POTENTIAL IMPACT OF VACCINATION ON CURBING AMR FROM A UK AND GLOBAL PERSPECTIVE

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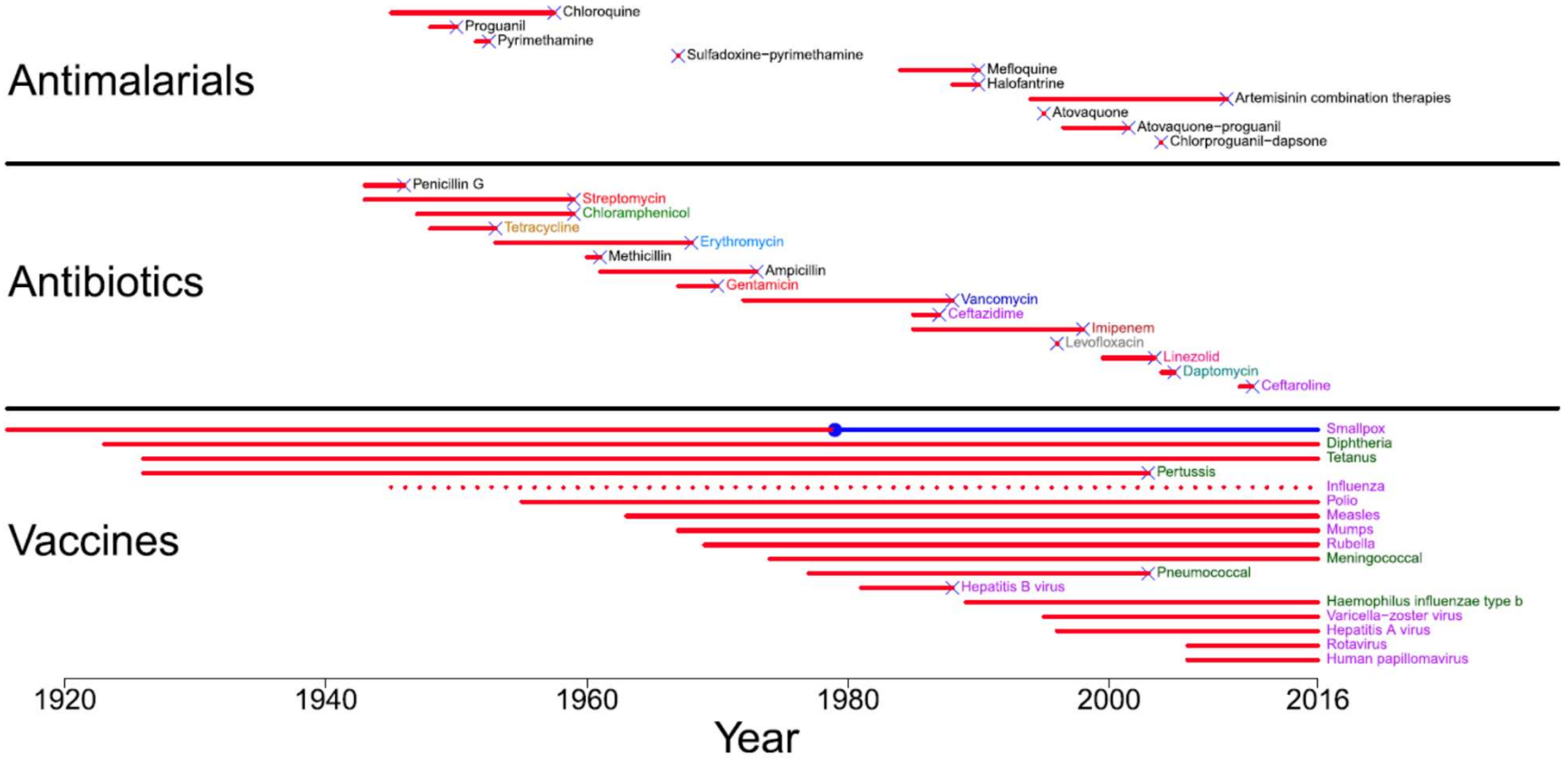
University of Birmingham – BactiVac Bacterial Vaccinology Network

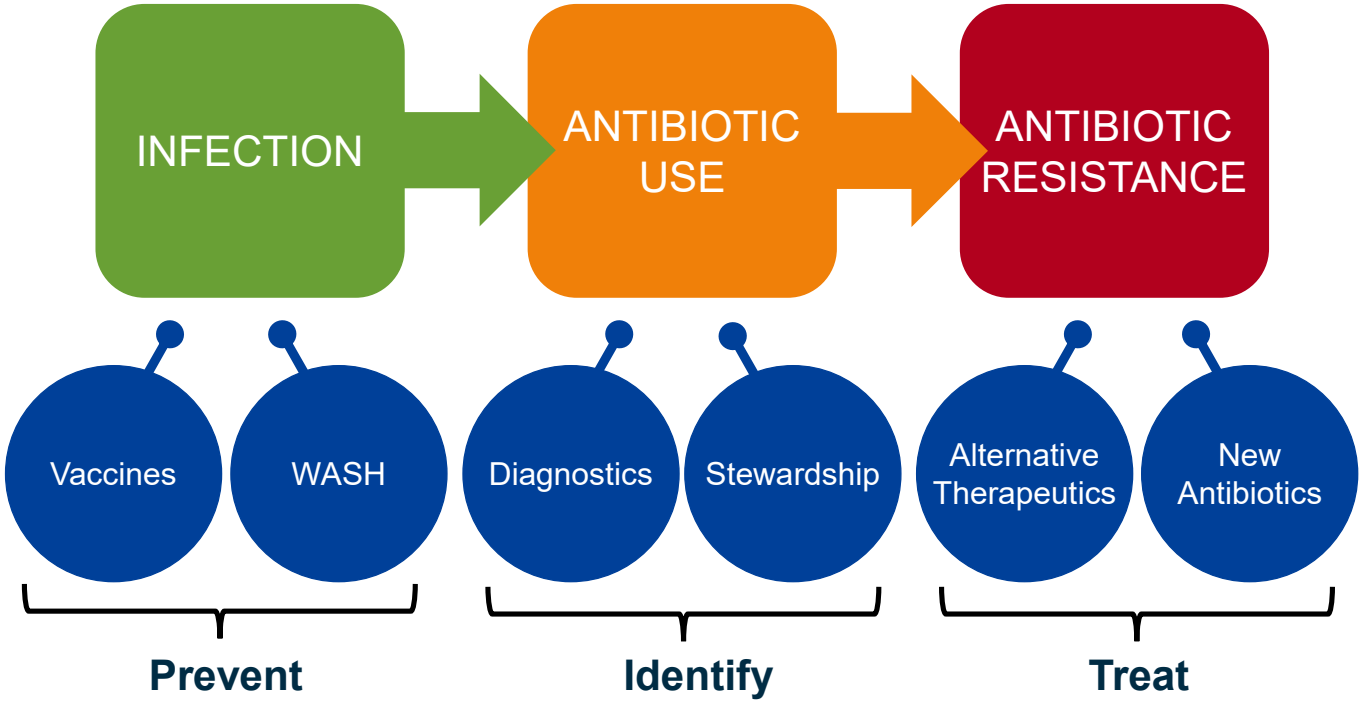
Virtual AMR Innovation Mission 2021
12 May 2021

