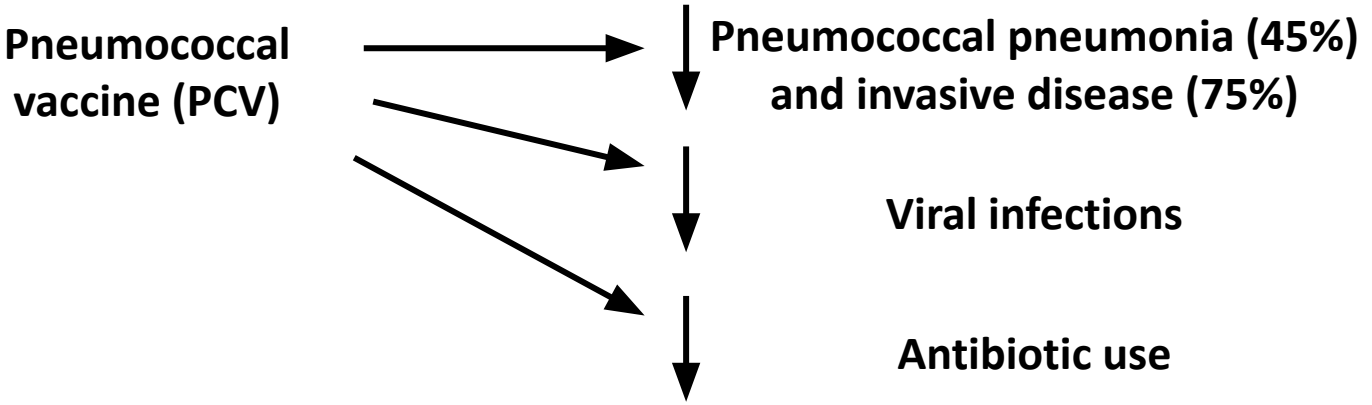


ORIGINAL ARTICLE

Polysaccharide Conjugate Vaccine against Pneumococcal Pneumonia in Adults

M.J.M. Bonten, S.M. Huijts, M. Bolkenbaas, C. Webber, S. Patterson, S. Gault, C.H. van Werkhoven, A.M.M. van Deursen, E.A.M. Sanders, T.J.M. Verheij, M. Patton, A. McDonough, A. Moradoghli-Haftvani, H. Smith, T. Mellelieu, M.W. Pride, G. Crowther, B. Schmoele-Thoma, D.A. Scott, K.U. Jansen, R. Lobatto, B. Oosterman, N. Visser, E. Caspers, A. Smorenburg, E.A. Emini, W.C. Gruber, and D.E. Grobbee

CAPiTA – key Dutch trial in >65 years



Immunization with pneumococcal conjugate vaccine can directly reduce the need for antibiotics

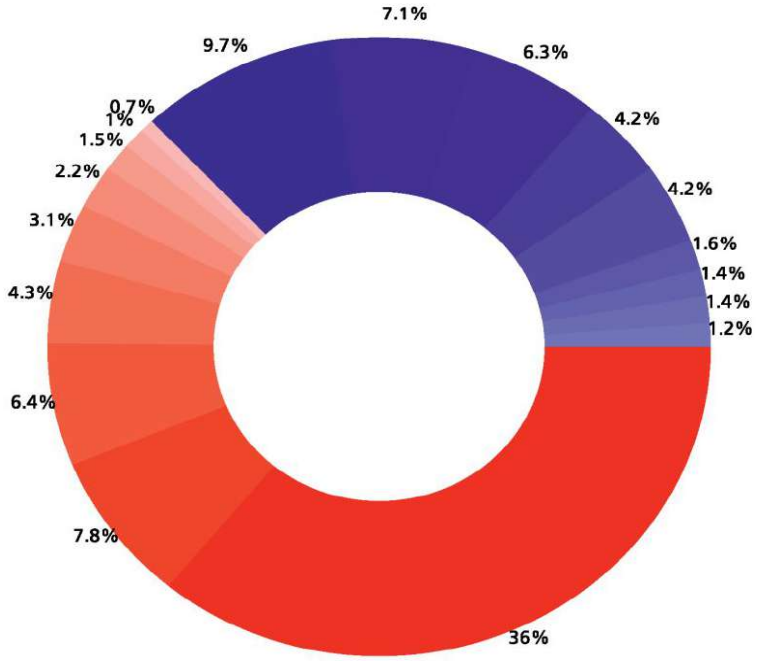
Reduces carriage, transmission, and prevalence of drug-resistant IPD by up to 33%

But…vaccinating against pneumococcus protects against some viral lung infections……(10-25%)

Pneumococcal vaccination reduces overall antibiotic usage in children but less well studied in adults

There are many pathogens against which there are no vaccines

Figure 1.1: Organisms causing blood stream infections in adults in England, Wales and Northern Ireland, April 2011-March 2012



Source: HPA. English National Point Prevalence Survey on Healthcare Associated Infections and Antimicrobial Use, 2011: Health Protection Agency, England; 2012. Note: excludes 13,206 episodes of bacteraemia with coagulase negative staphylococci.

Chief Medical Officer's Report 2011

Gram positive
- Staphylococcus aureus (MSSA) - 9.7%
- Non-pyogenic streptococci - 7.1%
- Enterococcus spp. - 6.3%
- Streptococcus pneumoniae - 4.2%
- Other Gram-positive - 4.2%
- Staphylococcus aureus (MRSA) - 1.6%
- Group B Streptococci - 1.4%
- Group A Streptococci - 1.4%
- Diphtheroids - 1.2%

Gram negative
- Eschericha coli - 36%
- Klebsiella spp. - 7.8%
- Other Gram-negative - 6.4%
- Pseudomonas spp. - 4.3%
- Proteus spp. -3.1%
- Enterobacter spp. - 2.2%
- Bacteroides spp. - 1.5%
- Serratia spp. - 1.0%
- Acinetobacter spp. - 0.7%

Technical advances mean better diagnostics

***M. tuberculosis*, Group A and B *Streptococcus*, *Staphylococcus aureus, E. coli, Klebsiella pneumoniae*….**

But vaccines can have 'off-target' benefits – innate training, cross-protection (Meningitis B – gonorrhoea)

Reducing AMR requires using less antibiotics – vaccines are a major way to achieve this

Summary and points for discussion

Getting vaccinated as an adult, especially older adults, can reduce risk of infection and sequelae

Vaccination can aid antibiotic stewardship / use, prevent AMR or help prevent infection by an AMR pathogen

Vaccinating against pneumococcus can help reduce many different viral infections (moderate protection)

Vaccinating against flu can help reduce bacterial infections

Wider vaccine uptake in older adults may benefit AMR and antibiotic use

Studies reveal more benefits from vaccination – flu vaccine and cardiovascular associated disease (33% drop)

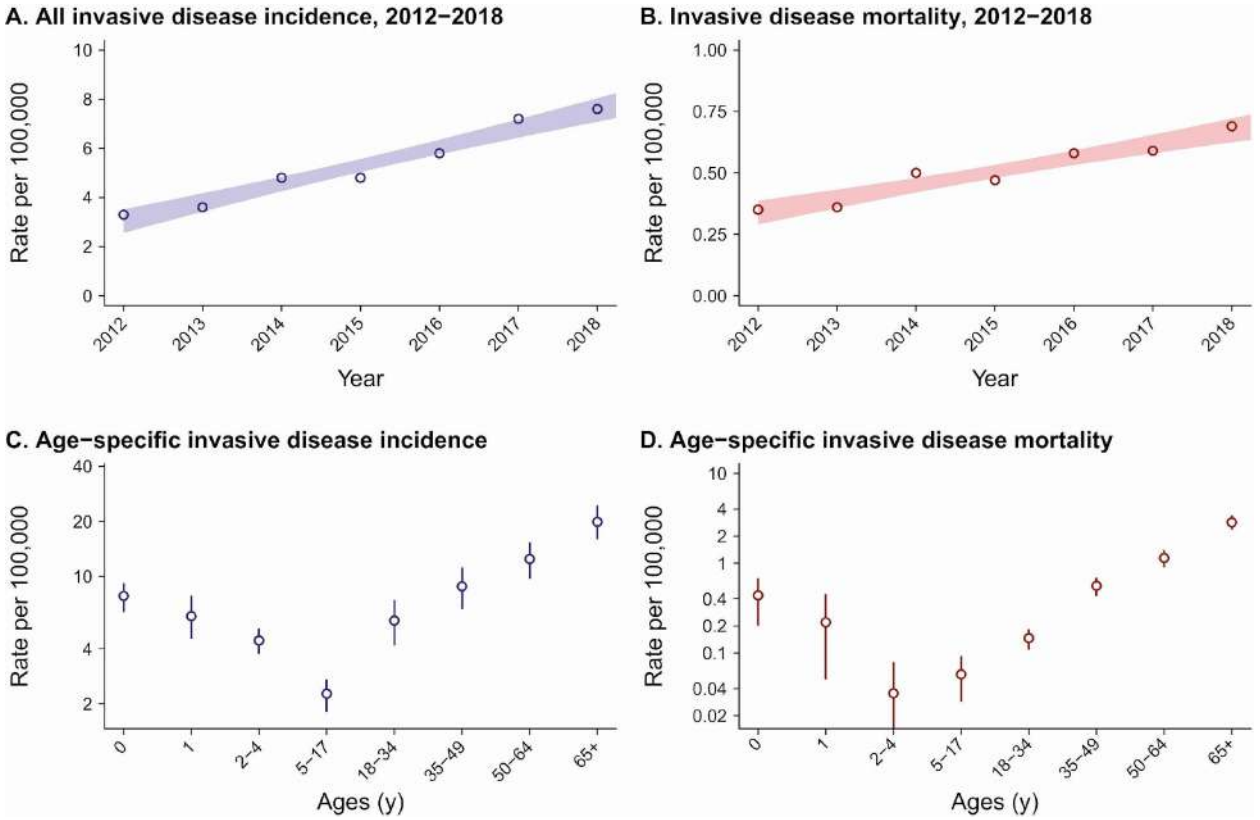
Future vaccines – RSV, new bacterial vaccines needed (many in the pipeline)

Widening vaccine usage and development is as much a political problem as a scientific one

We need to learn the lessons from COVID-19 – boosting enhances and maintains responses

Vaccines can save lives but only when used!! Vaccines don’t save lives, vaccination does

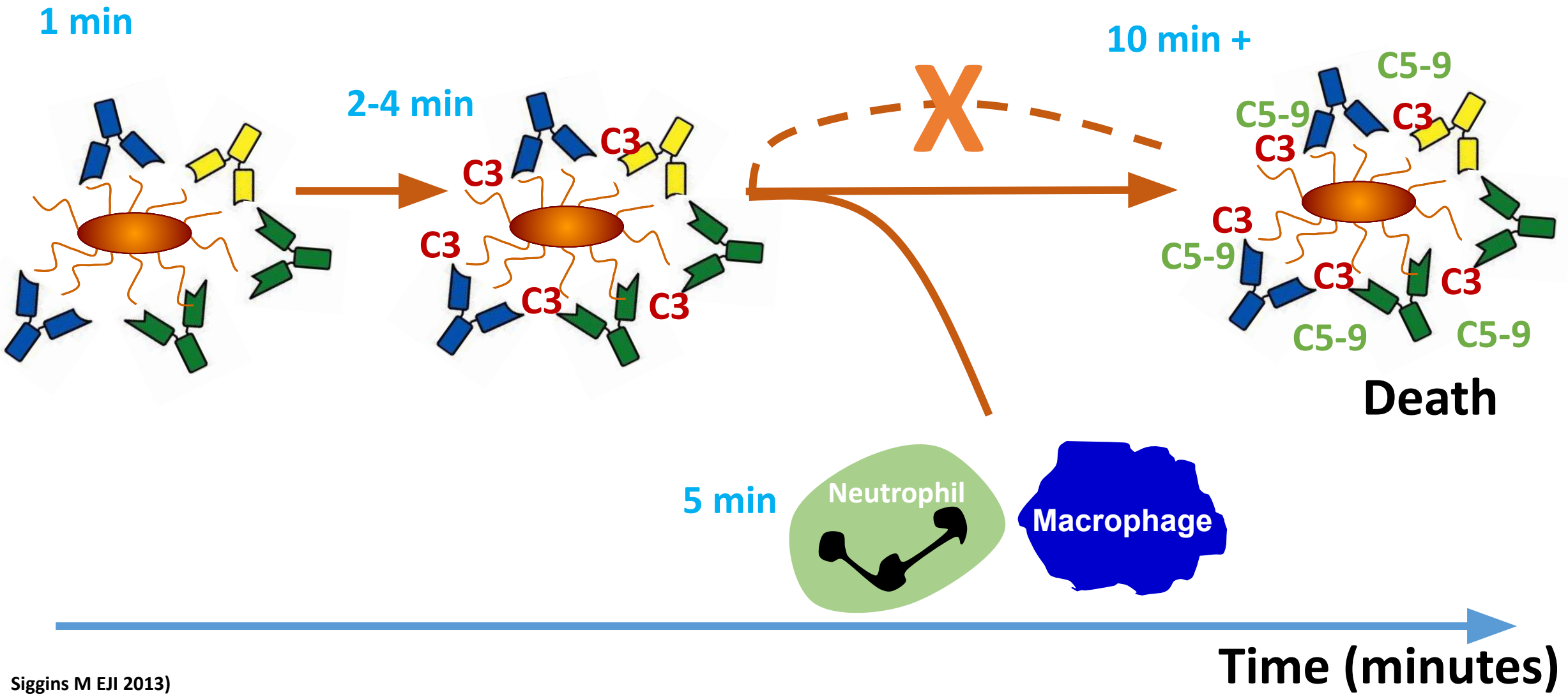
Figure 1. Projecting incidence of invasive group A Streptococcus (GAS) disease. We plot increases from 2012 to 2018 in ...



Clin Infect Dis, Volume 74, Issue 6, 15 March 2022, Pages 983–992, https://doi.org/10.1093/cid/ciab597

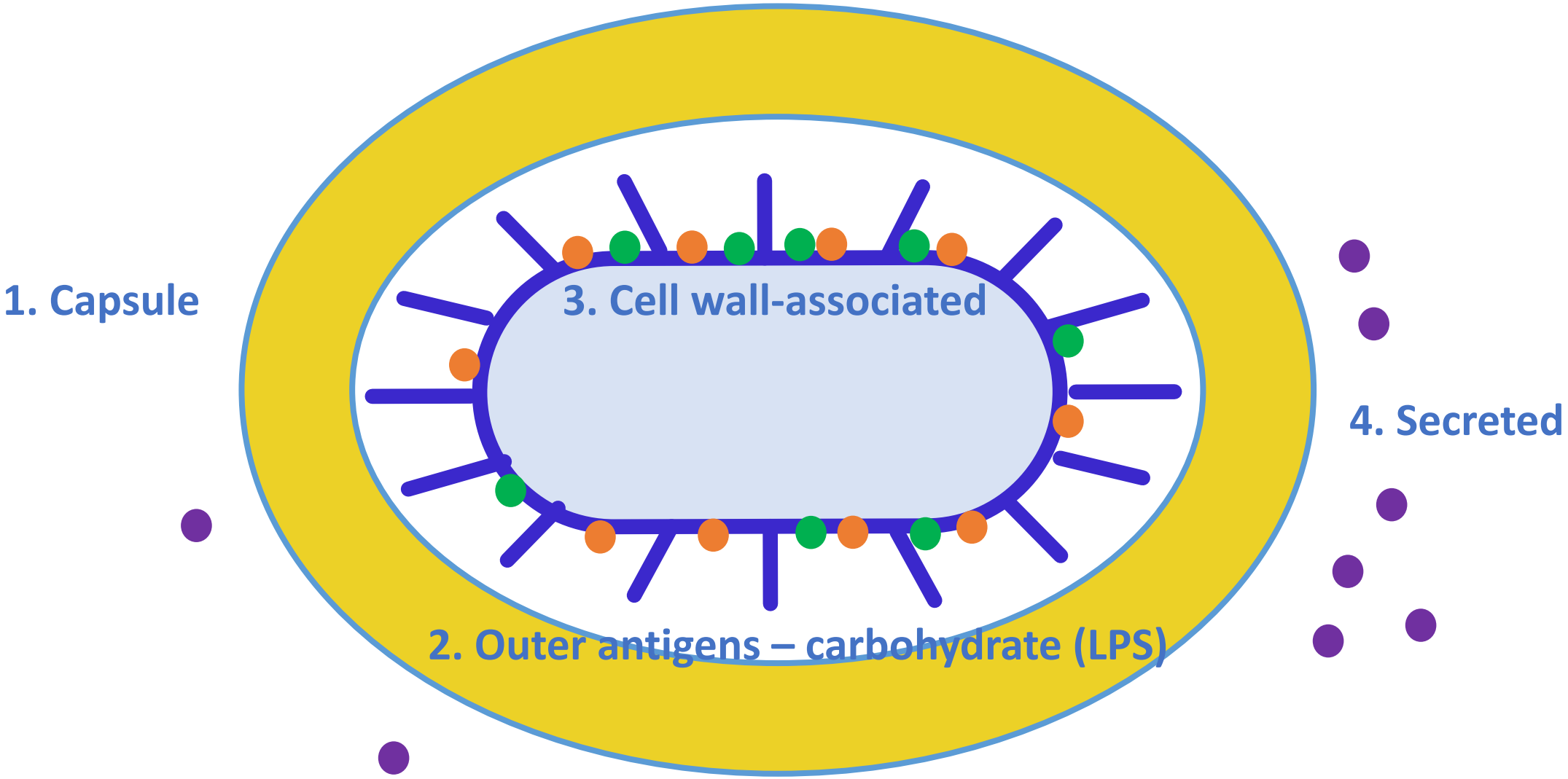
Why are antibodies protective in vivo?