TIME BETWEEN DEPLOYMENT AND THE FIRST DOCUMENTED FAILURE IN HUMANS DUE TO RESISTANCE: ANTIMICROBIALS VS. VACCINES



Source: Kennedy, et al. Proc Natl Acad Sci, 2019

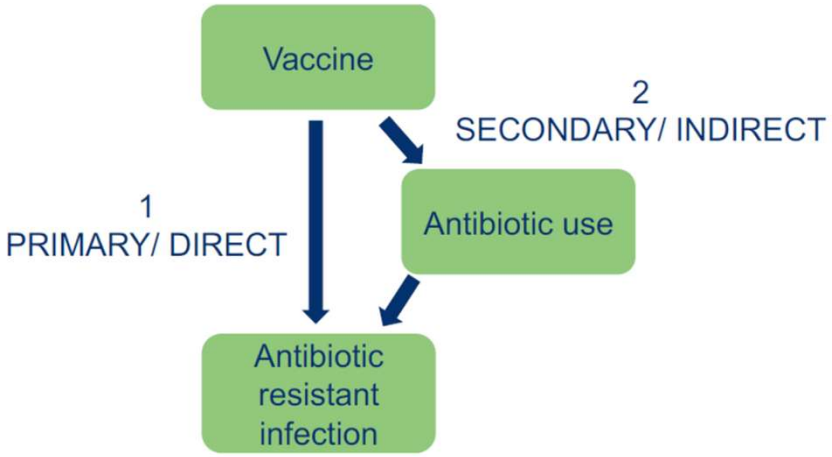
Tackling AMR requires a multi-faceted approach



How do vaccines contribute to tackling AMR?

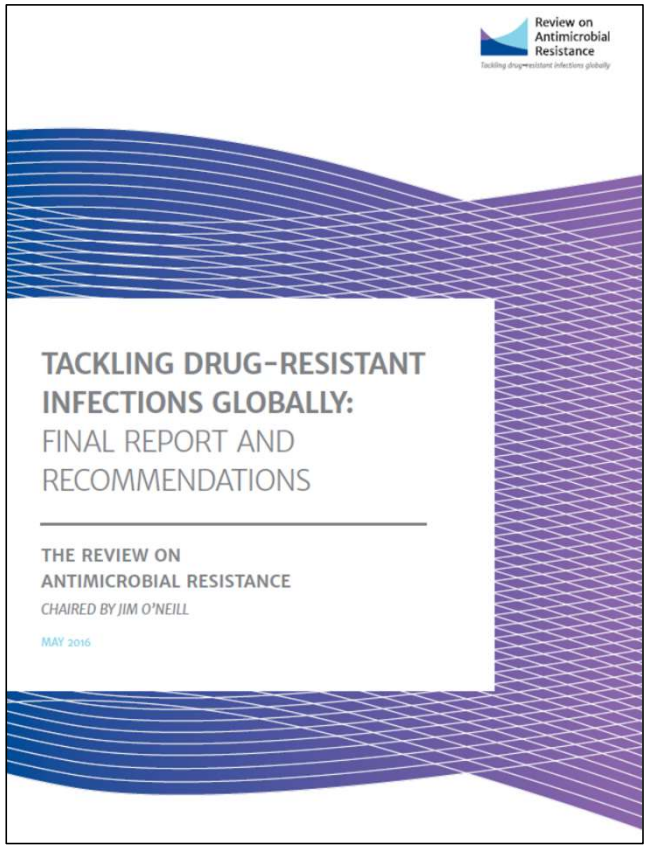
	Vaccines for AMR pathogens	Vaccines for non-AMR pathogens (e.g. viruses)
Directly prevent infection, carriage, and transmission of drug-resistant organisms	✓	
Reduce occurrence of symptoms and antibiotic use	✓	✓
Prevent secondary infections with drug-resistant organisms	✓	✓

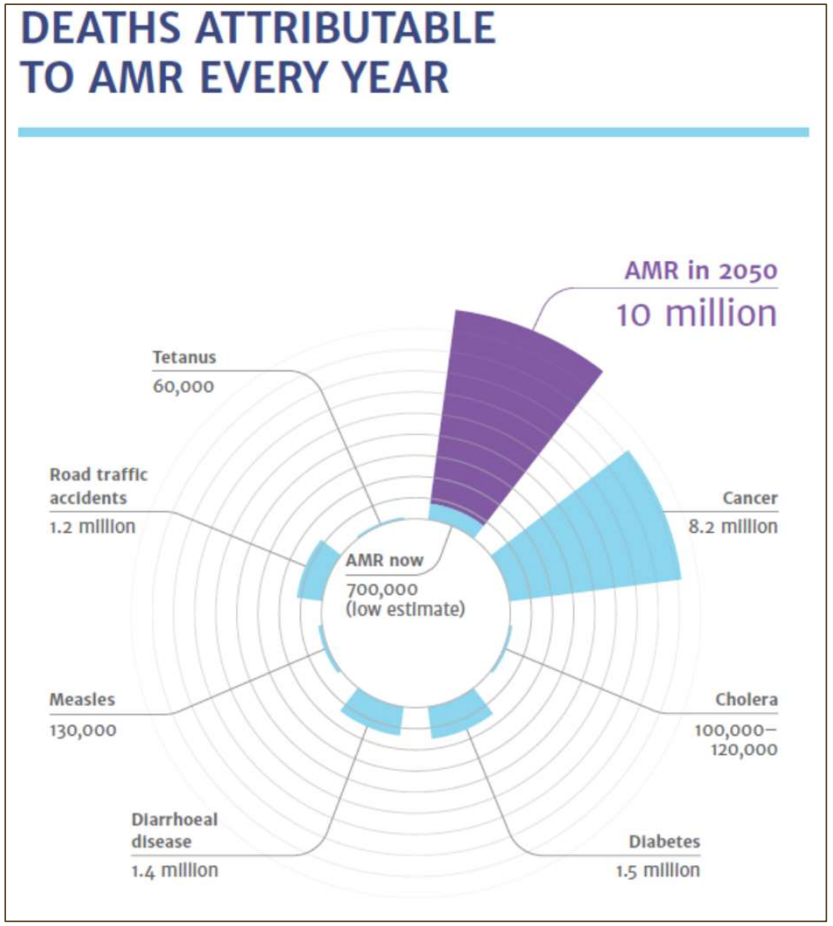
IMMUNIZATION AGAINST A BACTERIAL PATHOGEN AND ITS EFFECT ON ANTIBIOTIC USE AND SPREAD OF AMR