Timing of effector functions are often ignored

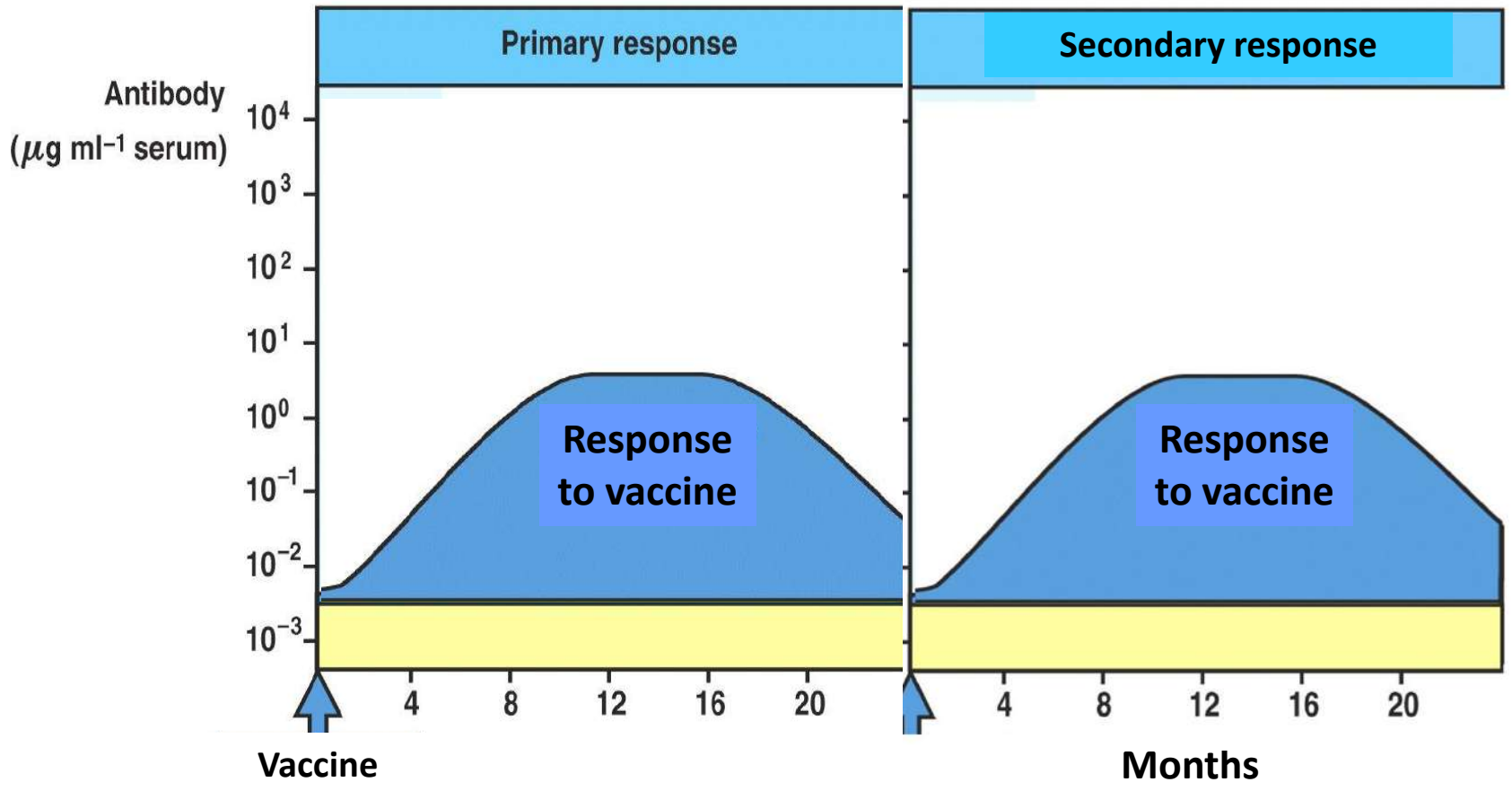


Siggins M EJI 2013)

Licensed human vaccines are either single antigens (capsules) or are antigenically complex



TI responses are shorter lived (months to years) and do not induce memory



Antibodies to Gram-negative bacteria, induced after natural infection or vaccination, save 100 000s of lives each year

Cons

Targeting the bug or its products

Sometimes known, often not

Natural infection vs vaccination

Immunodominant vs artificially skewing

The right antibody induced

IgM v IgG v isotypes

Cross-protection induced

Many bacteria “related”

The right amount induced

Excess IgG dangerous?

Long-lived responses

Years between vaccination and infection

Target population

Immunocompetent vs compromised

Where is Ab needed?

Systemic vs mucosal

What does this mean in practice?

T-independent - Purified Capsular Polysaccharides

IgM, some IgG of modest affinity (no GC), little IgA (Bone marrow)

Protection modest longevity (typically 2-3 years)

No boost, but potential hyporesponsiveness

No T cell immunity

T-dependent - Conjugate capsular polysaccharides, protein subunits, vesicles, protein subunits, live vaccines

IgM, lots IgG of high affinity (GC), (lots IgA) (Bone marrow)

Protection potentially long-lasting

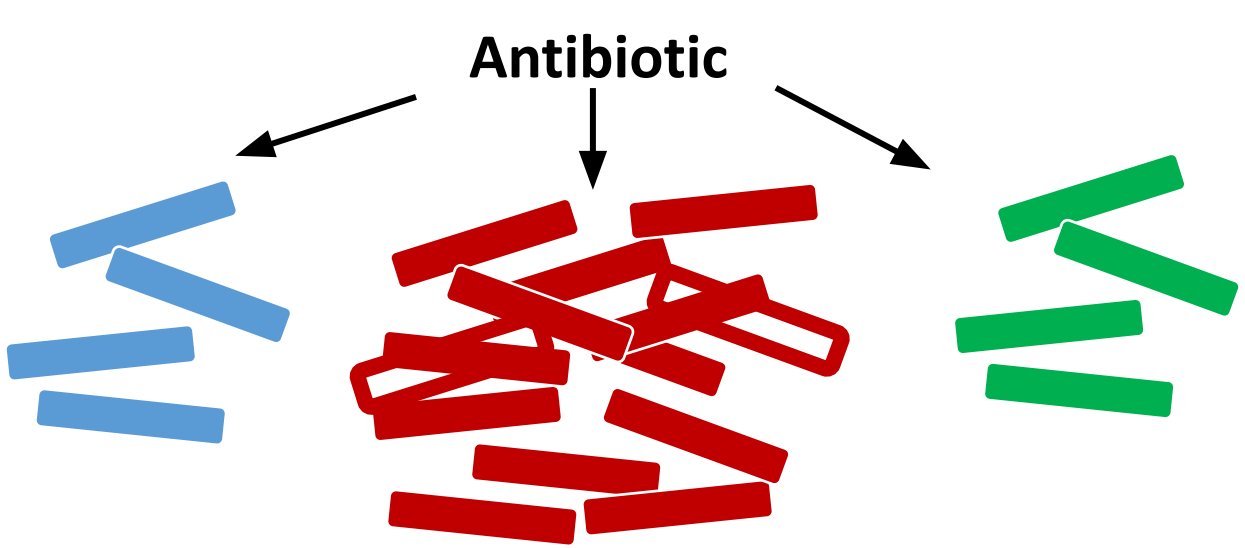
Boosting

Strong T cell immunity

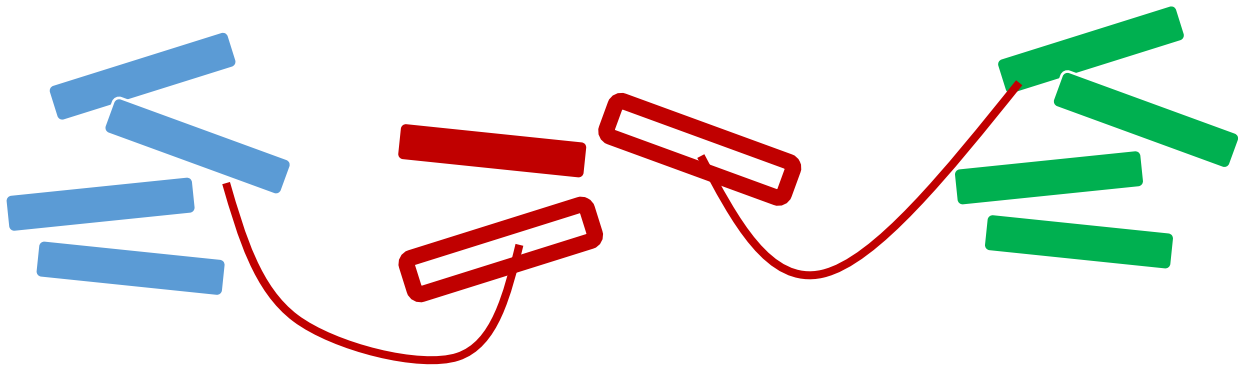
It will consist in the following activities:
- Participation, as trainer, in 1 online training seminar of a maximum duration of two hours, to be held on 14 December 2023. The seminar will be held in English.
Seminar topics: a proper vaccine culture, in particular to overcome the idea that vaccination is only needed at early ages, and to shift to a life-course vaccination approach and to a harmonised "for-life calendar" at the EU level. the essential role of vaccines in combating AMR, exploring the question of "why new-generation antibiotics alone cannot effectively address the AMR crisis." The session will shed light on the cause-and-effect relationship in AMR mitigation, emphasizing that vaccines target the root causes, while antibiotics primarily manage the consequences.
- The commitment foreseen will entail the production of a speech for the webinar accompanied by a **presentation in the form of slides/.ppt in English to be sent to the organiser one week before** the event takes place, authorising Cittadinanzattiva APS to publish the presentation produced online.

Differences between vaccines and antibiotics

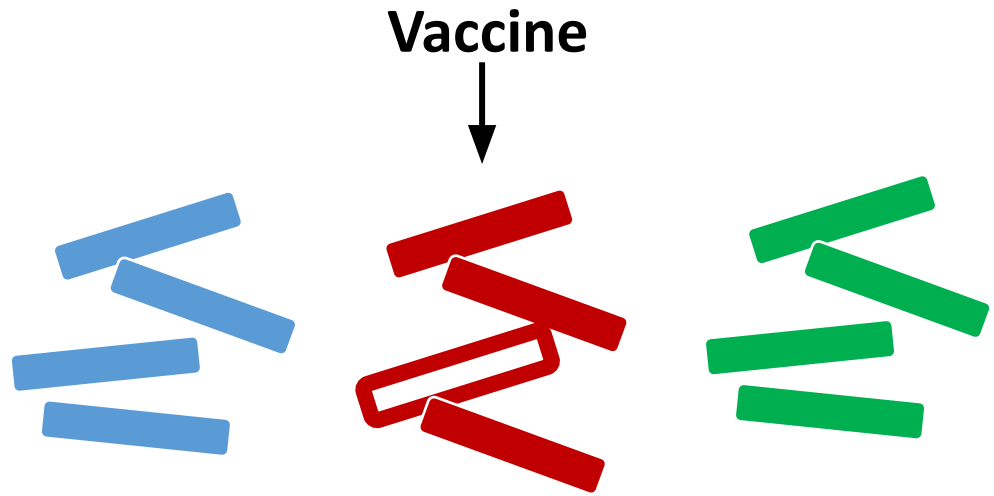
There is a direct link between antibiotic use and AMR



Some bacteria survive

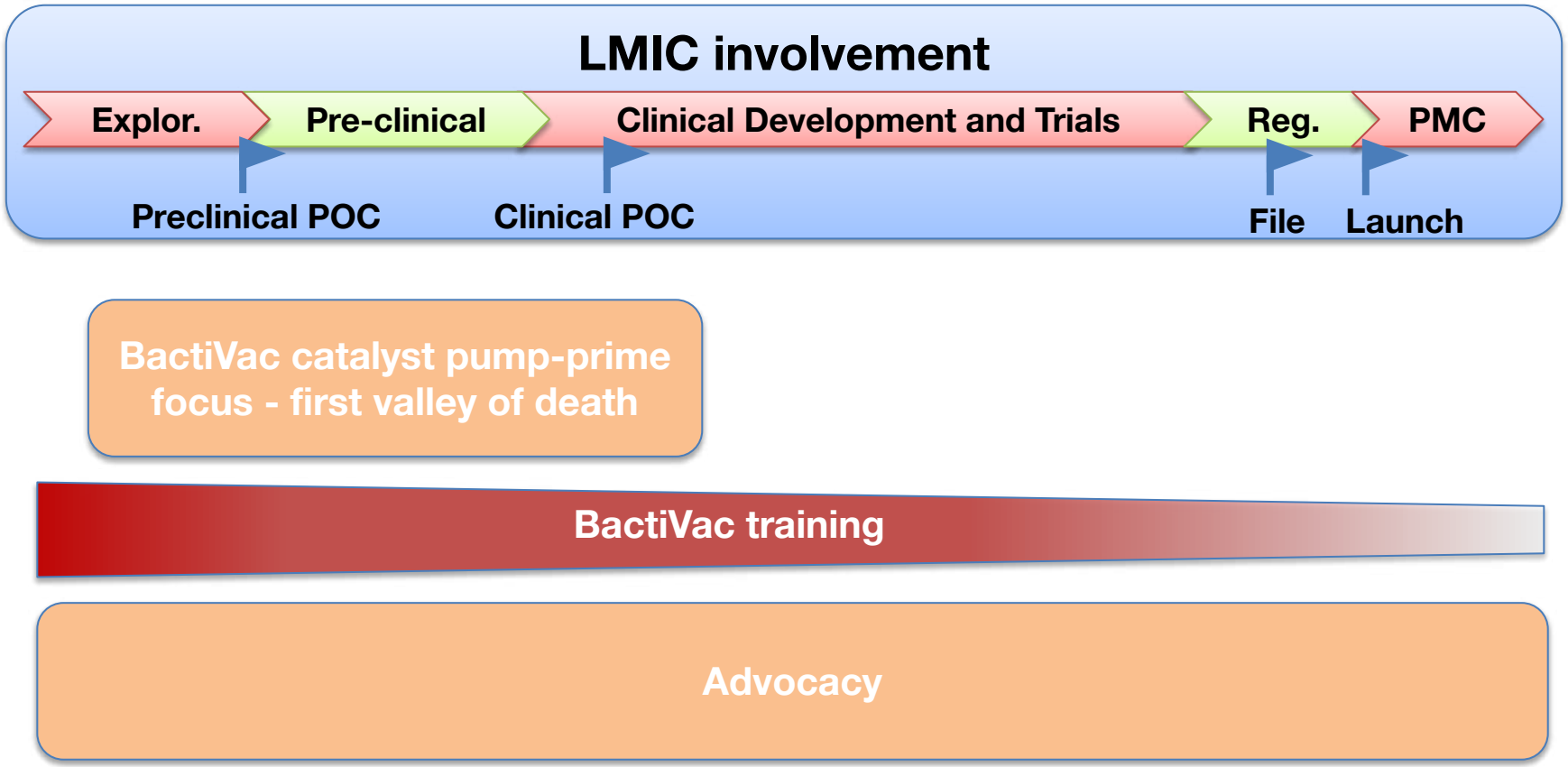


Potential spread of resistance



No bacteria survive = no transmission / resistance

BactiVac is there to help vaccine development along the whole pipeline



UNIVERSITY OF BIRMINGHAM | BactiVac network

Membership

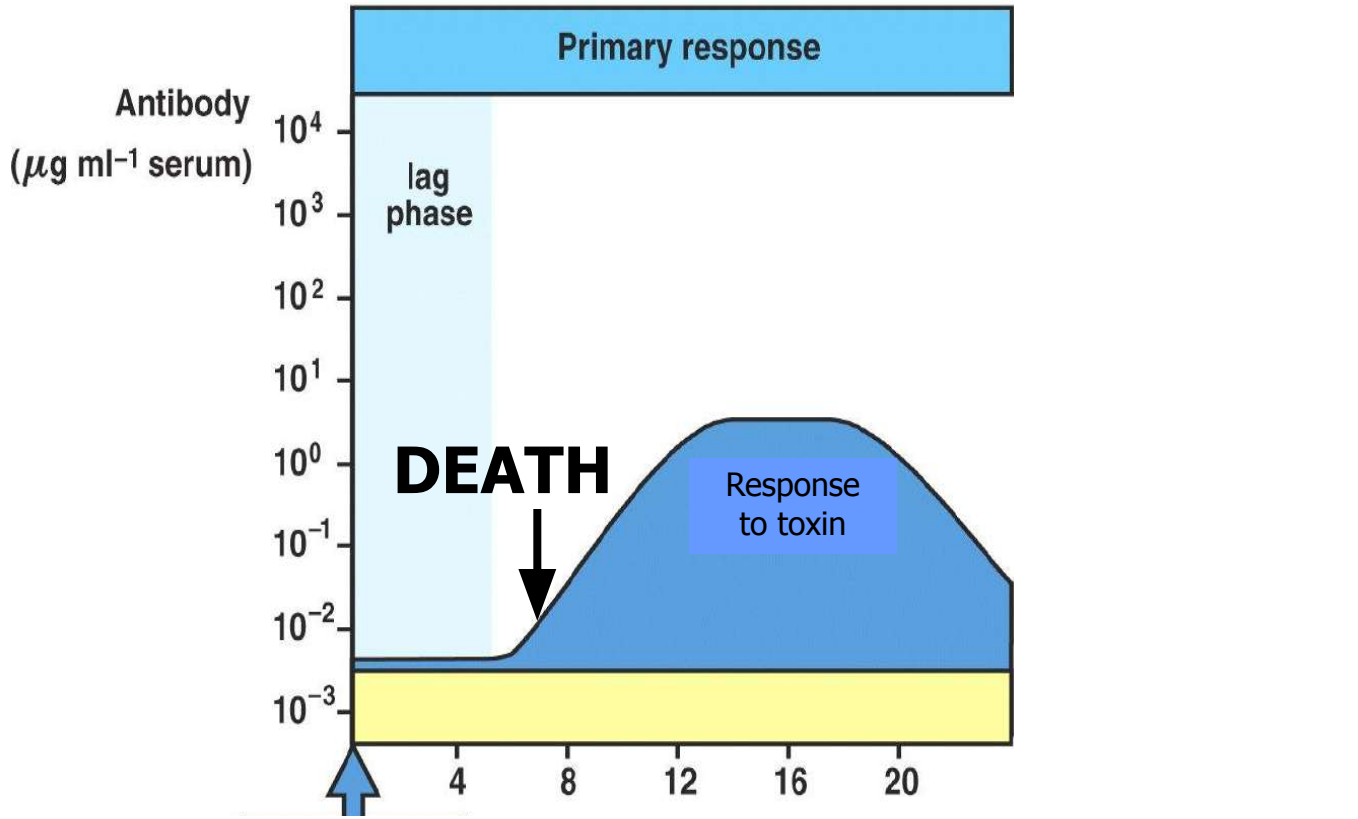
- Grown from 0 to over 1,600 members since 2017
- Members from 84 different countries
- 49% based in low- and middle-income countries (LMICs)
- 14% are based in industry

Not yet a member of BactiVac? Membership is free!

www.birmingham.ac.uk/bactivac

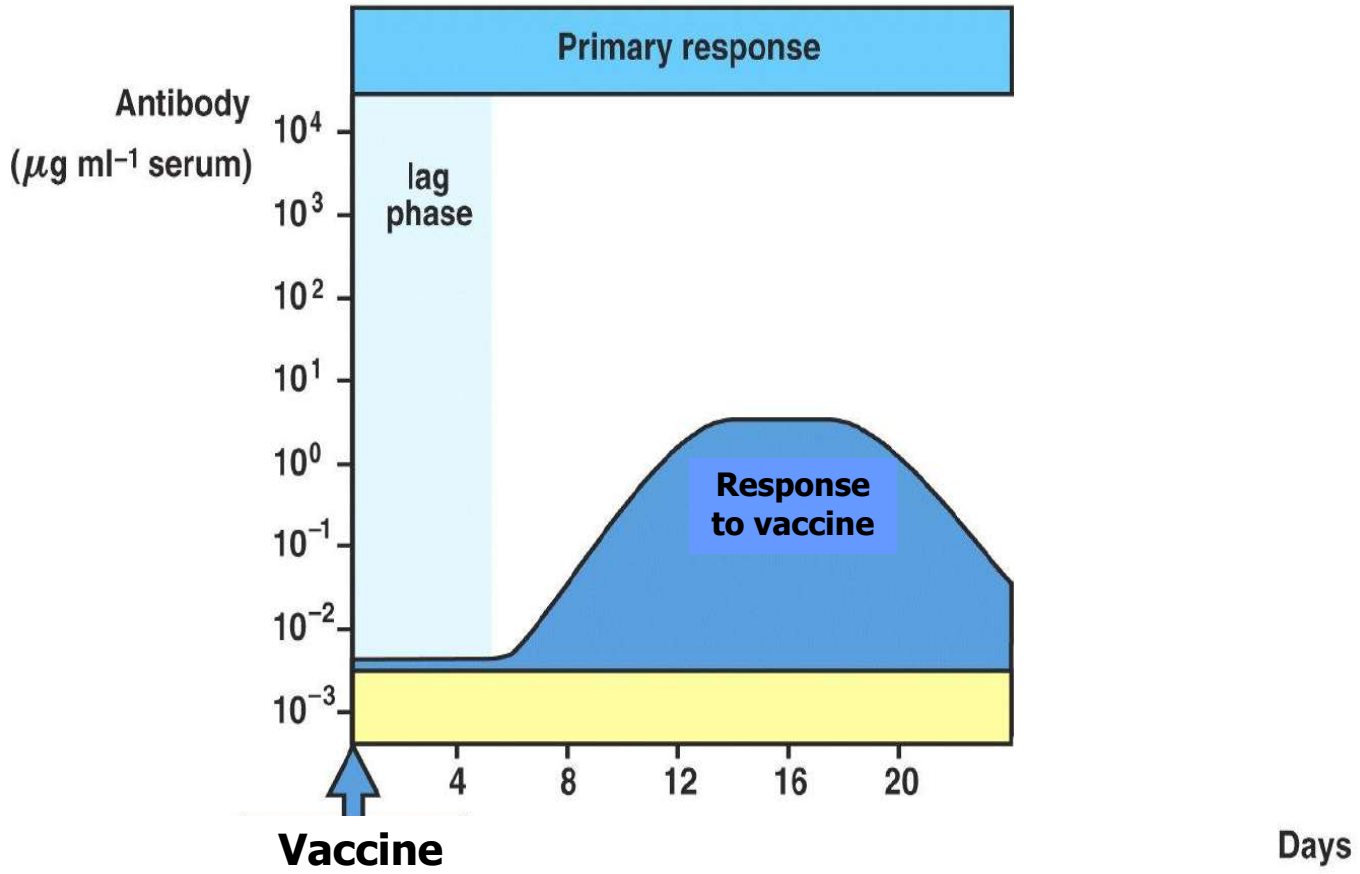
UNIVERSITY OF BIRMINGHAM | BactiVac network

The benefit of vaccines is timing of their activity



Corynebacterium diphtheriae

The benefit of vaccines is timing of their activity



The residual “shoulder” of antibody and the speed of the recall response can combine to prevent disease

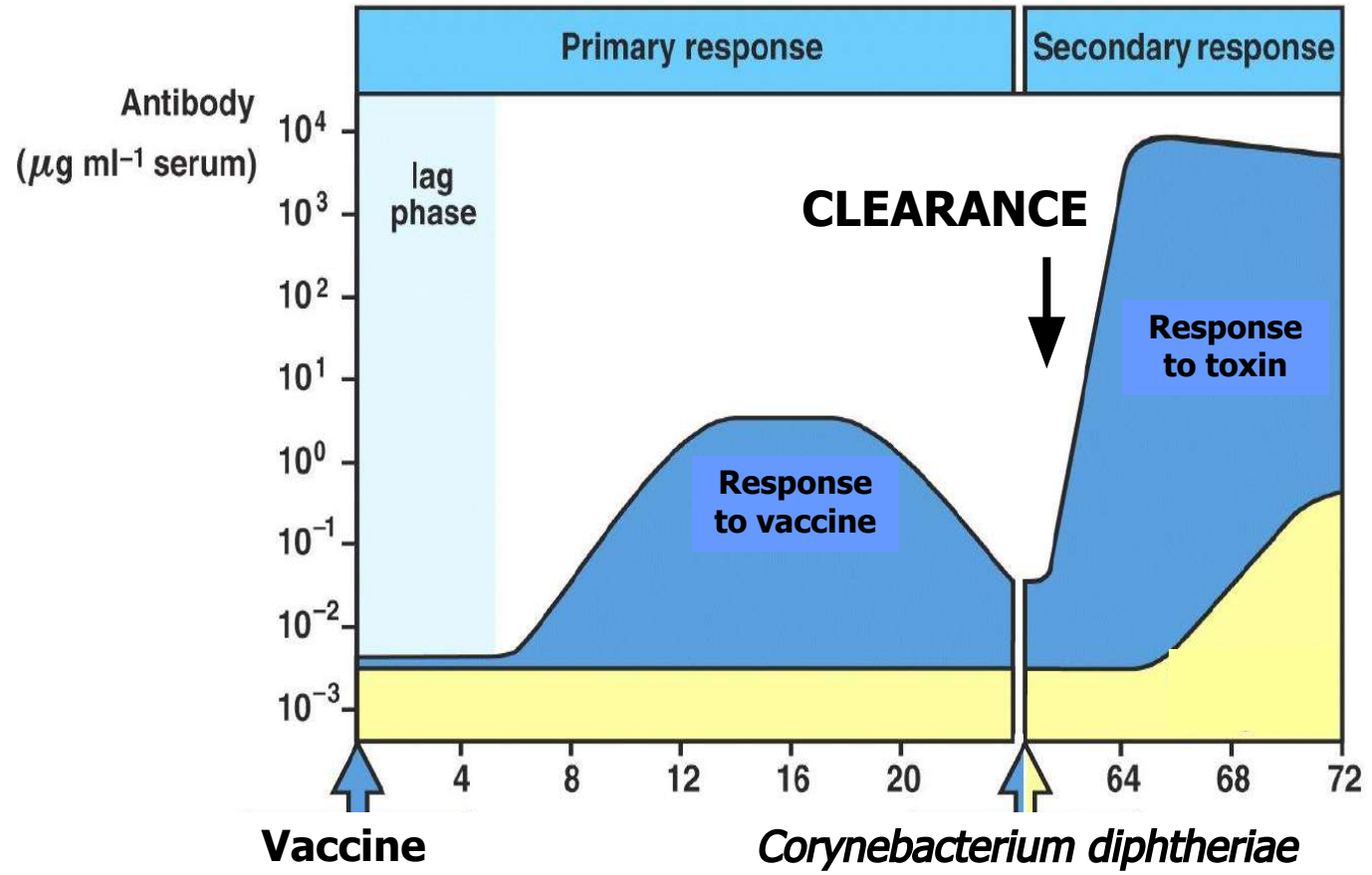
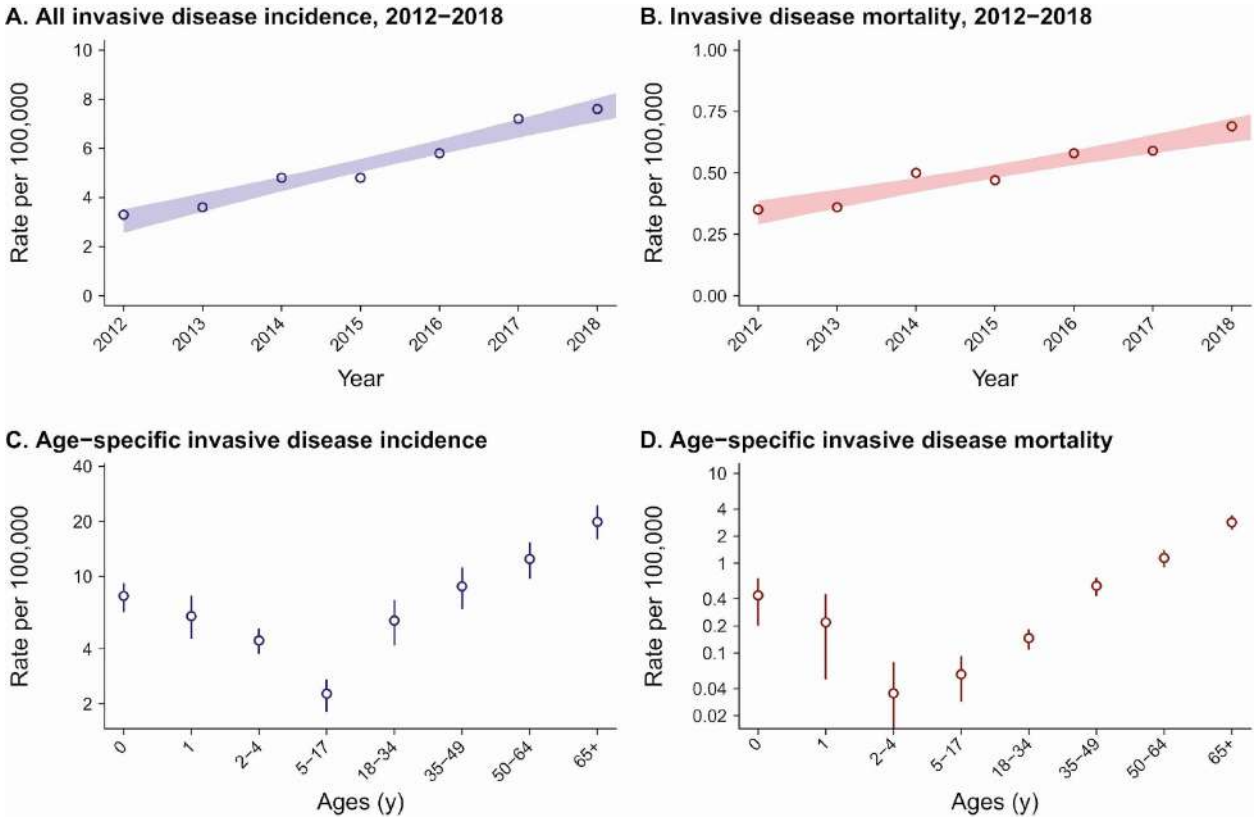
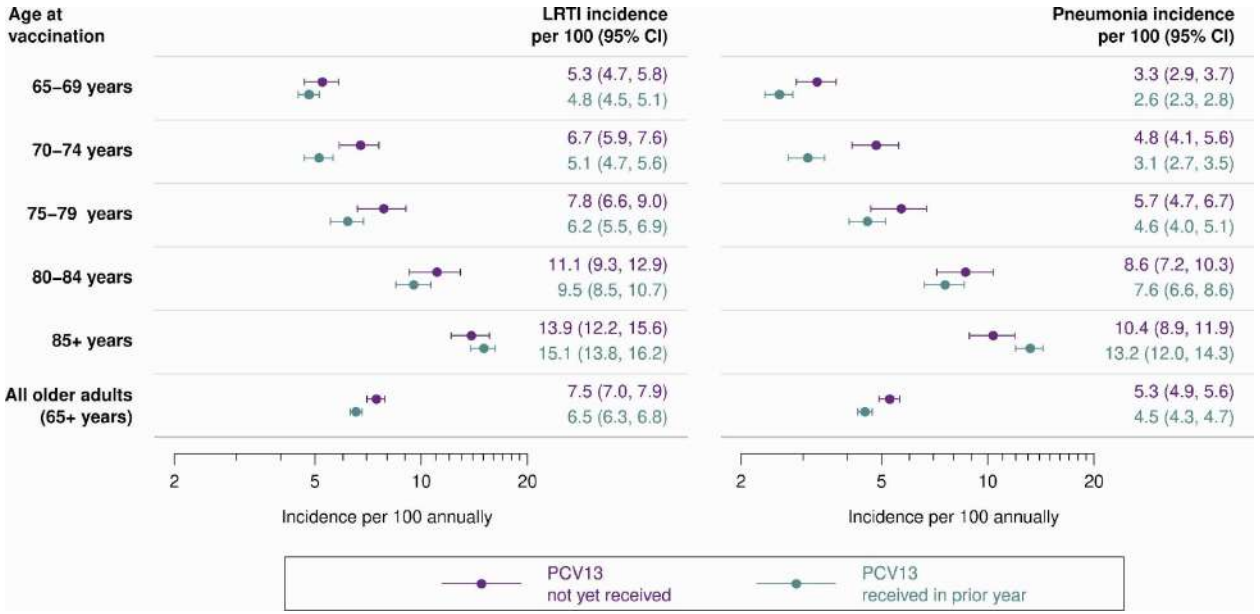


Figure 1. Projecting incidence of invasive group A Streptococcus (GAS) disease. We plot increases from 2012 to 2018 in ...



Clin Infect Dis, Volume 74, Issue 6, 15 March 2022, Pages 983–992, https://doi.org/10.1093/cid/ciab597

Figure 1. Age-specific incidence of first LRTI and pneumonia during years before and after receipt of PCV13. We present ...