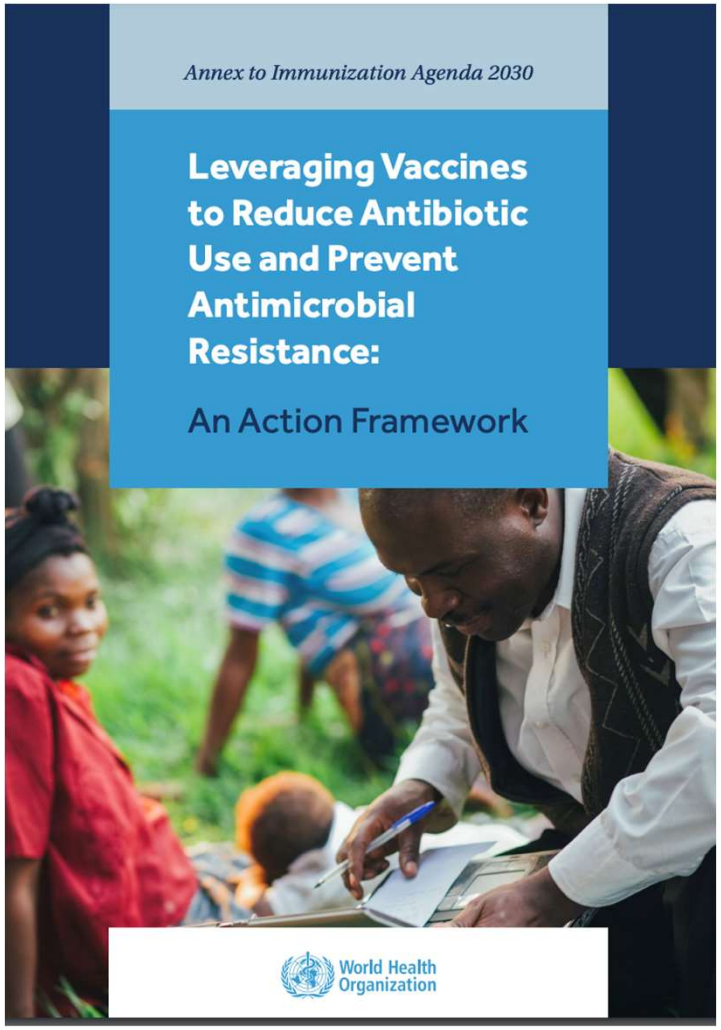


Source: Figure: Elizabeth Klemm; Jansen, Nature Medicine, 2018

REVIEW ON ANTIMICROBIAL RESISTANCE: O'NEILL REPORT, 2016







1. Expanding use of licensed vaccines to maximize impact on AMR

2. Developing new vaccines that contribute to prevention and control of AMR

3. Expanding and sharing knowledge of vaccine impact on AMR

BMGF PERSPECTIVE ON ANTIMICROBIAL RESISTANCE

- Our interest in AMR relates to our current health strategies in low- and middle-income countries
  - How does AMR jeopardize the ability to achieve defined health impact targets?
  - How can we prevent and reduce the burden of AMR?
- Focused on supporting the development of tools to reduce mortality and disease burden among the world's most vulnerable populations
  - Appropriate antibiotic use has the power to save lives in these populations
- The threat of AMR reinforces the importance of prevention of infections through vaccines – which is a core focus of foundation work

BMGF CURRENTLY SUPPORTS PREVENTION, INFECTION CONTROL, AND APPROPRIATE USE OF ANTIBIOTICS

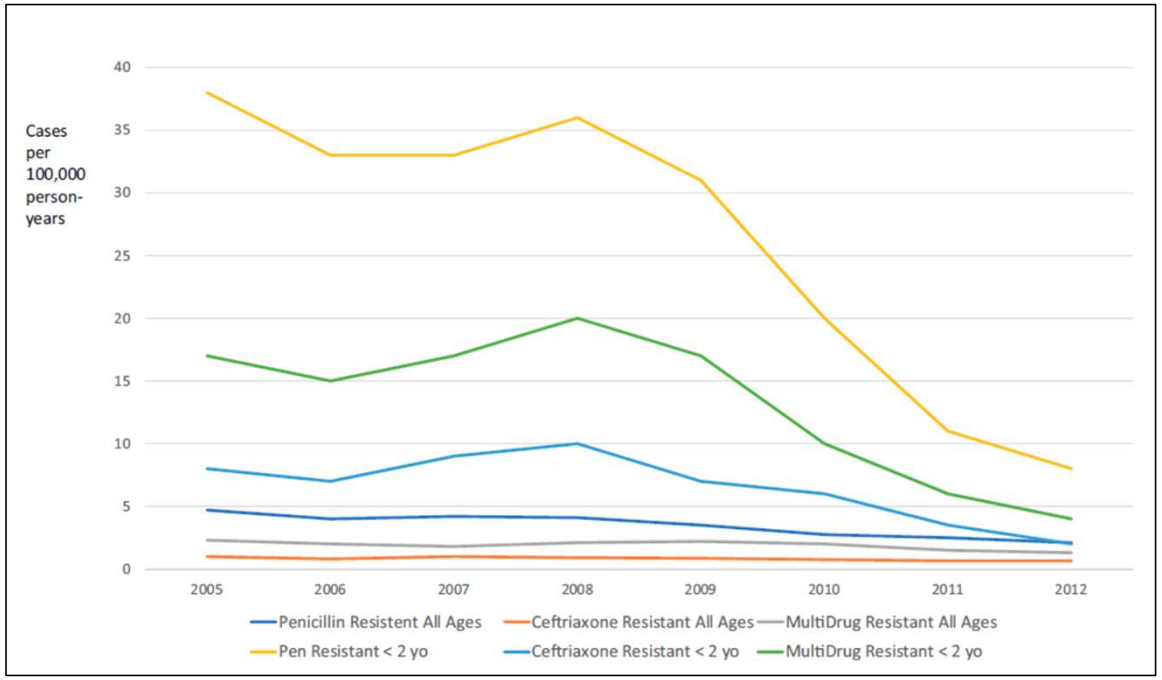
Our continued support for the following activities are expected to have a meaningful impact on AMR:

Prevention

- Vaccine development for RSV, GBS, typhoid, *Shigella*, cholera, pneumococcus, HIV, TB, and malaria
- Vaccine delivery to maximize coverage for vaccine-preventable disease

IMPACT OF PNEUMOCOCCAL CONJUGATE VACCINE ON PENICILLIN NON-SUSCEPTIBLE STRAINS

Trends in Invasive Pneumococcal Disease in South Africa, pre and post PCV Introduction

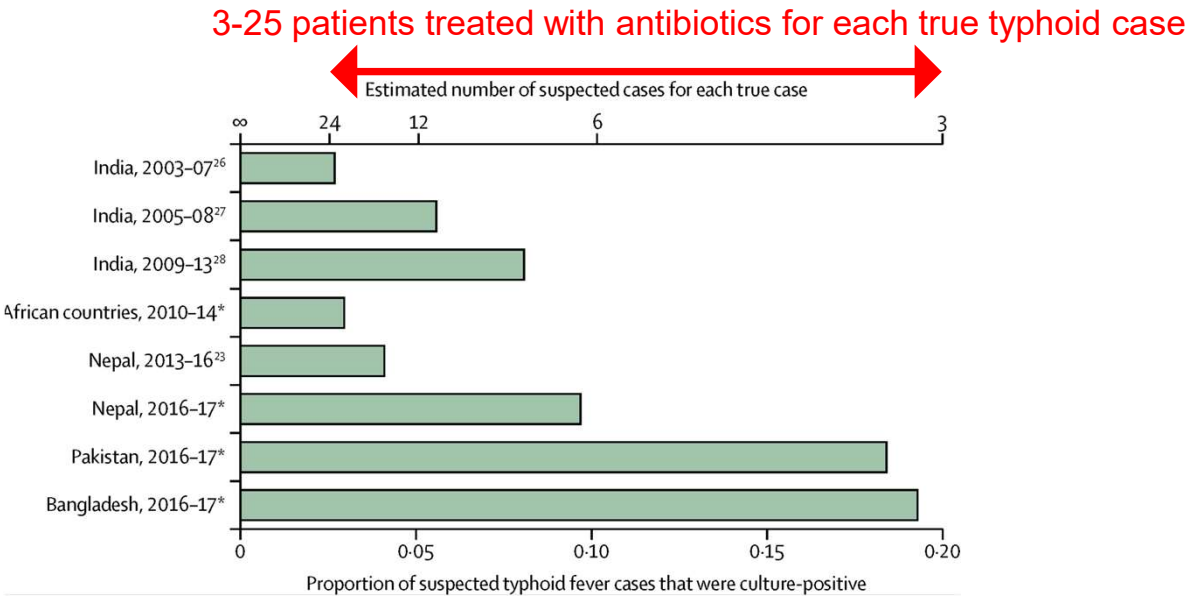


- In South Africa, PCV10 and PCV13 introduction associated with
  - 82% reduction in PCN-resistant invasive pneumococcal disease (IPD) in children
  - 85% reduction in ceftriaxone non-susceptible strains
- Introduction of PCV was associated with a reduction in antibiotic use due to the decrease in pneumococcal infections