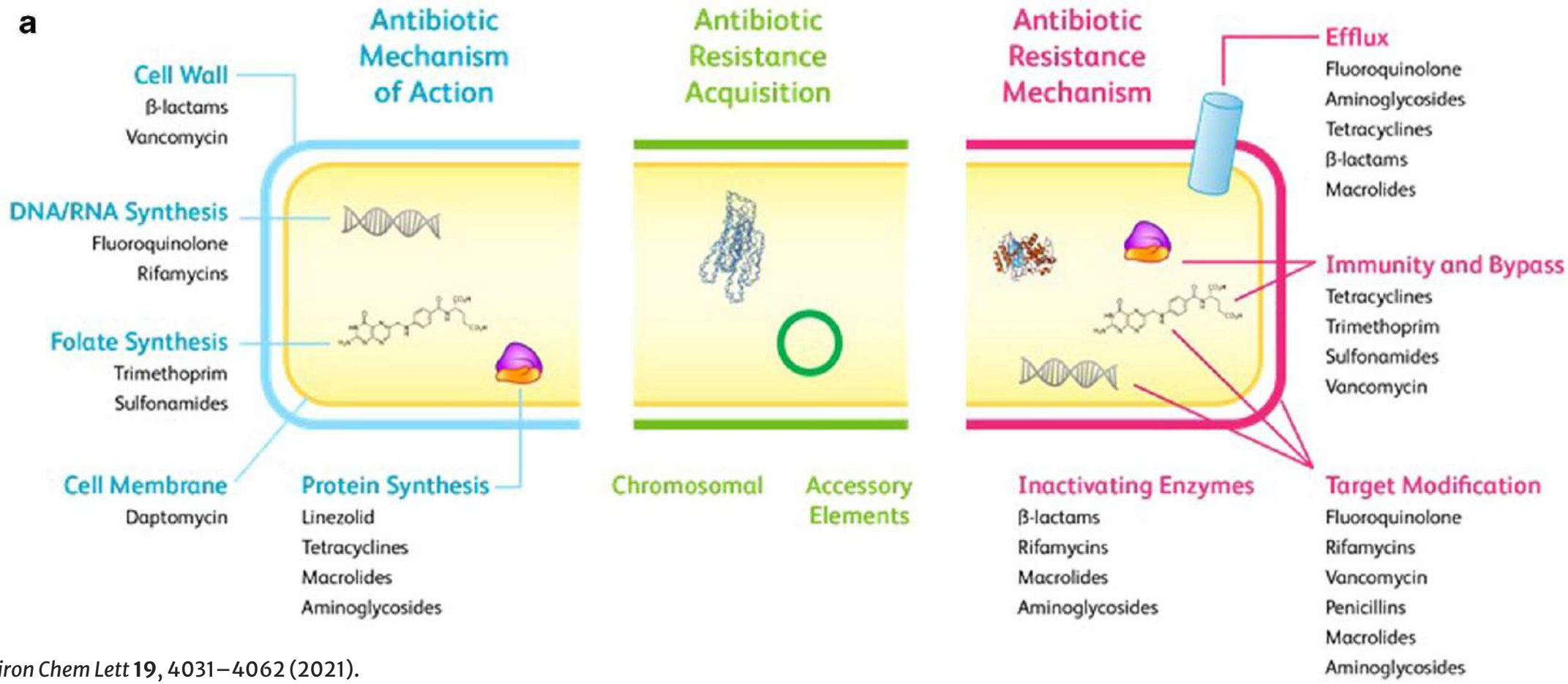
Approx 10%-25% VE overall depending upon study BUT THIS IS LRTI AND PNEUMONIAC AUSED BY VIRUSES NOT INVASIVE PNEUMO

https://doi.org/10.1093/infdis/jiac098

Clin Infect Dis, Volume 75, Issue 5, 1 September 2022, Pages 832–841, https://doi.org/10.1093/cid/ciab1051

There are multiple routes that lead to antimicrobial failure – reflective of an ancient arms race that humans and their actions have accelerated

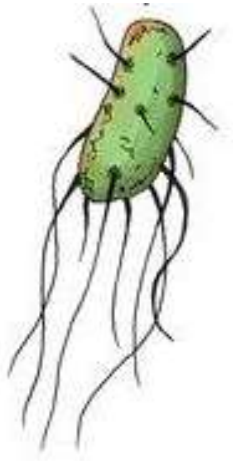
Antibiotics **Active infection** High pathogen numbers

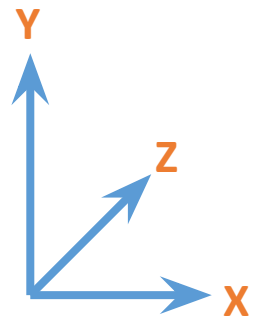


Jansen, K.U., *et al. Environ Chem Lett* **19**, 4031–4062 (2021).

The differences between bacteria and viruses can impact vaccine “success”

SARS-CoV-2 | ***E. coli*** | **IgG**

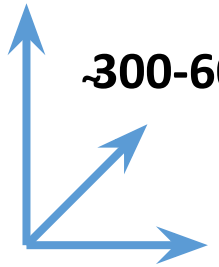




60-140 nm

1000-4000nm

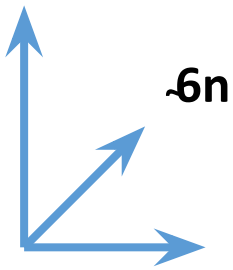
~300-600nm



~300-600nm

~10nm

~6nm



~12nm

Virus

Intracellular

Host-dependent

Few surface Ag (spike 25-100 copies)

Low 10(0)s Abs can bind

Bacterium

Different niches

Metabolism not host-dependent

100s different surface Ag

1000s Abs can bind

E. coli surface area >>>200 fold; volume ~2000 fold than SARS-2

Adapted from https://scienceexchange.caltech.edu/topics/covid-19-coronavirus-sars-cov-2/what-is-a-virus

The limitations of vaccines compared to antibiotics - there are >90 capsule serotypes of pneumococcus, all need specific recognition by Ab but not abiotics

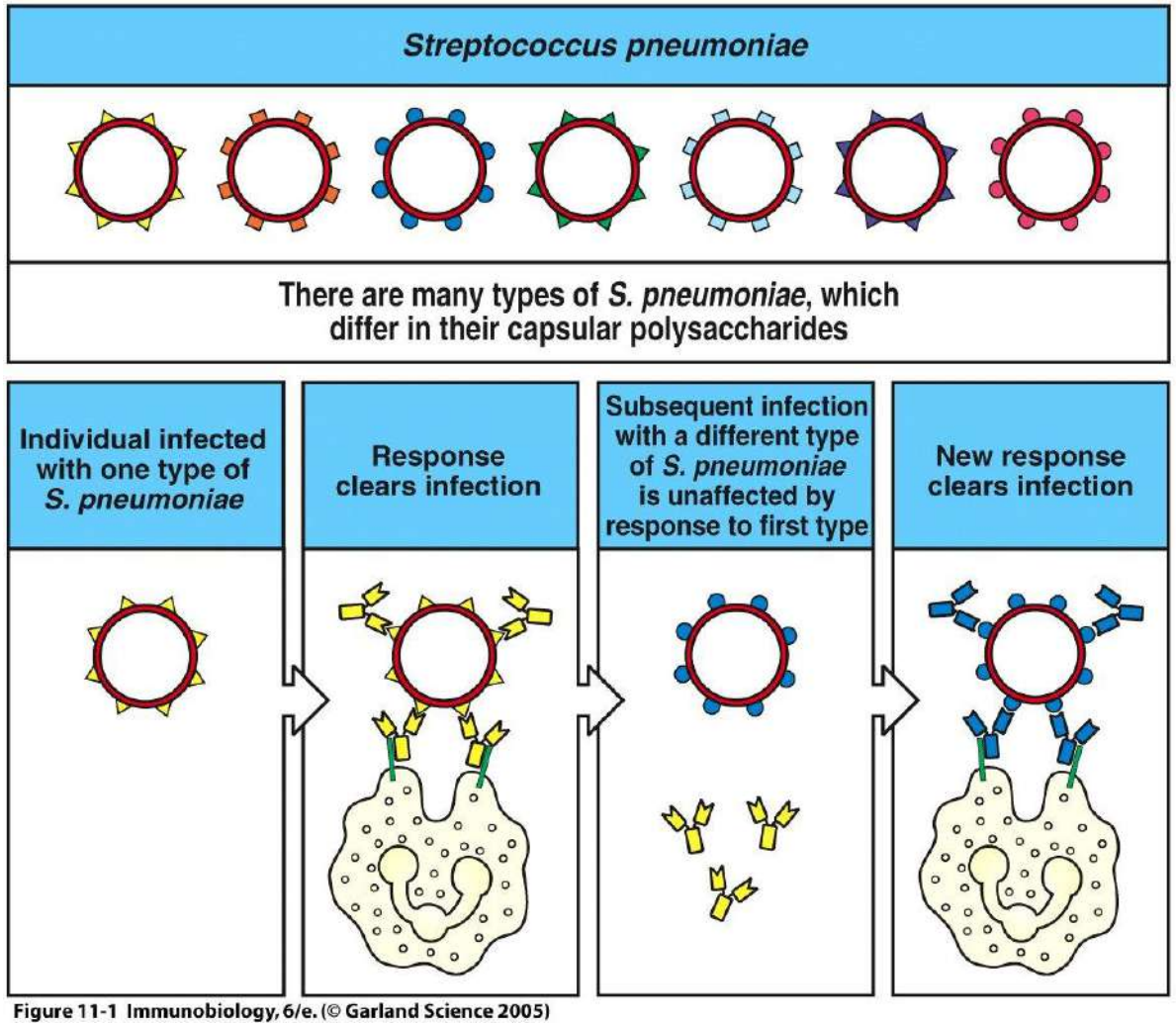


Figure 11-1 Immunobiology, 6/e. (© Garland Science 2005)

Hyporesponsiveness

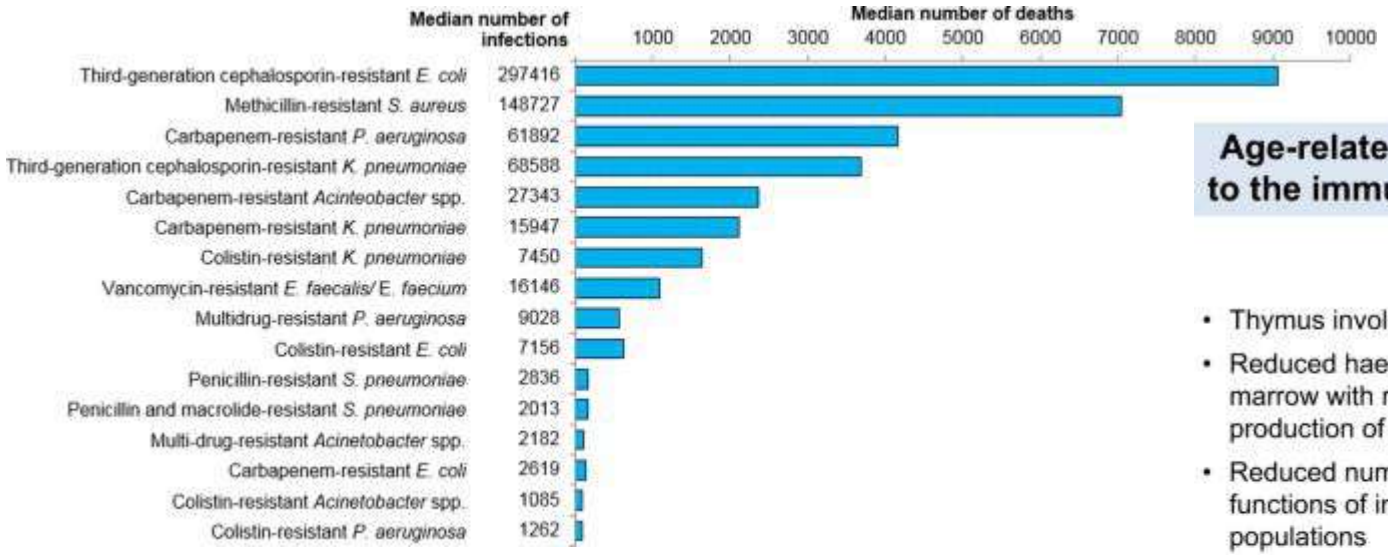
Serotype diversity

Vaccine fatigue/scheduling

Population targeting (who, age group)

Failure? Ab-independent, killing mechanisms

Economic modelling, QALY, measures of value?

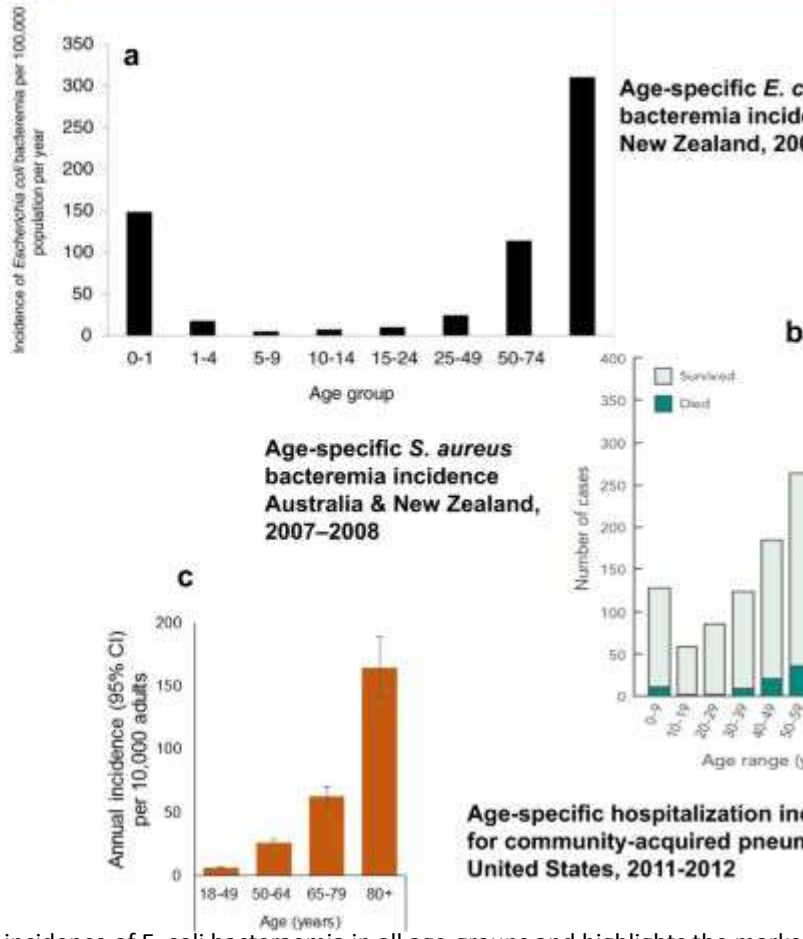


The burden of disease and death was modelled using 2015 data from the European Antimicrobial R Network (EARS-Net) country-corrected for population coverage. The graph shows the median estim and deaths caused by 16 antibiotic-resistant pathogens of public health importance.

Age-related changes to the immune system

- Thymus involution
- Reduced haemopoietic bone marrow with reduced production of naïve cells
- Reduced number and functions of immune cell populations
- Proliferation of T memory cells and lowered capacity to respond to new antigens
- Imbalances in innate inflammatory mediators leading to chronic low grade inflammation

Increased susceptibility to bacterial infections



a The age-specific incidence of E. coli bacteraemia in all age-groups and highlights the marke burden after age 50 years. b The number of cases of S. aureus bacteraemia with higher case proportion of patients who died also increased with age. c The incidence of hospitalised com pneumonia in adults in the US, which increases substantially with age. Insert a reproduced fr Insert b reproduced with permission from Turnidge et al.127. Data for insert c from Jain et al

oolman, J.T. Expanding the role of bacterial vaccines into e-course vaccination strategies and prevention of ntimicrobial-resistant infections. *npj Vaccines* **5**, 84 (2020). ttps://doi.org/10.1038/s41541-020-00232-0

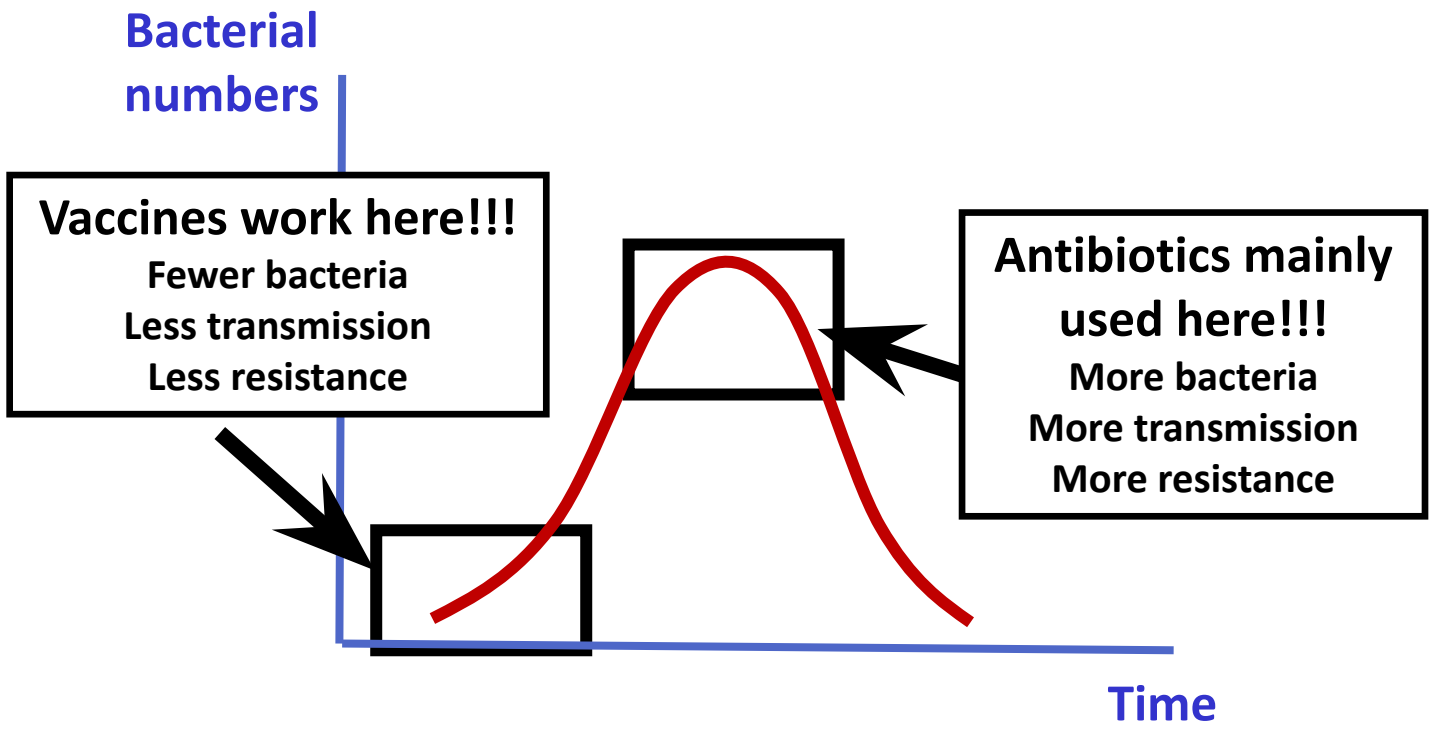
Available vaccines

- Cholera
- COVID-19 (corona virus)
- Dengue
- Diphtheria
- Hepatitis
- *Haemophilus influenzae* type b (Hib)
- Human papillomavirus (HPV)
- Influenza
- Japanese encephalitis
- Malaria
- Measles
- Meningococcal meningitis
- Mumps
- Pertussis
- Pneumococcal disease
- Poliomyelitis
- Rabies
- Rotavirus
- Rubella
- Tetanus
- Tick-borne encephalitis
- Tuberculosis
- Typhoid
- Varicella
- Yellow Fever