Sources: Klugman, PNAS 2019, Von Gottberg, NEJM, 2014

Potential to change antibiotic prescribing behaviour beyond the target pathogen

- Fever in typhoid endemic areas is often treated empirically with antibiotics
- The majority of febrile cases are actually due to viral infections
- Elimination of typhoid through vaccination would reduce need for empiric antibiotic treatment
- Similar arguments for Group A Strep vaccines

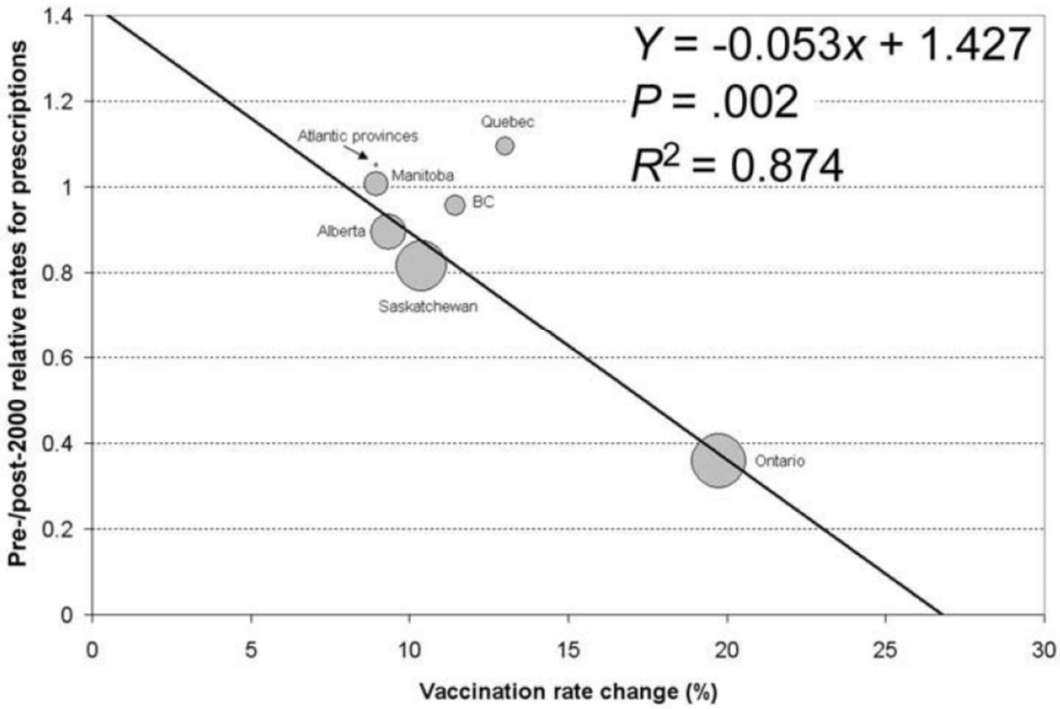


Andrews *et. al.* Lancet ID 2019

UNIVERSAL INFLUENZA IMMUNIZATION PROGRAM IN ONTARIO, CANADA: IMPACT ON ANTIBIOTIC PRESCRIPTIONS

- Ontario introduced free universal seasonal influenza vaccination in 2000
  - Comparison of rates of respiratory antibiotic prescriptions before and after universal influenza vaccination
  - 64% reduction in antibiotic prescriptions
- Prevent influenza infections and disease
  - Decrease likelihood of secondary bacterial infections (pneumonia and otitis media)
  - Reductions in antibiotic prescriptions and use

Dose response relationship between change in respiratory antibiotic prescription and influenza vaccination, Ontario, Canada



Source: Kwong, CID, 2009

WHO AMR PRIORITY PATHOGENS

	WHO AMR priority pathogens
Vaccine Available	S. pneumoniae H. influenzae S. Typhi
No Effective Vaccine Available	M. tuberculosis Shigella spp. E. coli Non-typhoidal Salmonella S. Paratyphi A N. gonorrhoeae S. aureus K. pneumoniae H. pylori Campylobacter A. baumanii P. aeruginosa Enterobacteriaceae E. faecium

VaccinesforAMR.org

An analysis of the WHO AMR priority pathogens for suitability to vaccine development
scored on health impact, R&D feasibility, and probability of uptake
to provide actionable recommendations for funders and biotech companies
launched in October 2018