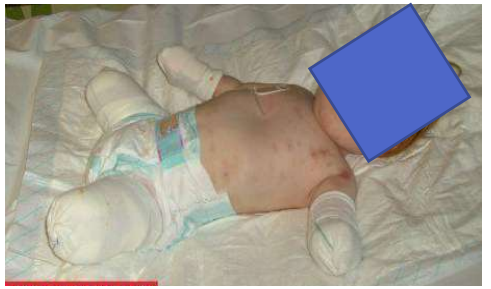
9 bacterial diseases

15 viral diseases

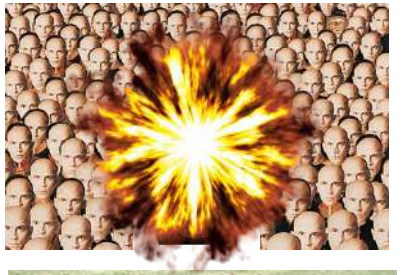
Vaccines are active at the time of pathogen encounter, antibiotics are usually used later or (sometimes) not appropriate



Vaccines save lives



Antibiotics save lives

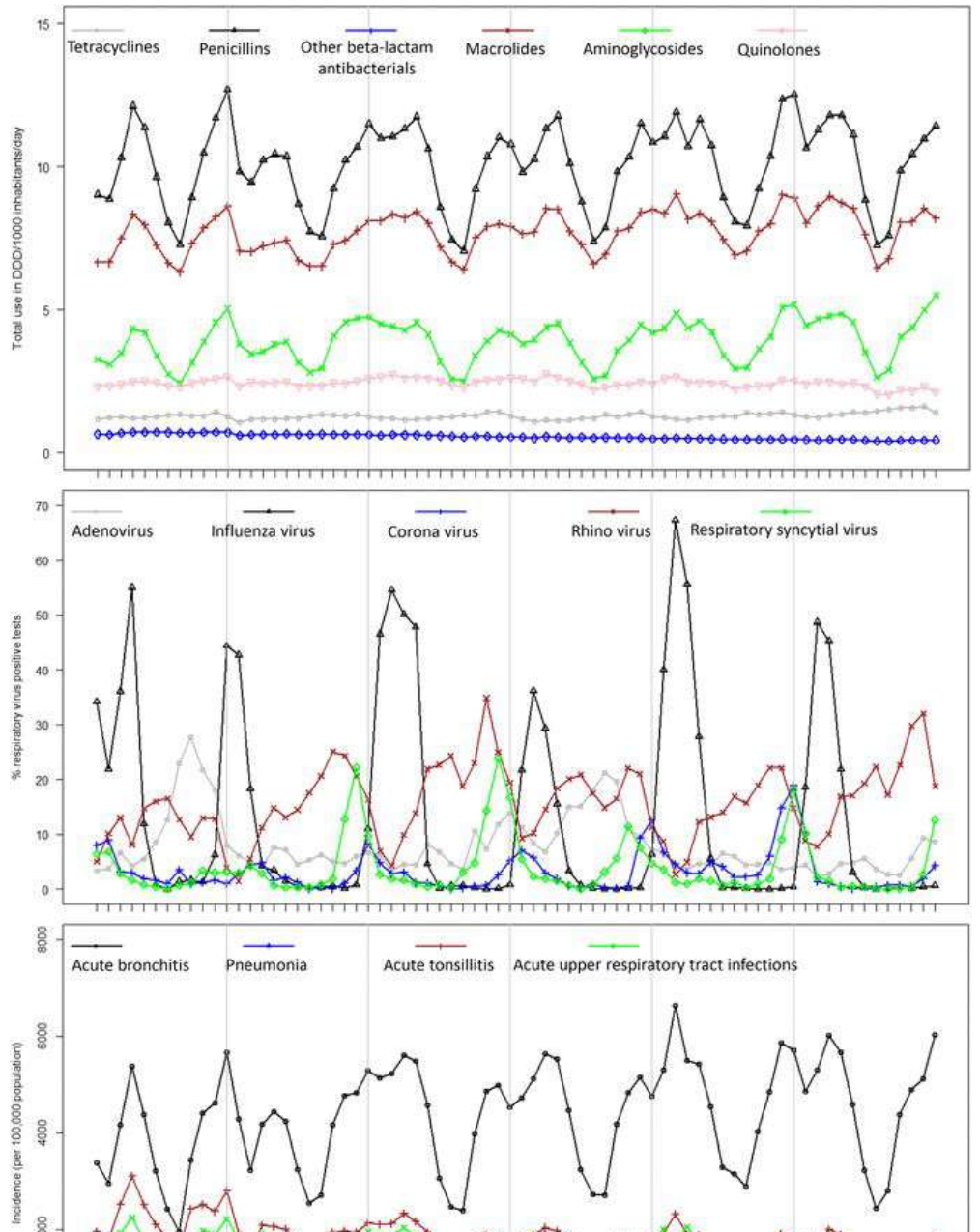


Consequences of prophylactic antibiotic use?

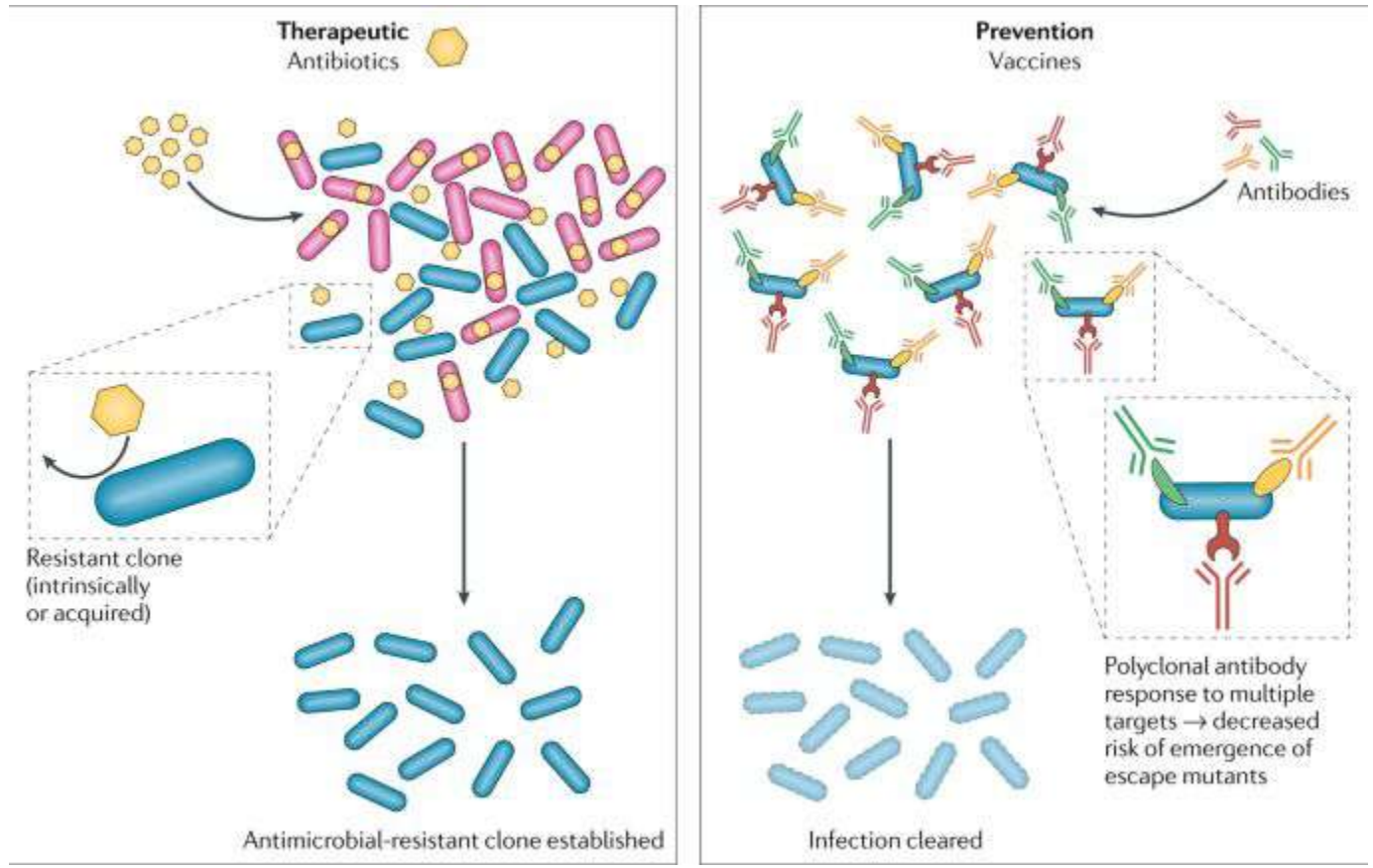
MR bacteria – typhoid

o use abiotics

ctions – flu and pneumo



7, 56 (2018).


Therapeutic
Antibiotics
Resistant clone
(intrinsically
or acquired)
Antimicrobial-resistant clone established
Prevention
Vaccines
Antibodies
Polyclonal antibody
response to multiple
targets → decreased
risk of emergence of
escape mutants
Infection cleared

The consequences of infection

The more infections, the more likely you are to die earlier

Inflammatory Bowel Disease

CMV and persistent viruses

Cancer

Cardiovascular disease

Autoimmunity

Deafness

Type 1 diabetes

Arthritis

Fertility

Cystic fibrosis

Obesity?