wellcome

BCG
The Boston Consulting Group

Scorecard for pathogen assessment

Health Impact

- Mortality and morbidity
- Urgency of AMR threat
- Attributable antibiotic use

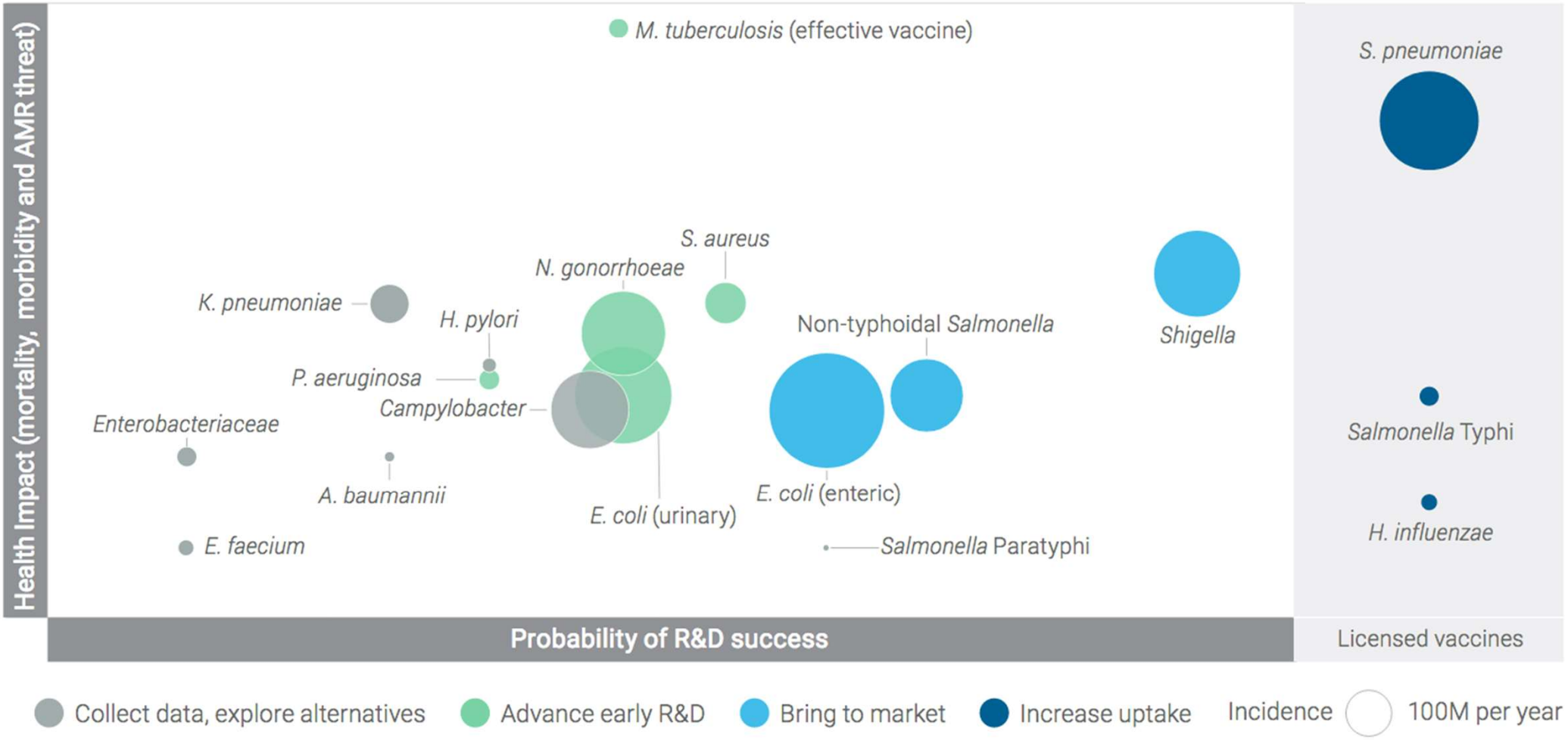
Probability of R&D success

- Pipeline robustness
- Pathogen biology
- Ease of pre-clinical and clinical R&D

Probability of uptake

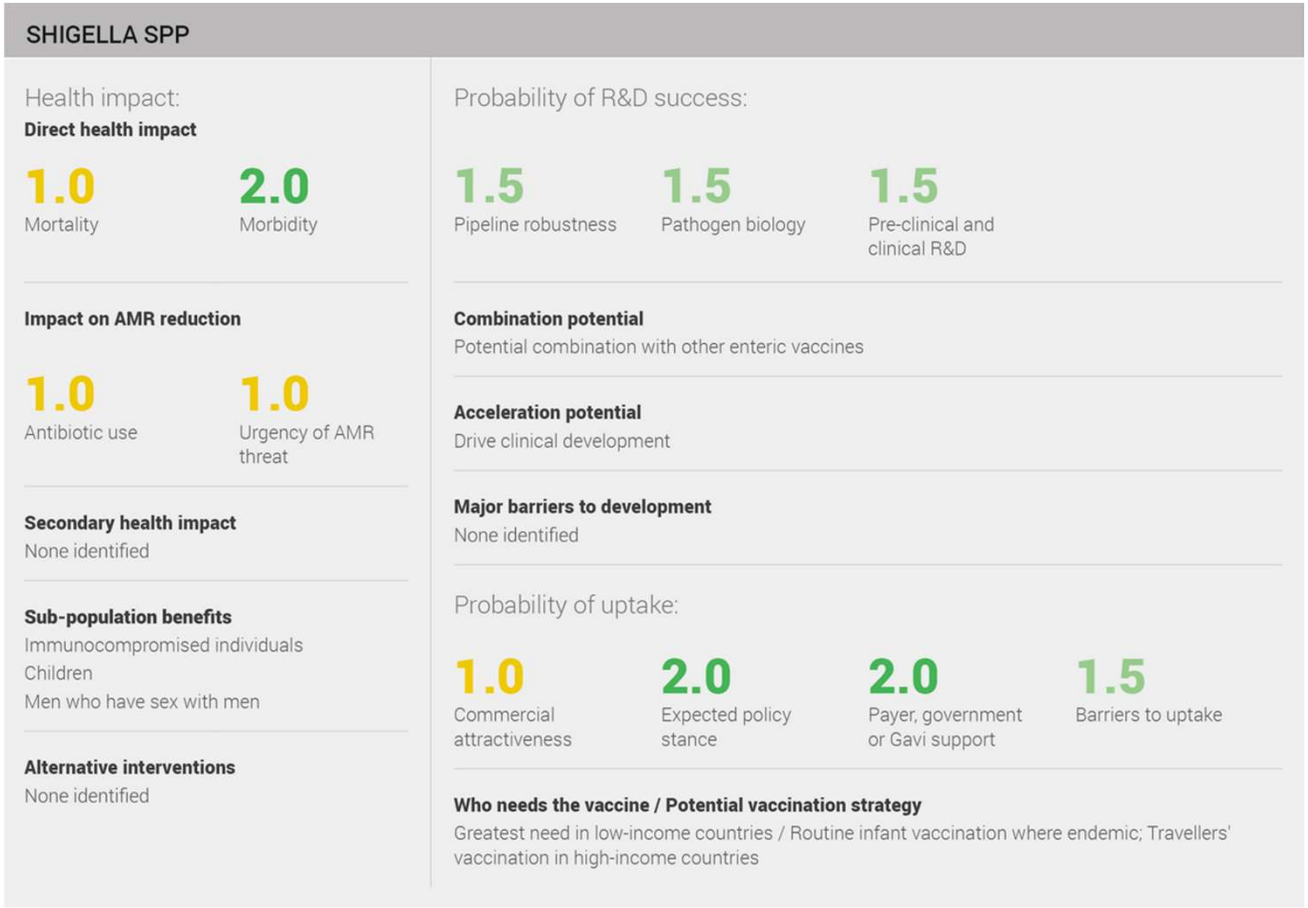
- Expected policy stance
- Payer, government and Gavi support
- Barriers to uptake
- Commercial attractiveness

Pathogen clusters for prioritised action



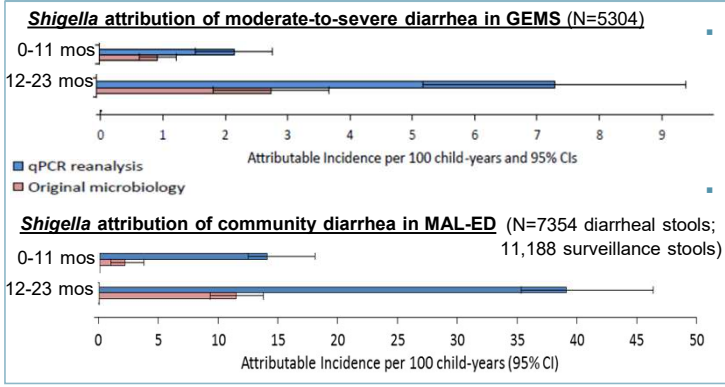
1	2	3	4
Increase uptake and access for existing, effective vaccines	**Bring to market** new vaccines where the pathogen is better understood by accelerating clinical development	**Advance early R&D** for high impact pathogens with unclear R&D feasibility, by investing in early stage research	**Collect data and explore alternatives** for pathogens currently less well-suited to vaccine development
H. influenzae	*E.coli* (enteric)	*M. tuberculosis*	*S.* Paratyphi
S. pneumoniae	Non-typhoidal *Salmonella*	*N. gonorrhoeae*	*Campylobacter*
S. Typhi	*Shigella spp.*	*E. coli* (urinary)	*H. pylori*
		P. aeruginosa	*K. pneumoniae*
		S. aureus	*A. baumanii*
			Enterobacteriaceae
			E. faecium

Example scorecard: *Shigella spp.*



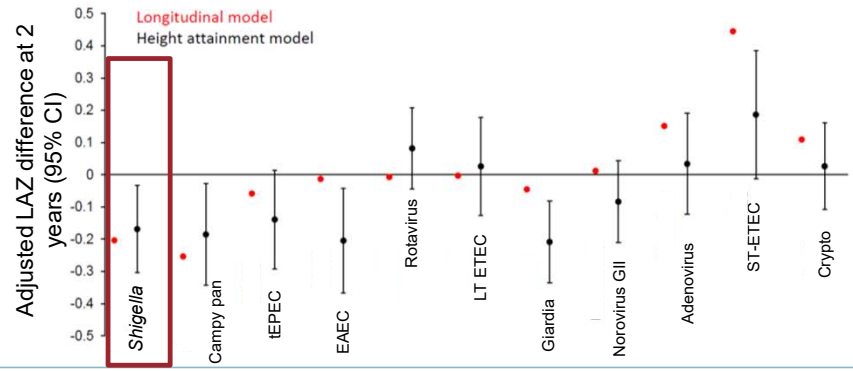
CASE FOR A *SHIGELLA* VACCINE

1 *Shigella* burden is greater than we thought…

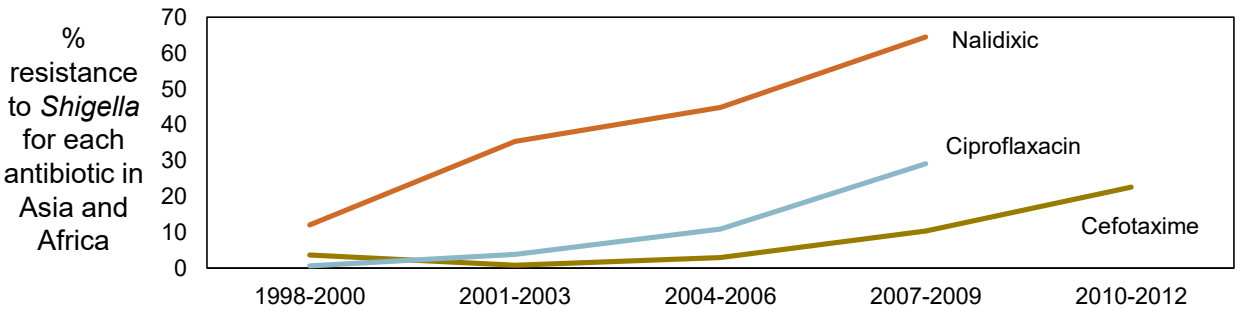


- Quantitative PCR re-analysis of GEMS increased *Shigella* attribution of moderate-to-severe diarrhea by ~2-3X per 100 child-years
- Quantitative PCR re-analysis of MAL-ED increased *Shigella* attribution of community diarrhea by ~7X and ~3X per 100 child-years among infants 0-11m and 12-23m, respectively

2 …its impact on growth faltering is significant…



3 …and the threat of AMR is growing



Adapted from Gu B et al. Int J Antimicrob Agents 2012 and Gu B et al, Epidemiol Infect 2015

From GEMS:

- Only 35% of Indian *Shigella* isolates were sensitive to ciprofloxacin (WHO-recommended antibiotic for *Shigella* dysentery)
- > 80% of African *Shigella* isolates were resistant to cotrimoxazole (most commonly prescribed antibiotic in African sites)

Source: GEMS; MAL-ED; AMR data adapted from Gu et al. *2012 and 2015*

SHIGELLA VACCINE PIPELINE: O-ANTIGEN VACCINES

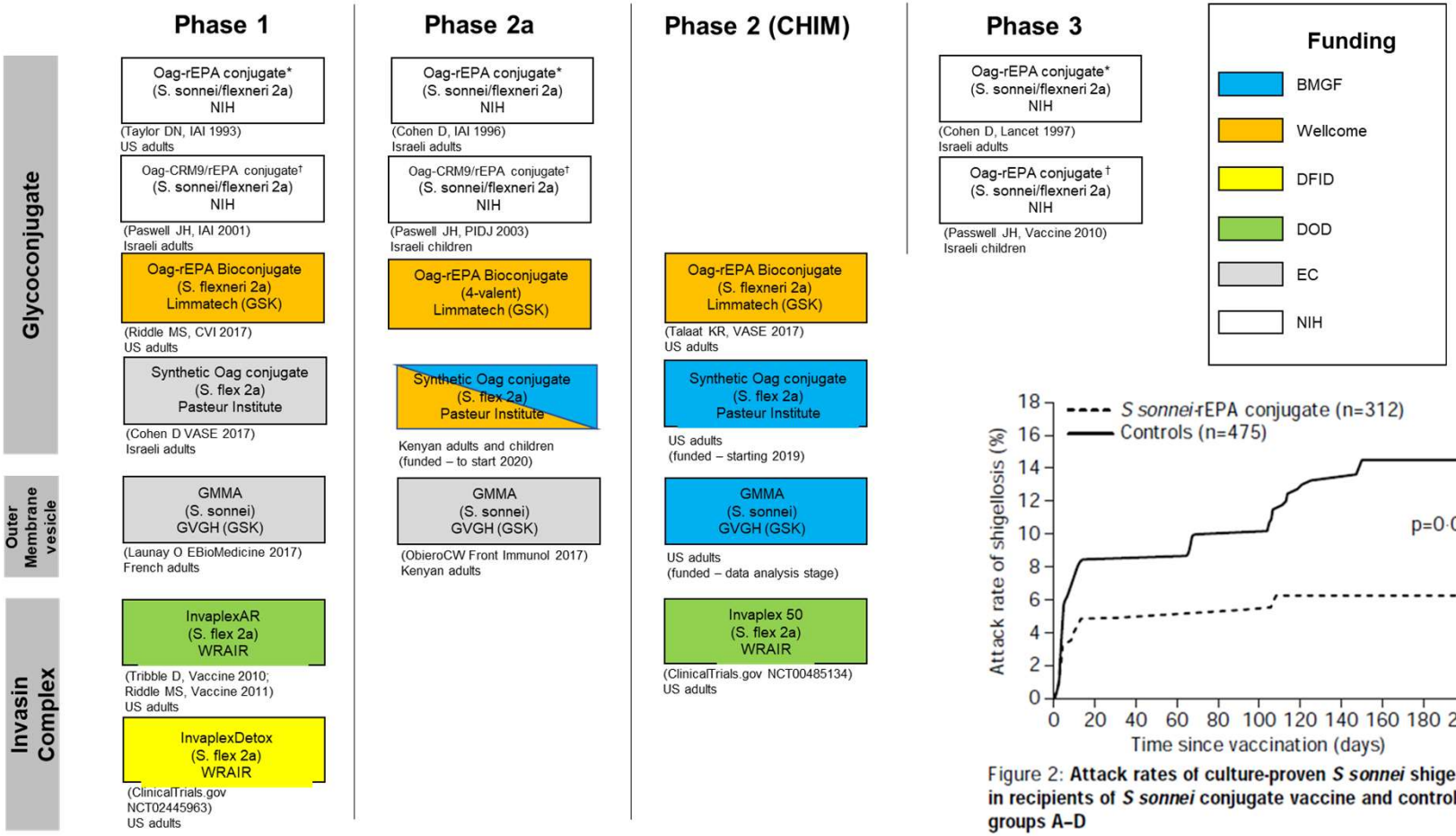


Figure 2: **Attack rates of culture-proven *S sonnei* shigellosis in recipients of *S sonnei* conjugate vaccine and controls in groups A–D**

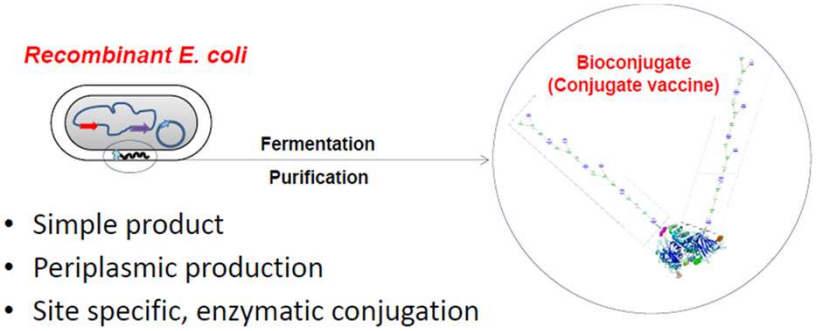
- Overall Vaccine Efficacy **74% (95%CI 28-100)**
- Serum O-antigen IgG a likely correlate of protection
- Failure of vaccine in children < 3 years with falling serum O-antigen IgG level