Hepatitis

Homeostasis

Guillain Barre Syndrome

Behaviour

Blindness

Ageing

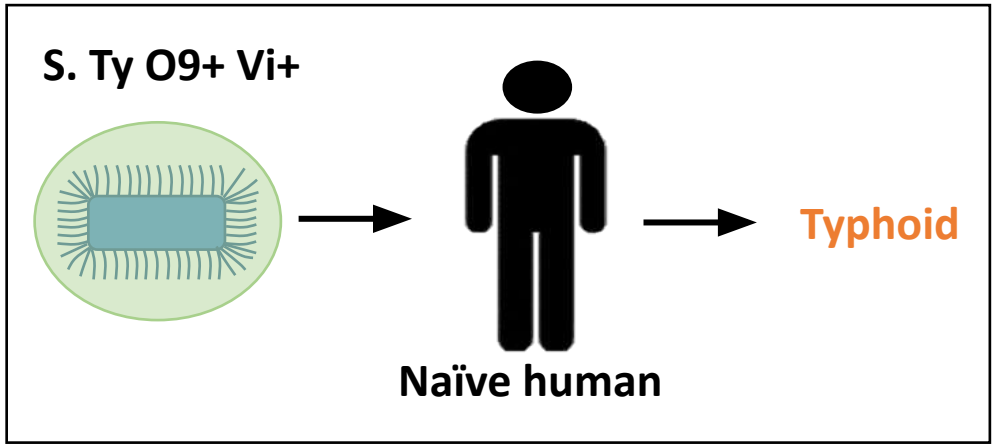
Chronic Obstructive Pulmonary Disease

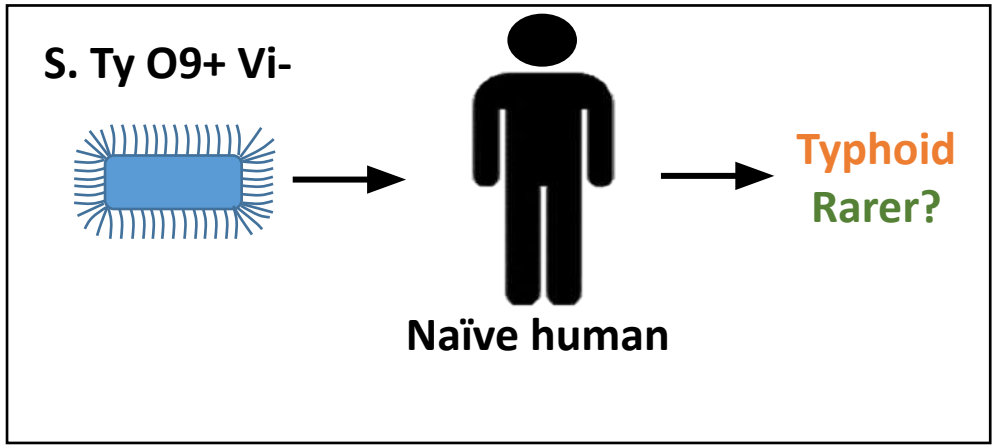
Amputation

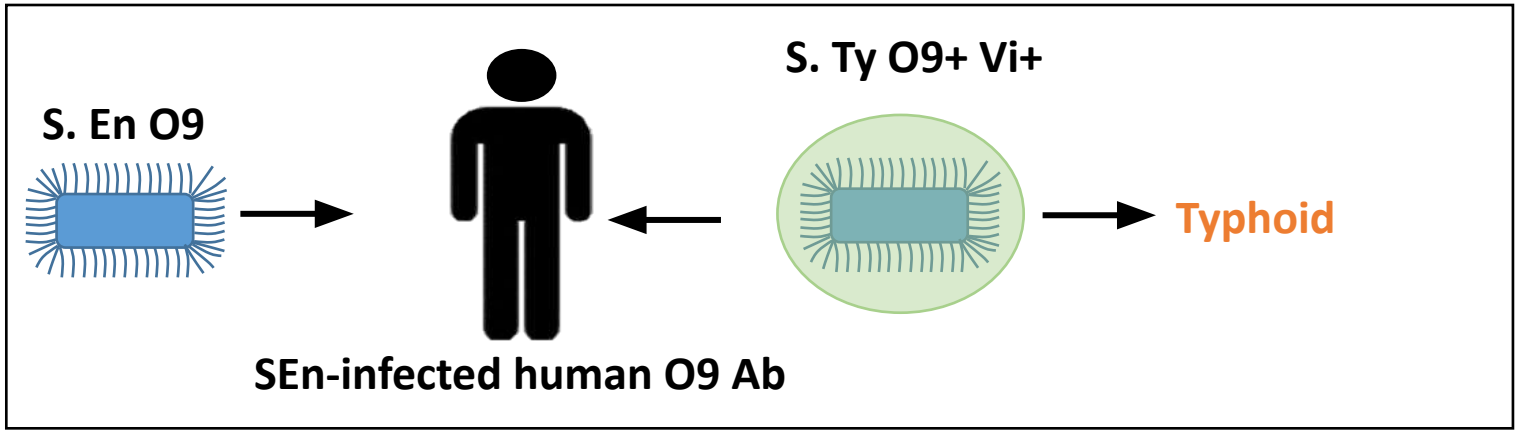
Bronchiectasis

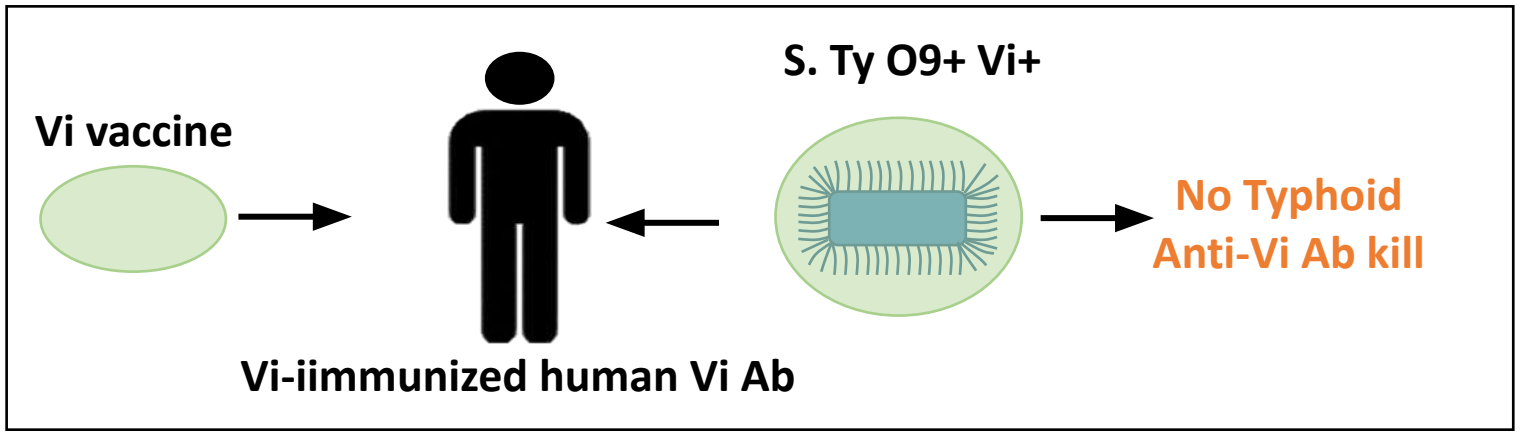
Asthma

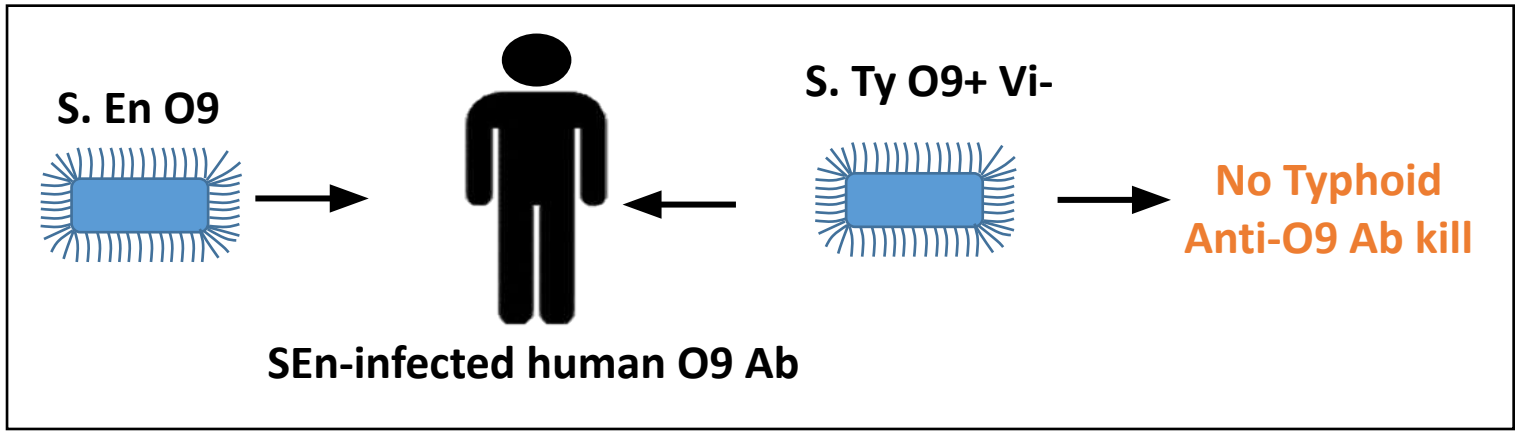
Herd immunity





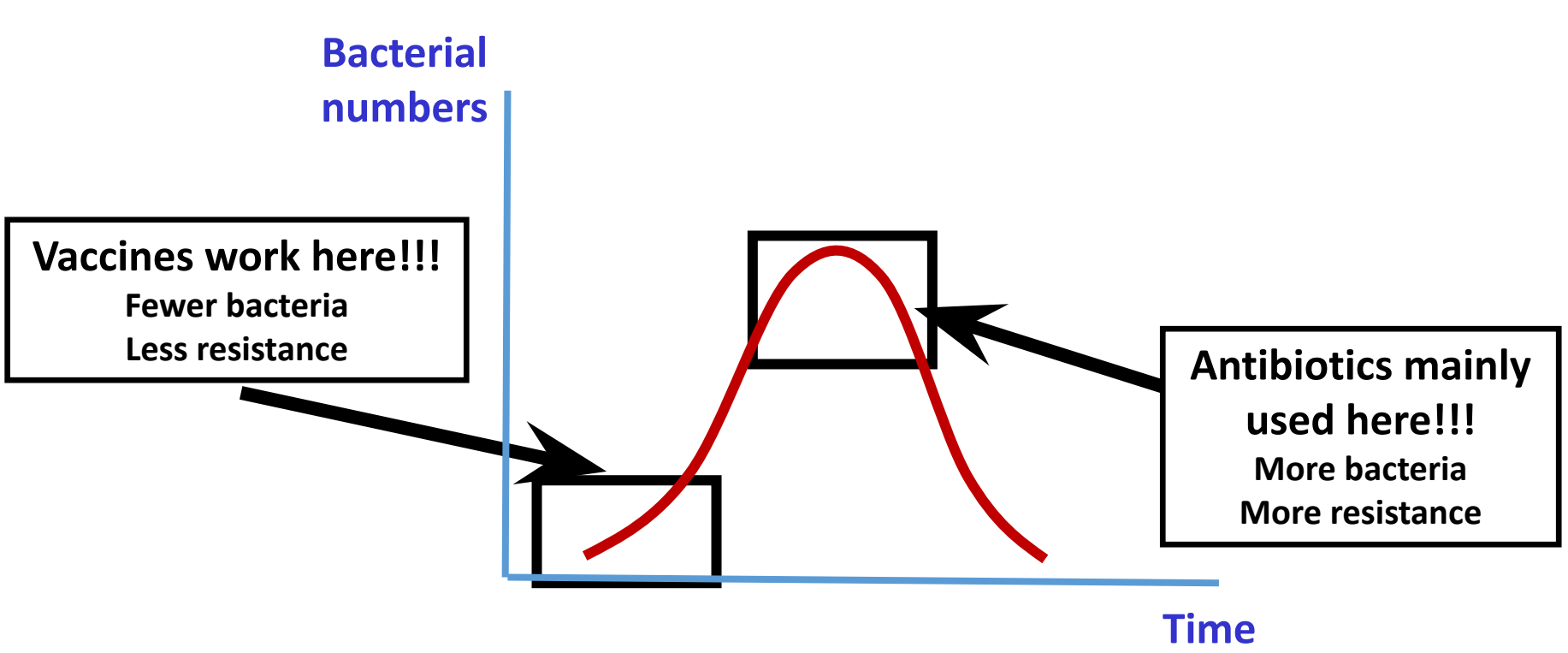




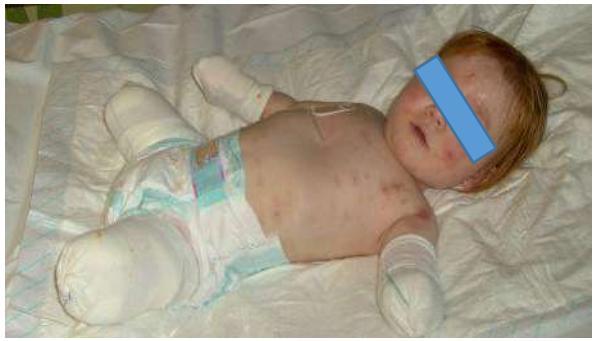


Vaccines democratise opportunity across the life course

There are limited options to treat active infections



Vaccines save lives

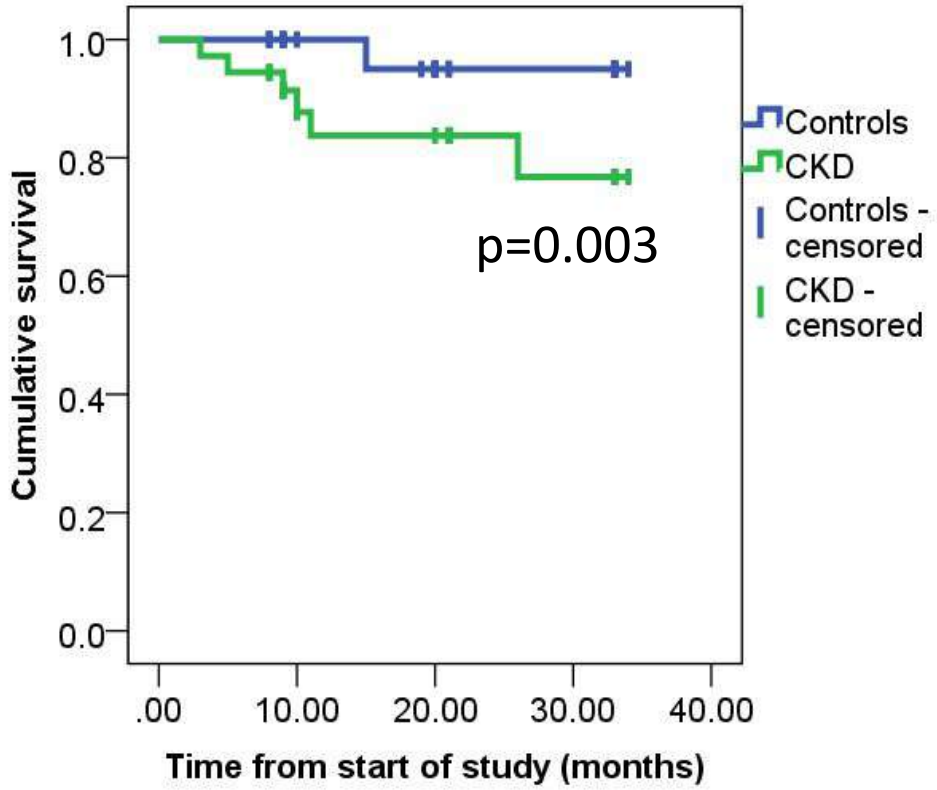


Antibiotics save lives

The success of vaccines (we rarely know when they have save our life) can make selling their importance more difficult cf antibiotics

CKD is associated with more infections and higher mortality

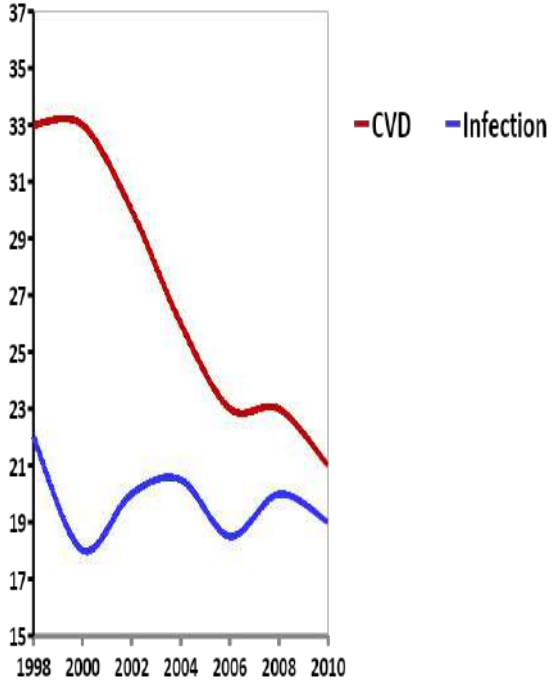
	Controls	CKD	p value
Incidence of ALL infections (per 1000 person days)	1.8 (0.9-3.9)	3.4 (2.2-5.2)	0.09
Incidence of RESPIRATORY infections (per 1000 person days)	1.1 (0.4-2.4)	2.7 (1.6-4.3)	**0.05**



Chronic Kidney Disease massively increases risk of serious infection and poor response to vaccination

Infection-related mortality unchanged over 10 years

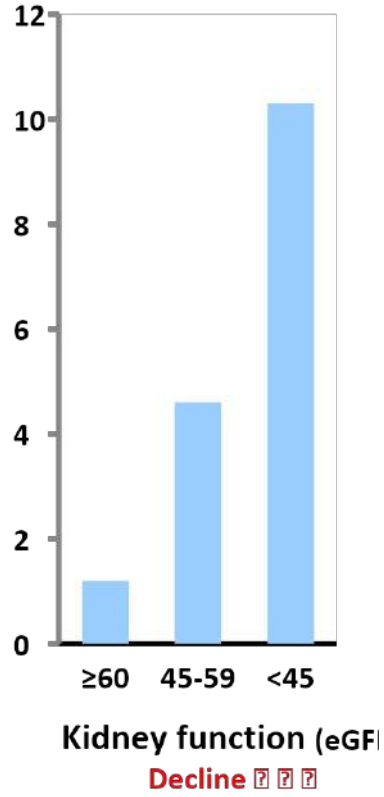
% cause of death



Steenkamp et al, Nephron Clin Pract 2013

Infection-related mortality ↑ with ↓ kidney function

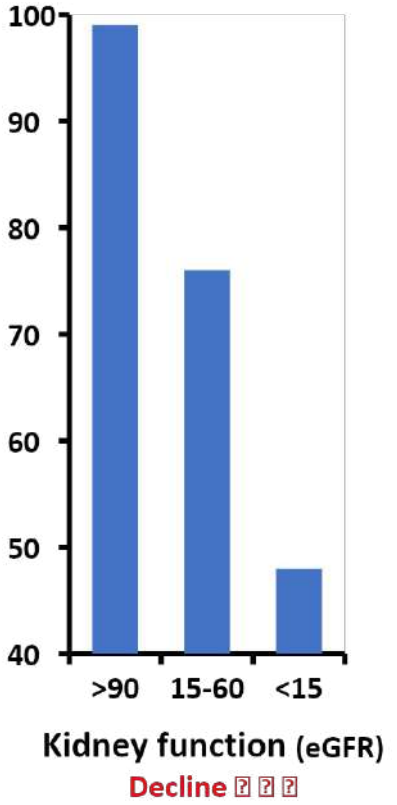
Deaths / 1000 person years



Wang et al, Am. J. Nephrology 2011

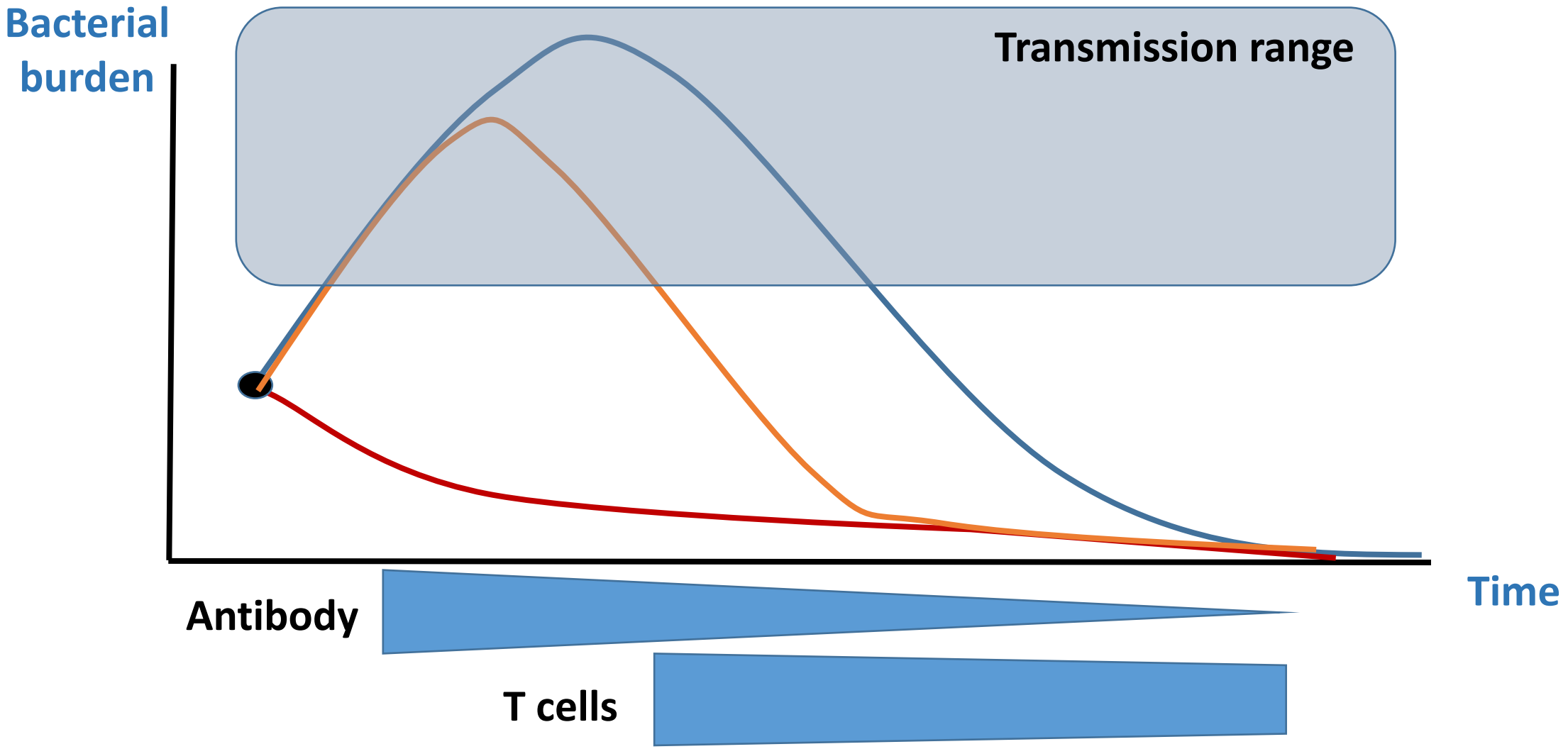
HBV vaccine seronversion ↓ with ↓ kidney function

% seroconversion



Ghadiani et al, J. Res Med Sci 2012

B cell responses help reduce the bacterial burden at the time of first encounter
T cell responses contribute later