Source: Cohen D Lancet 1997; Passwell JH Vaccine 2010

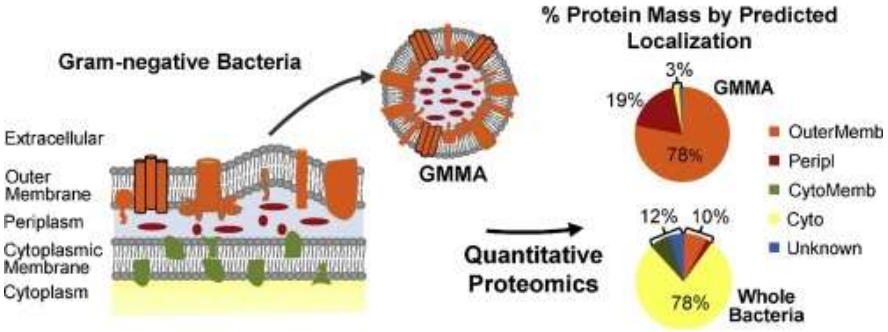
LEAD SHIGELLA VACCINE CANDIDATES

- All O-antigen based, three different technologies:
  - **O-antigen – rEPA bioconjugate vaccine ,** Limmatech/GSK
  - **Outer Membrane Vesicle (mdOMV/GMMA)**, GVGH
  - **Synthetic O-antigen – TT conjugate**, Institut Pasteur

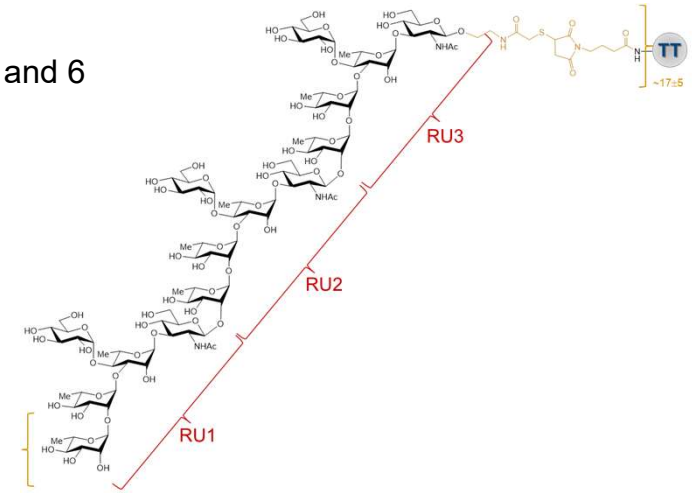
- Bioconjugate efficacy in controlled human infection model:
- Descending-age study into target population: LMIC infants
- Early development: monovalent formulation *S. sonnei or S. flexneri* 2a
- Global epidemiology requires 4-valent: *S. sonnei* **and** *S. flexneri* 2a, 3a and 6



Source: Limmatech



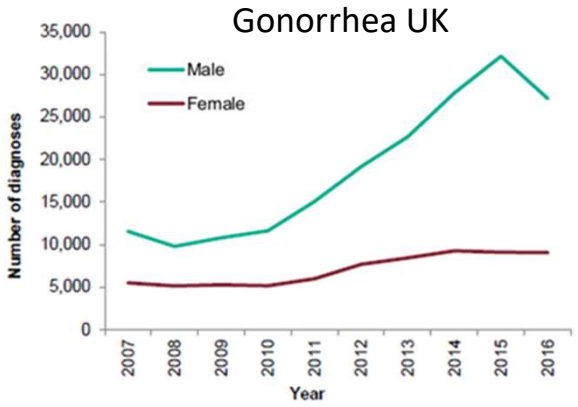
Source: Maggiore L Int J Med Microbiol. 2016



Source: Institut Pasteur

Gonorrhoea is a global threat

- *Neisseria gonorrhoeae*
  - Adverse reproductive health outcomes in women
  - Increases risk of HIV infection



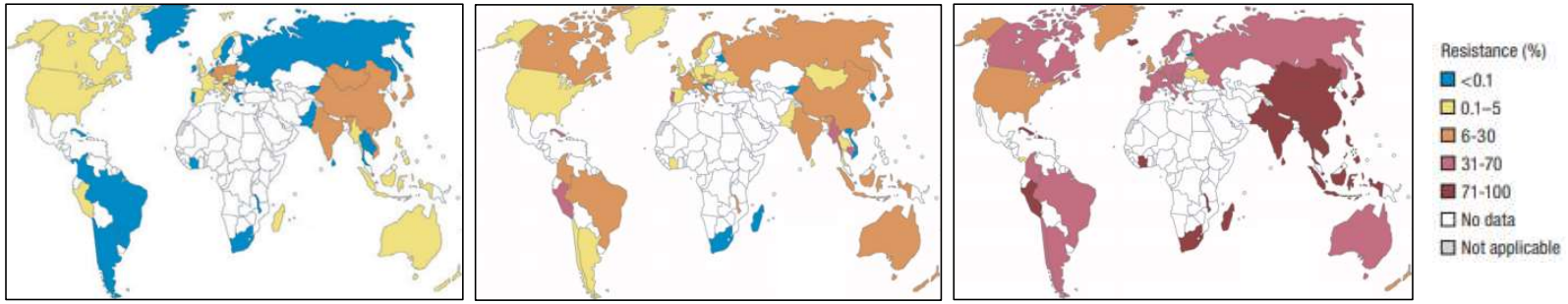
- 87 million new cases per year
  - LMICs disproportionately affected

Prevalence	Men	Women
Global	0.7%	0.9%
Africa	1.6%	1.9%

Absence of single, reliable monotherapy to treat gonorrhoea

WHO data indicate increasing gonococcal resistance to:

Extended-spectrum cephalosporins | Azithromycin | Ciprofloxacin



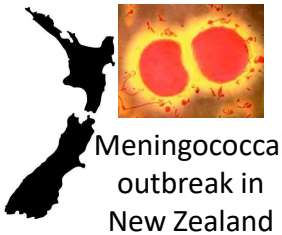
WHO Gonococcal Antimicrobial Surveillance Programme (GASP), 2017

2018 strains resistant to ceftriaxone and azithromycin

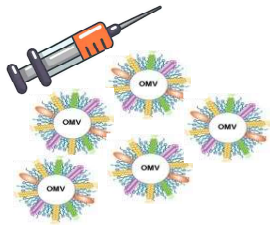
'High priority' for R&D of new treatments (WHO) and 'urgent' AMR threat (CDC)

Outer Membrane Vesicle (OMV) vaccines are effective against gonorrhoea

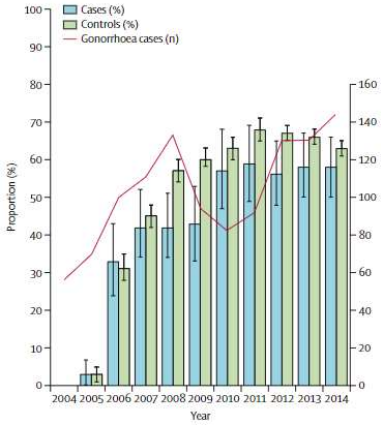
No gonococcal vaccine currently available with no clinical trial in ~30 years, but…



Meningococcal outbreak in New Zealand



Meningococcal OMV vaccine (MeNZB) administered to one million individuals in a two year period



THE LANCET
Volume 390, Issue 10102, 30 September–6 October 2017, Pages 1603-1610

Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study

Dr Helen Petousis-Harris PhD [a,b], Janine Paynter PhD [a], Jane Morgan MD [b,a], Peter Saxton PhD [c], Barbara McAndie MCE [a], Prof Felicity Goodyear-Smith MD [a], Prof Steven Black MD [d]

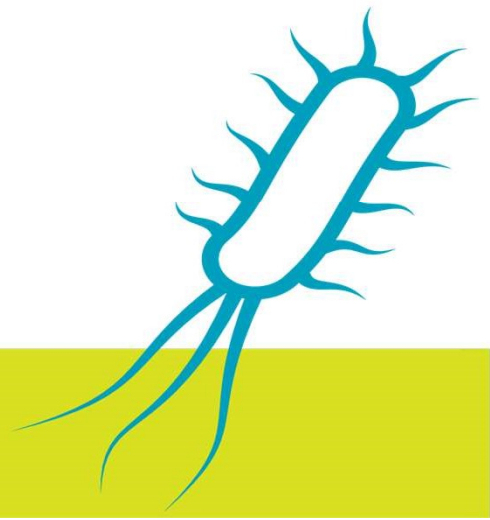
Exposure to MeNZB was associated with reduced rates of gonorrhea diagnosis

Estimated effectiveness of 31% (95% CI 21-39)

Hypothesis A gonococcal OMV-based vaccine will have greater efficacy against gonorrhoea than a meningococcal OMV-based vaccine

The BactiVac Bacterial Vaccinology Network

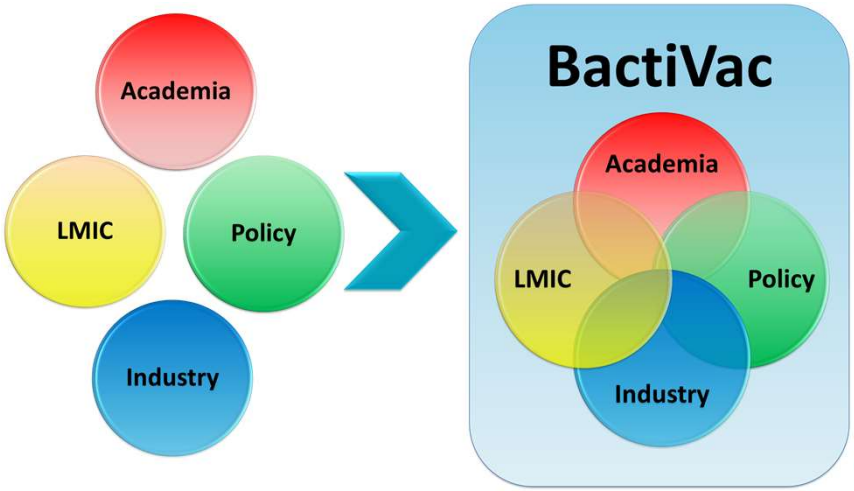
- 5 million die from bacterial infections / year
- No vaccines for many bacterial infections of global significance
- Threat of antimicrobial resistance (AMR)
- Proven strategies for bacterial vaccines
- Key expertise in UK, LMICs and globally
- No existing bacterial vaccine network
- Contrast with vaccine for viral/outbreak pathogens



BactiVac: what is our mission?

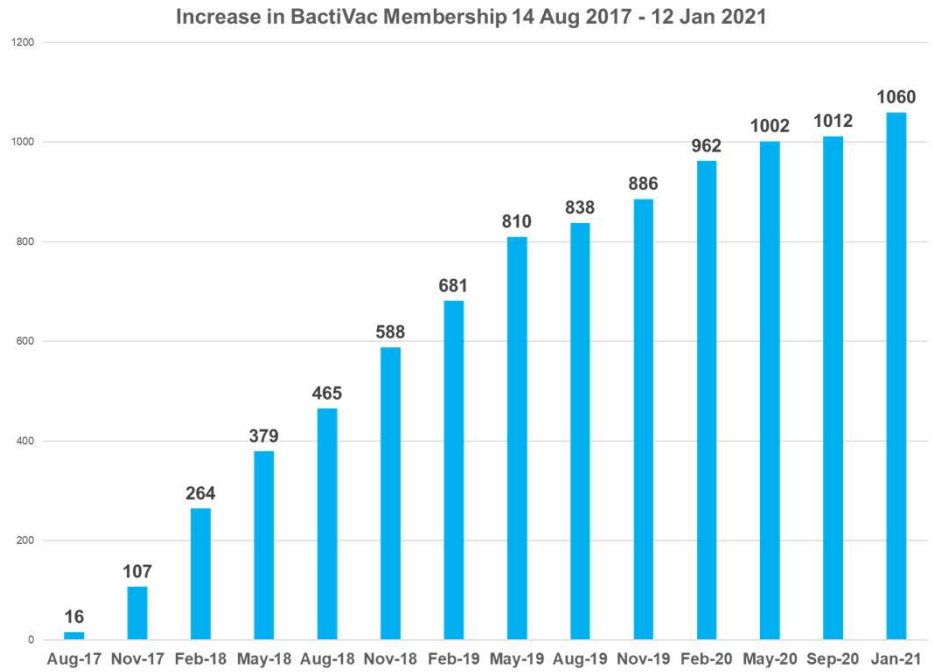
We are a global voice for bacterial vaccinology

- Create a sustainable network for vaccine development
- Catalyst project and training funding
- Attract investment/leverage funding for LMICs/UK
- Advocacy for the development of bacterial vaccines



Growing our Network

1,140 members across 74 countries
48% LMIC, 13% industry



Funding leveraged for catalyst projects

No. projects funded (29 completed)	40
Total funding awarded	£2,102,125
Funding leveraged to support project delivery	£1,626,214 + 77%
Total follow-on funding leveraged by projects (19 awards from 11 projects)	£12,653,703 + 602%

Advocacy

You Retweeted

Brit Soc Imm @britsocimm · 26 Mar

Watch this excellent video from BactiVac Director, Professor Cal MacLennan on the importance of vaccines #CelebrateVaccines 👇

> **BactiVac Network** @BactiVac · 26 Mar
> We're partnering with the @BritSocImm to #CelebrateVaccines. BactiVac Director, Professor Cal MacLennan on the importance of vaccines. #CelebrateVaccines #ProtectTheNextGeneration #VaccinesWork @unibirm_MDS @hic_vac @ImmunologyUoB @NetworkValidate @IMPRINT_network @IntVetVaccNet

8 14

BactiVac Network @BactiVac · 14 Apr

.@constantinolm from the National Medical Centre in Mexico City on the current challenging times and his experience of applying for Catalyst Funding. @britsocimm @IMIBirmingham @unibirm_MDS @ImmunologyUoB @hic_vac @NetworkValidate @IntVetVaccNet @IMPRINT_network @UKRI_News

1 1

BactiVac Network @BactiVac · 11 Feb

Happy International Day of Women and Girls in Science #IDWGS! The BactiVac Network have over 400 female members! Here's one of our members Dr Marisol Perez-Toledo - @WomenScienceDay @unibirm_MDS @news_ub @unibirmingham @ImmunologyUoB #WomenInScience @UoB_MDSRKTO

7 18

BactiVac Network @BactiVac · 25 Feb

Professor Adam Cunningham has been in Parliament today to attend @POST_UK's Superbugs event #POSTUKlive @unibirm_MDS @news_ub @unibirmingham @UoB_MDSRKTO @ITMBirmingham @BHPComms @IntVetVaccNet @CMO_England

5 16

BactiVac Network @BactiVac · 13 Feb

Dr Johanna Dean on attending the UK Vaccine Network Event in London @UKgovGHS @UKRI_News @KTNUK @KTNUK_Health #VaccinesWork

3 8

BactiVac Network @BactiVac · 24 Feb

The BactiVac Network is growing! @unibirm_MDS @news_ub @UoB_MDSRKTO @ImmunologyUoB @BHPComms @ITMBirmingham

5 10

SUMMARY

Vaccines play an important role in AMR by:

1. Reducing drug-resistant infections
2. Reducing antibiotic use
3. Reducing secondary infections

Action is needed to:

1. Expand the use of existing vaccines
2. Develop new vaccines
3. Collect more data - Quantifying the impact is challenging

ACKNOWLEDGEMENTS

Padmini Srikantiah – BMGF

Elizabeth Klemm – Wellcome

birmingham.ac.uk/bactivac