B cell responses help reduce the bacterial burden at the time of first encounter
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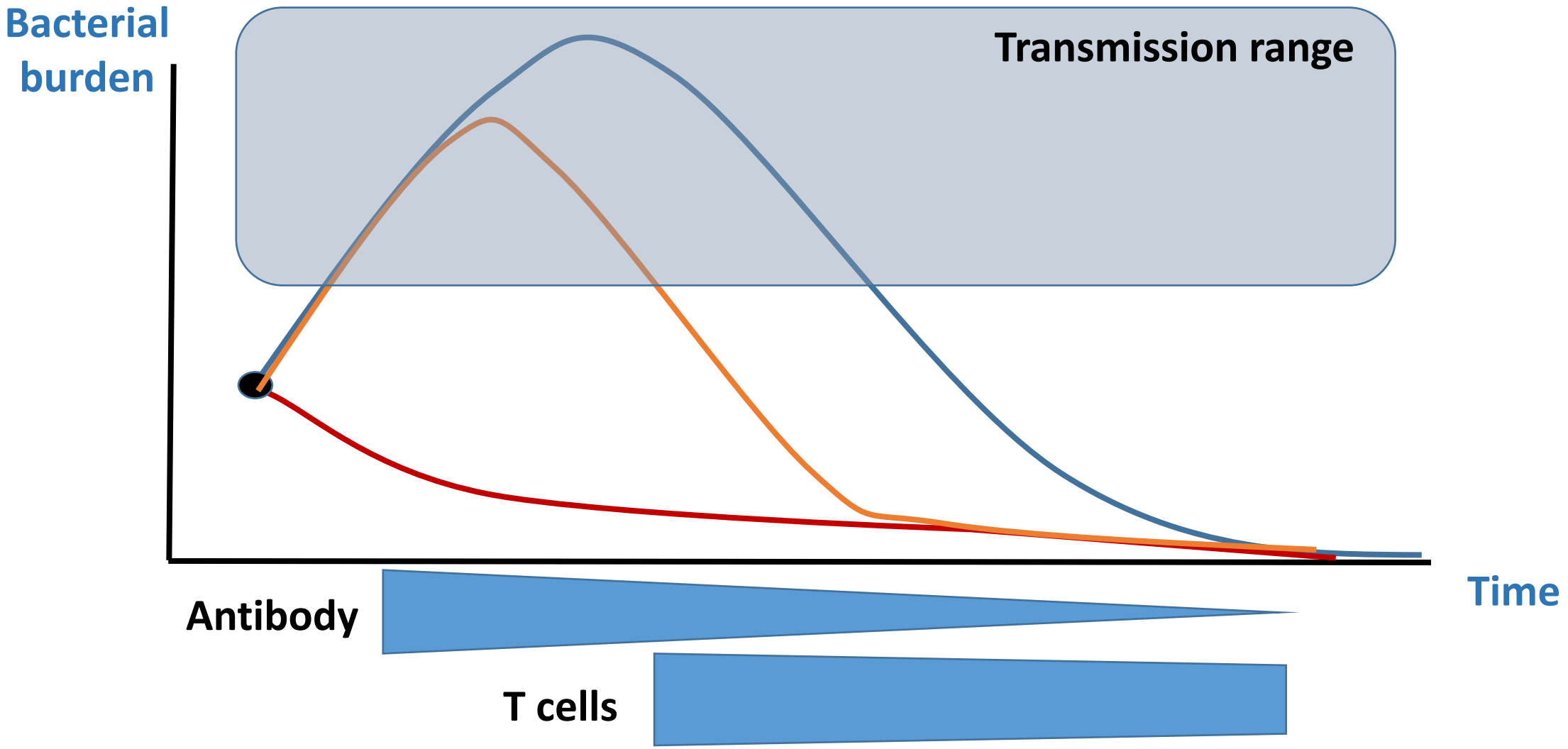
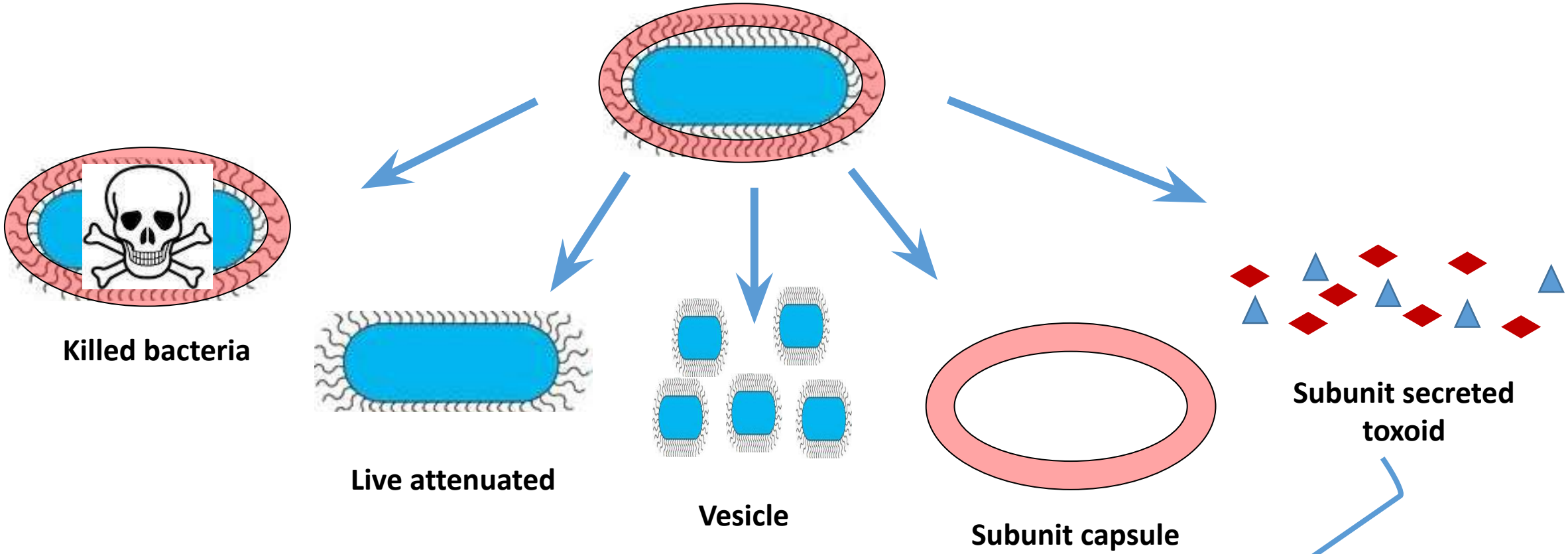


What types of vaccines are licensed for use against bacterial infections in humans?



Differences in cost, stability etc…

Vaccines can induce T-dependent immunity (e.g. to proteinaceous molecules such as tetanus toxoid or live vaccines) or T-independent immunity (such as capsular polysaccharides)

T-independent antigens can become T-dependent antigens by conjugation to proteins

Vaccines often target multiple antigens or multiple epitopes within an antigen-wide coverage – potentially lots of changes needed to introduce evasion

AMR rapid and widespread – vaccine resistance rare and limited (real/semantics) – 6 years staph penicillin, 100s years smallpox. AMR can develop even inside patients fully compliant

There is a difference between evasion and strain replacement and selection based on contact with the vaccine inside a person. The veterinary context may be slightly different as may be wider

That said resistance is more narrow to vaccines and takes longer to appear

Vaccines work before infection and often before transmission – kills potential for transfer

The larger the bacterial population size at the time of treatment, the more likely there is resistance to appear

UNKNOWN – evidence of resistance to bactericidal killing mediated by abs

Drug often interferes with a narrow range of cell activities, vaccine can be more widespread BUT think capsule vaccines – so in some way acts like combination therapy

Pertussis evasion – pertactin-deficient strains, assoc with acellular vac,

Vaccines can be direct – kill pathogen, indirect eg flu reduce abiotic use because no idea what is infection g you or reduce abiotic uxse because less flu and less secondary infection

CKD patients can maintain immune responses to historic antigens

GFR<60ml/min/1.73m^2 or **1+ markers of kidney damage**

Prevalent - Affects 1 in 10 adults, ~2.5% NHS budget

Caused by different pathological processes

- **Diabetes mellitus (DM)**
- **Hypertension (HTN)**
- **Atherosclerosis (ischaemic nephropathy)**

CKD patients have higher inflammatory markers – CRP, TNF etc

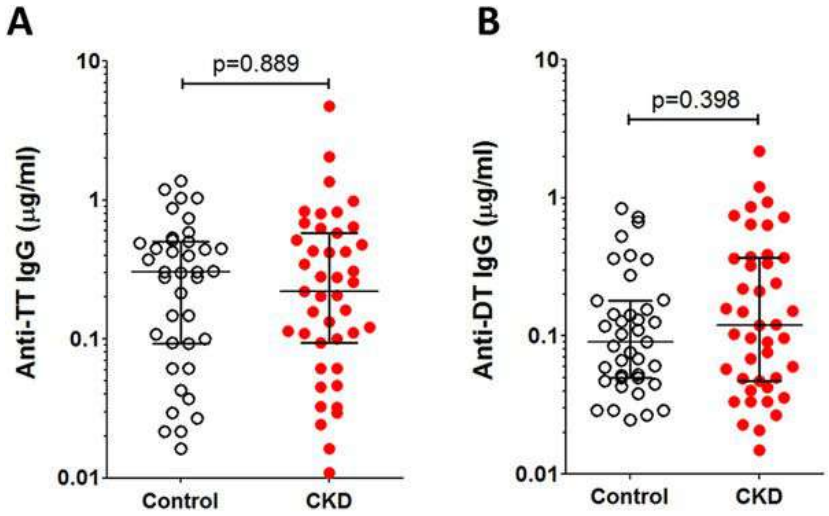
Sepsis mortality 30-50x greater in dialysis patients

1 year mortality = 13% in severe CKD

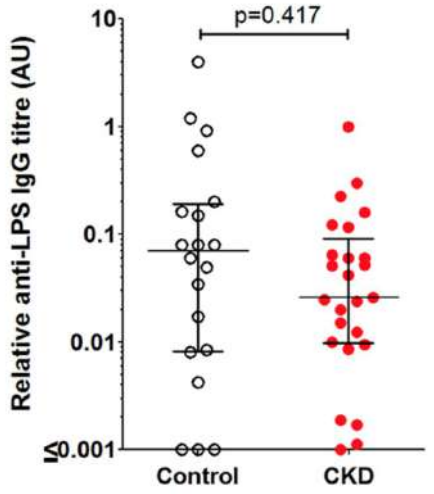
Risk of death increases stepwise with ↓ eGFR

Is this because of a failure to mount immunity?

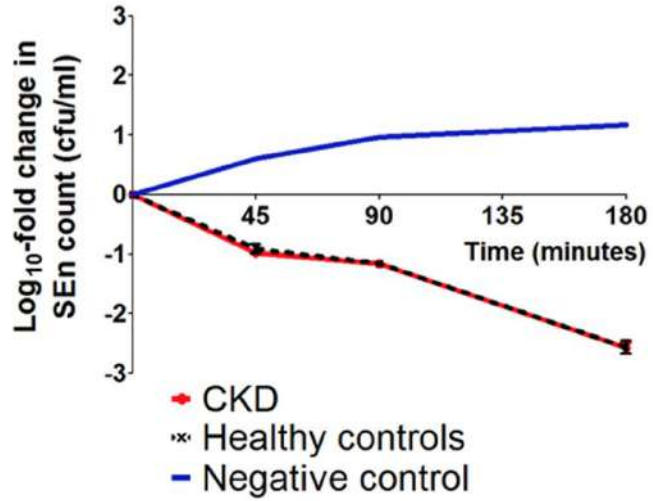
How about responses to historic antigens?



Anti-*Salmonella* IgG titres



Bactericidal activity of anti-*Salmonella* IgG



Wall N et al PLoSOne 2018

en vaccines and treatments
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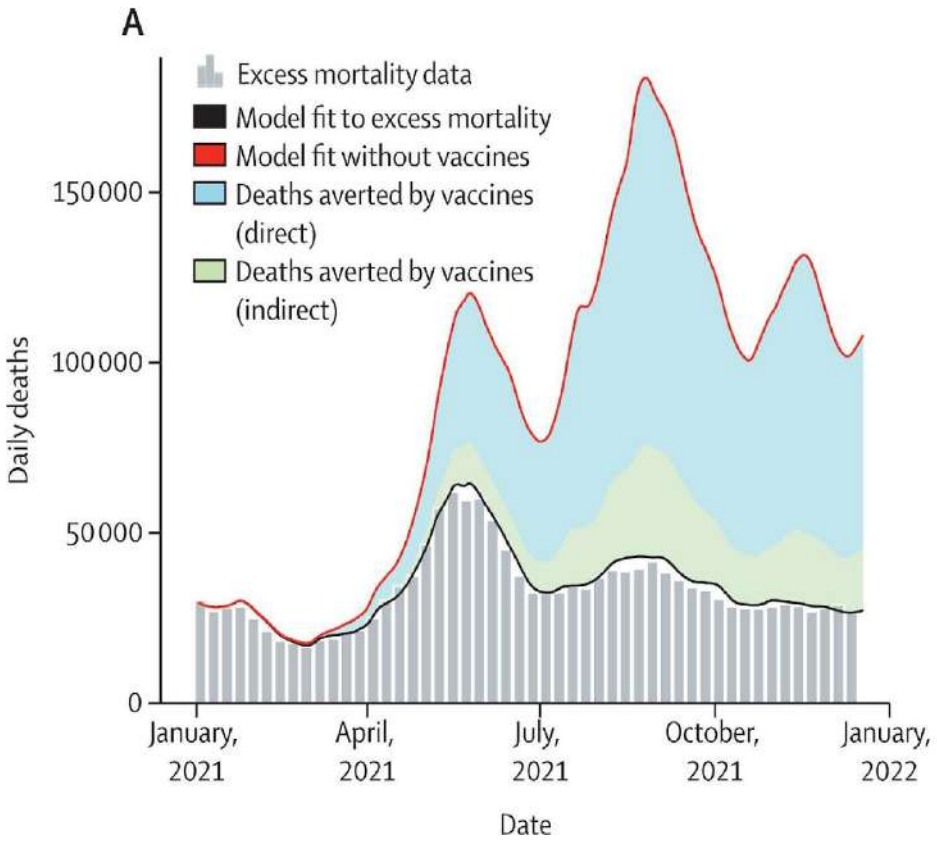
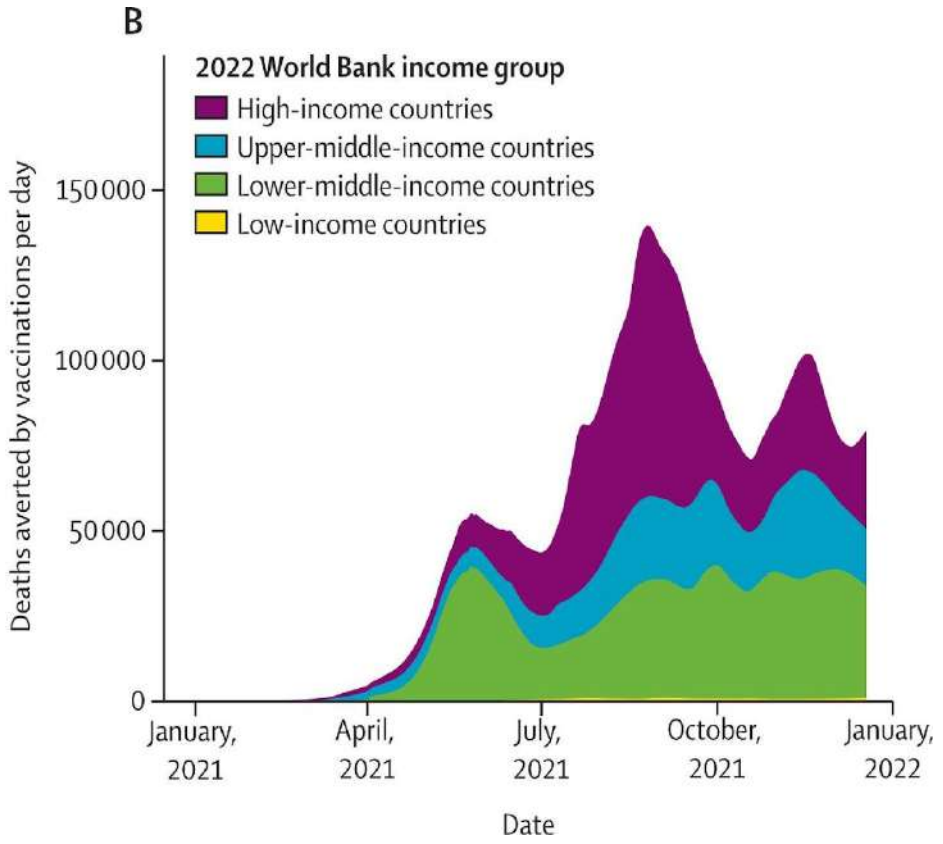




How can vaccines help reduce AMR?

Vaccines can help directly and indirectly – prevent infection, block transmission

Direct –

Can be differentially beneficial in reducing antibiotic use for mild infections

Reduce development of resistance – Tetanus, pertussis and diphtheria

Reduce burden of infections with existing AMR – HiB, pneumococcus, *Neisseria* spp

Reduce bacterial transmission – Herd immunity

Reduce opportunity for genetic exchange by bacteria in shared niches

Indirect –

Block transmission – target "similar" pathogens (Bexsero and gonococcus)

50% antibiotic use inappropriate – flu season correlates with antibiotic use - diagnostics

Flu vaccine reduces secondary bacterial infections and antibiotic treatments

How can vaccines help protect against infection?

Direct

Prevent infection, reduce severity etc

Reduce NCD sequelae (flu and exacerbations of cardiovascular disease)

Protect near certain acquisition (HepB vac of infants born to infected mothers)

Indirect

Herd immunity – e.g. pneumococcus infants and grandparents

Prevent damage and associated secondary infection (e.g. flu and pneumococcus)

Prevent infection in offspring (e.g. maternal immunization)

Prevent complications of NCD – e.g. bronchiectasis

“Innate immune training”

Immunological concepts behind vaccination in the context of military medicine:

1. Herd immunity – unlikely during active deployment?
2. Skewing of adaptive immunity (antibody) to a narrow spectrum of antigens – global pathogen diversity and time before deployment? Cf outbreak pathogens (menB and OMV)
3. Protection from death – balance between disease (+/- infection) most often in adults
4. Added benefits of innate immune training - shorter-lived non-specific benefits (BCG)
5. Reactogenicity vs immunogenicity – original killed typhoid vaccine vs cholera vaccine
6. Time – Induction and persistence, access to boost, need to boost - TT/DT 10 yrs, vs MMR 1000+ years - cholera
7. Some populations will not i) respond well to vaccination; ii) respond to vaccination but still be less protected (classical and non-classical immunodeficiencies) – less important in healthy military recruits?
8. COVID-19 has taught us many lessons – real-time benefit that lasts despite pathogen diversity

We have surprisingly few tools to prevent disease

Clean water, hand washing, public health

Vaccines

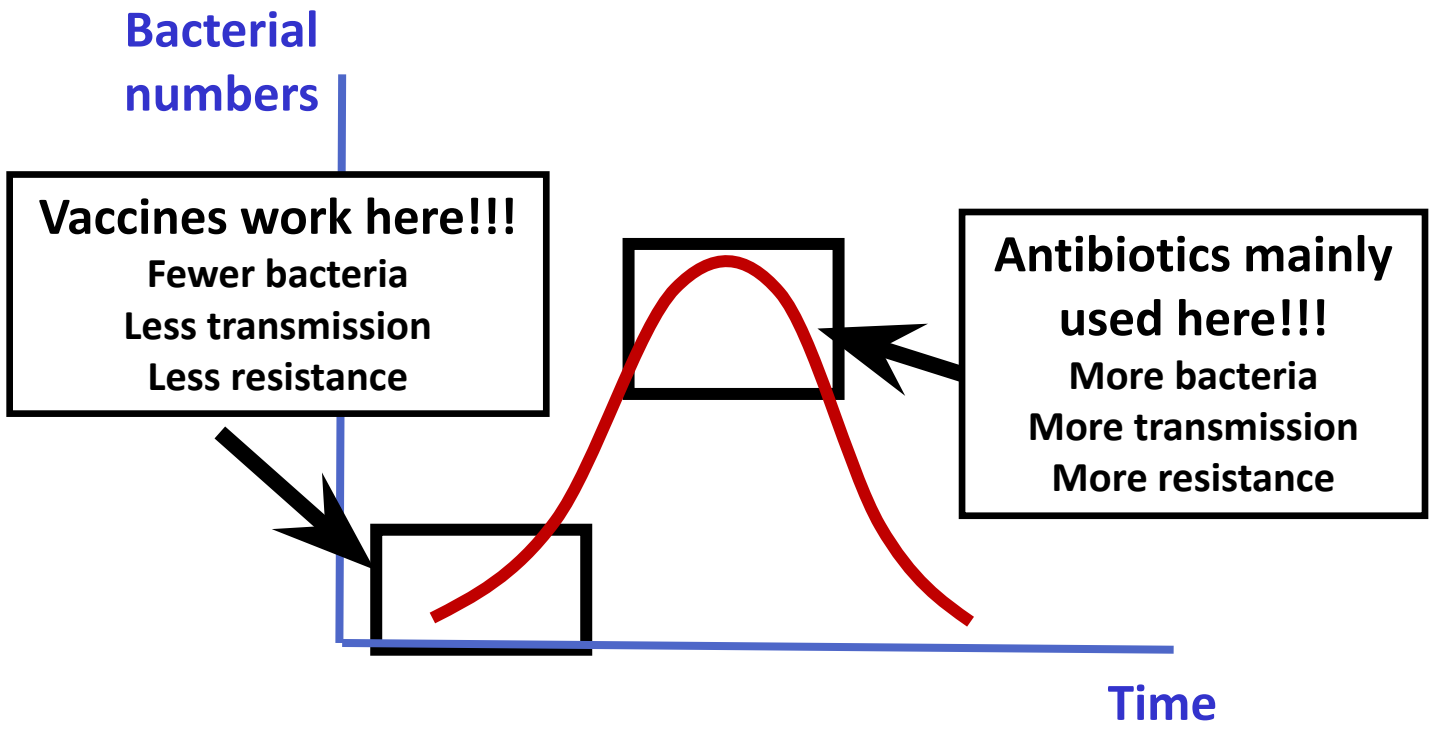
Antimicrobials

AMR

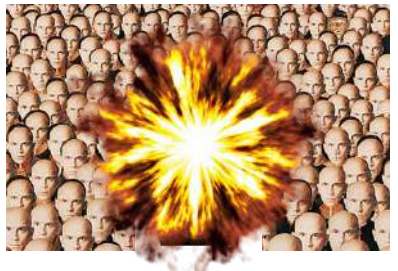
Cf COVID-19

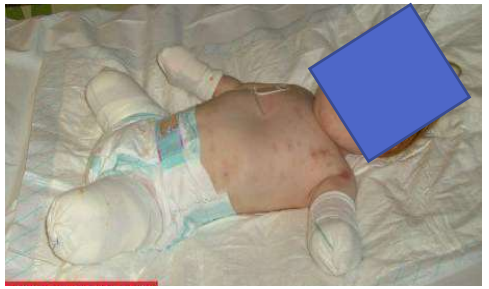
– Dec 2019 to Dec 2020 – Hands, Space, Face – Dexamethasone
– Vaccines enable return to “normal life”

Vaccines and antibiotics are active at different times after infection
The ultimate function is to control infectious disease



Vaccines save lives





Antibiotics save lives

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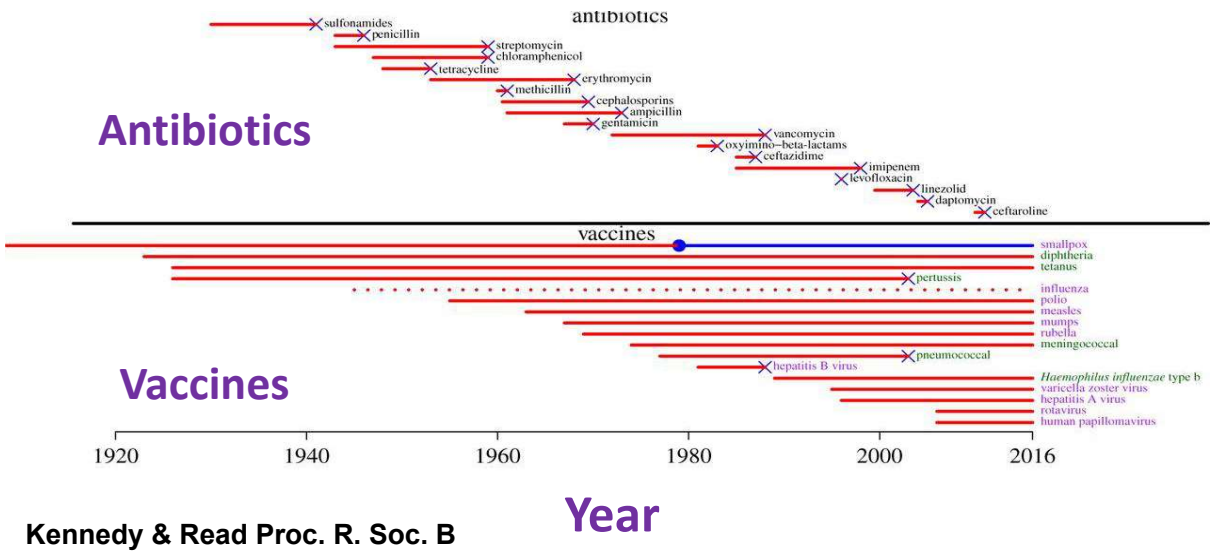
Vaccines offer sustained protection against disease, whilst antibiotics offer (broader but) short-term activity: *both differ in levels of resistance*

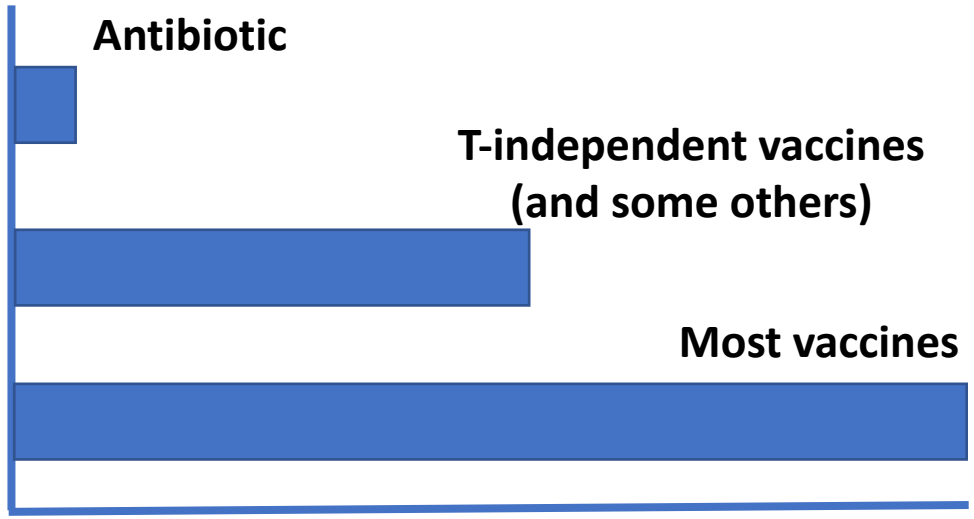
Persistence of responses and lack of acquisition of resistance help make vaccines effective

Year agent introduced and resistance detected



Kennedy & Read Proc. R. Soc. B 2017;284:20162562

Length of activity by class of agent



Activity after final dose

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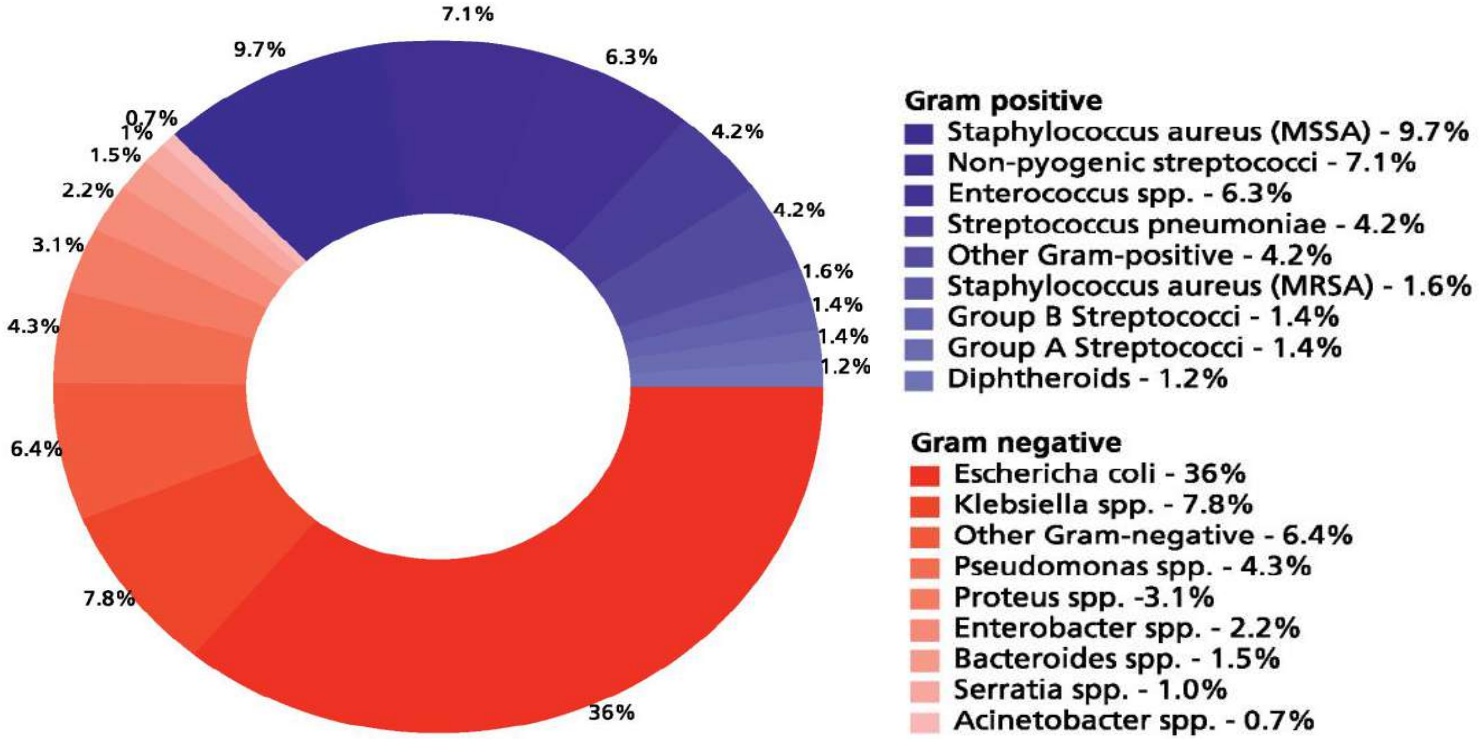
Herd immunity
Off target benefits – meningo BCG

Systemic infections are problems in High and low income countries – AMR & vulnerable groups

Figure 1.1: Organisms causing blood stream infections in adults in England, Wales and Northern Ireland, April 2011-March 2012



Source: HPA. English National Point Prevalence Survey on Healthcare Associated Infections and Antimicrobial Use, 2011: Health Protection Agency, England; 2012. Note: excludes 13,206 episodes of bacteraemia with coagulase negative staphylococci.

Chief Medical Officer's Report 2011

Susceptibility to infection with age can be due to multiple reasons

Classical and non-classical Primary immunodeficiency – sickle cell

Age

Classical secondary immunodeficiency

Non-classical secondary immunodeficiency

Metabolic conditions - diabetes

Vaccination can help vulnerable groups

Other advantages of studying vaccination in risk groups

Allows study of "immunity in action"

Examine immune "failure"

Different perspective to mechanistic work established in animals – real world

Risk of infection can correlate with poor vaccine responses

Vaccines a "window" to try and understand how to alter immune function

Also examine infectious history

Some infections have long-lasting impact

Cytomegalovirus (CMV) can skew tonal immunity

Table 2—Summary of infection rates during 2008–2015 and IRRs among people with diabetes versus matched control subjects

	People with T2DM (n = 96,630)		Control subjects (n = 191,822)	T2DM vs. control subjects	People with T1DM (n = 5,863)		Control subjects (n = 11,696)	T1DM vs. control subjects
Type of infection	Events	Rate†	Rate†	IRR* (95% CI)	Events	Rate†	Rate†	IRR* (95% CI)
Bone and joint infections	1,071	2.26	0.50	4.93 (4.34–5.61)	182	5.75	0.30	22.31 (12.12–41.20)
Cholecystitis (acute)	1,035	2.01	1.35	1.62 (1.48–1.77)	51	1.61	0.85	1.92 (1.22–3.03)
Endocarditis	100	0.20	0.13	1.84 (1.33–2.53)	8	0.25	0.08	6.70 (1.35–33.39)
[illegible]								
[illegible]								
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Summary groups								
Any plus prescription	132,661	265.52	183.60	1.47 (1.46–1.49)	7,842	247.57	152.09	1.66 (1.59–1.74)
[illegible]								
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Iain Carey et al Diabetes Care 2018

Vaccination can have a dramatic effect on the use of antibiotics

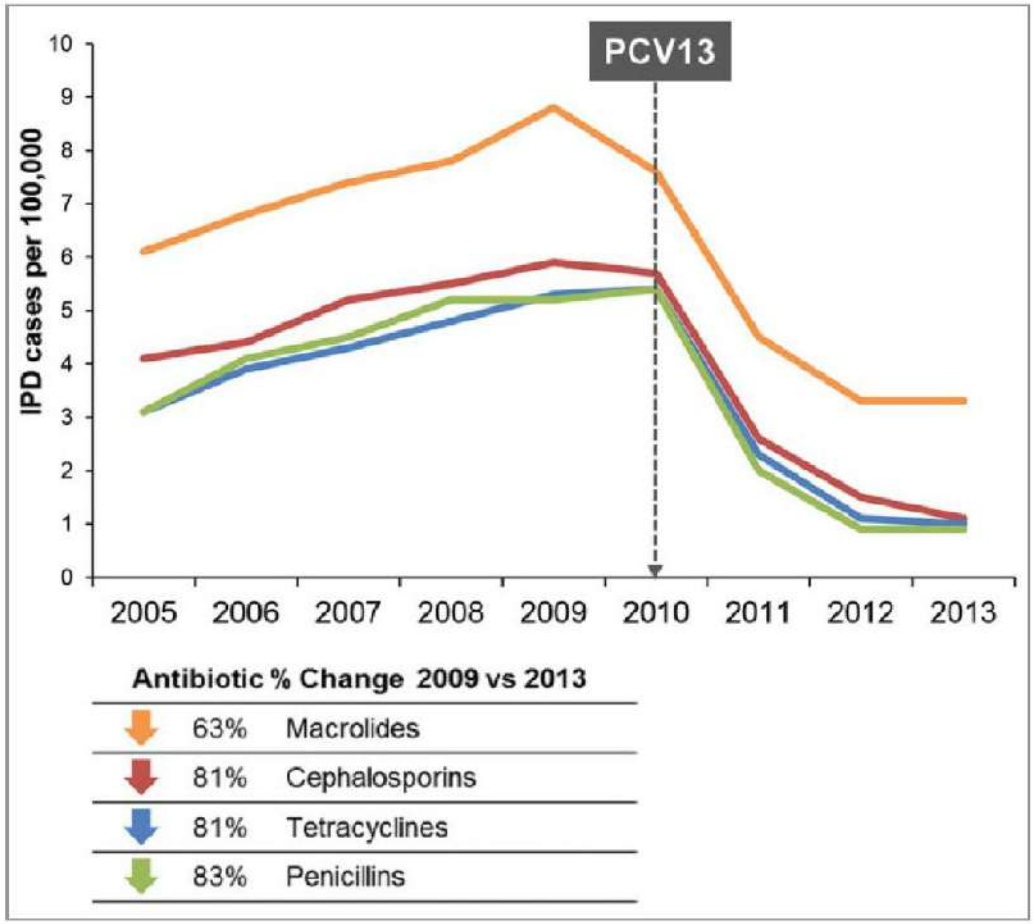

Figure 2. Rates of antibiotic non-susceptible invasive pneumococcal disease (<5 years) 2005–2013.[28].

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2018, VOL. 14, NO. 9, 2142–2149
https://doi.org/10.1080/21645515.2018.1476814

MINI-REVIEW

The role of vaccines in fighting antimicrobial resistance (AMR)

Kathrin U. Jansen and Annaliesa S. Anderson

Pfizer Vaccine Research and Development, Pearl River, NY, USA

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Indirect –

Block transmission – target similar infections (OMV in NZ meningo and gonococcus)

50% antibiotic use inappropriate – flu season correlates with antibiotic use - diagnostics

Flu vaccine reduces secondary bacterial infections and antibiotic treatments

Reduce use of antibiotics in farming / animal husbandry – growth promoters etc (>60% antibiotic use)