GLOBAL IMPACT OF ANTIMICROBIAL RESISTANCE: VACCINES AS PART OF THE SOLUTION

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Amsterdam

Advancing Data Technologies to corner AMR

What is antimicrobial resistance (AMR) ?

DEFINITIONS:

- Antimicrobials:
  - include antibiotics, antivirals, antifungals and antiprotozoals. They are active substances of synthetic or natural origin which kill or inhibit the growth of microorganisms.

- AMR definition:
  - is the ability of microorganisms, such as bacteria, to become increasingly resistant to an antimicrobial (to which they were previously susceptible).
  - AMR is a consequence of natural selection and genetic mutation. Such mutation is then passed on conferring resistance.
  - This natural selection process is exacerbated by human factors such as inappropriate use of antimicrobials in human and veterinary medicine, poor hygiene conditions and practices in healthcare settings or in the food chain facilitating the transmission of resistant microorganisms. Over time, this makes antimicrobials less effective and ultimately useless.

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AMR on a global and local level

Already now a serious social and economic burden

Deaths:

- Estimated to be responsible for 25.000 deaths per year in EU today
- 700.000 deaths per year globally today
- In 2050 AMR might cause more deaths than cancer today

Socio-economic impact:

- 1.5 billion € / y in healthcare costs and productivity losses in the EU today
- By 2050 global economic damage may be par with the 2008 financial crisis

3 (ECDC data & World Bank 2016 estimations)

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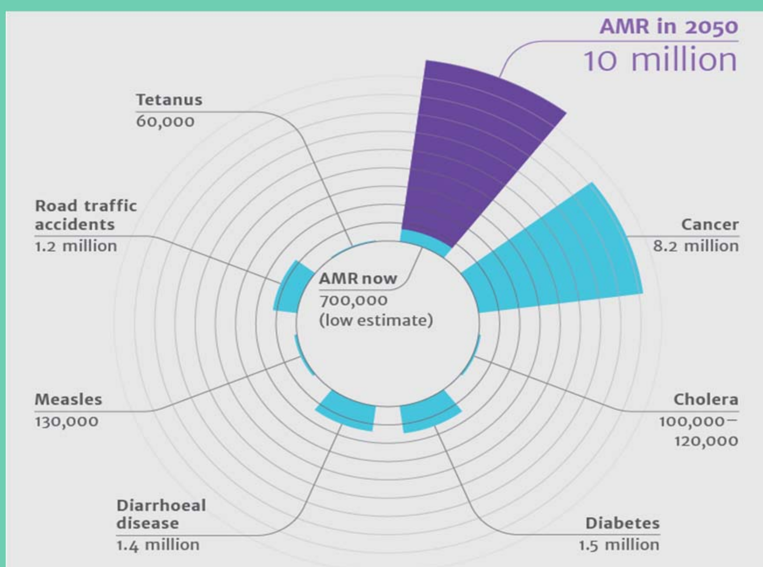
Deaths attributable to AMR every year worldwide

Compared to other major causes of death



4 (O'Neill Report 2014)

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The O'Neill Report (UK 2015)

Jim O'Neill

Macroeconomist

Commissioned by David Cameron in 2014 to establish a report on how to best address the problem of AMR

Strong focus on antimicrobial agents

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The O'Neill Report (UK 2015)

- 9 interventions
- 1 perspective

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Vaccines

https://amr-review.org/

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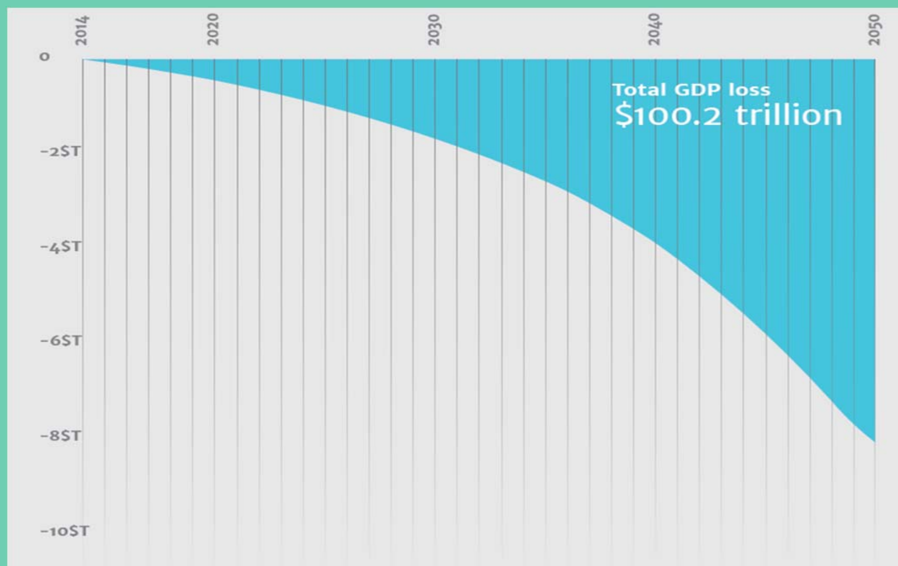
AMR's impact on World GDP in trillions of USD



(O'Neill Report 2014)

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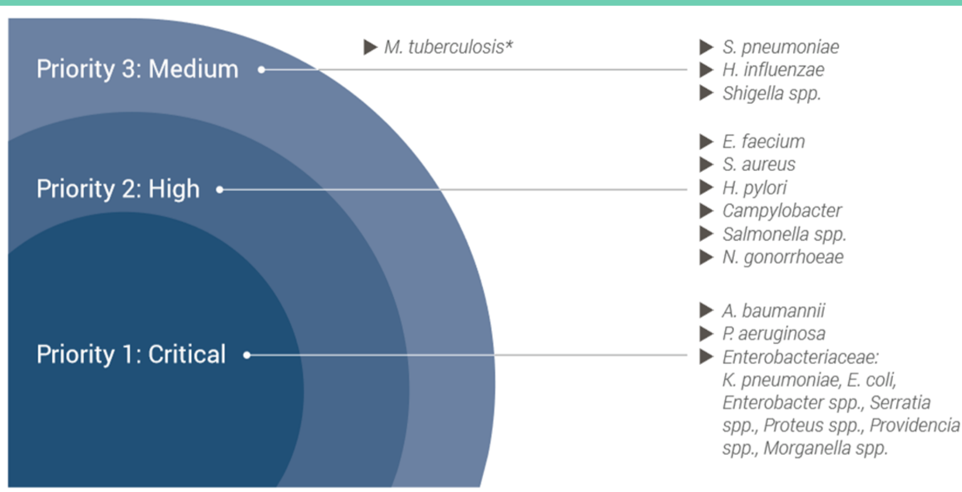
WHO – List of priority pathogens:



Note: WHO 2017: Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics; *M. tuberculosis was nc subjected to review for inclusion in the WHO priority list. However, it was specifically acknowledged as a globally established priority for which innovative new treatments are urgently needed. We therefore included this pathogen in our analysis.

8 (taken from: https://vaccinesforamr.org/wp-content/uploads/2018/09/Vaccines_for_AMR.pdf)

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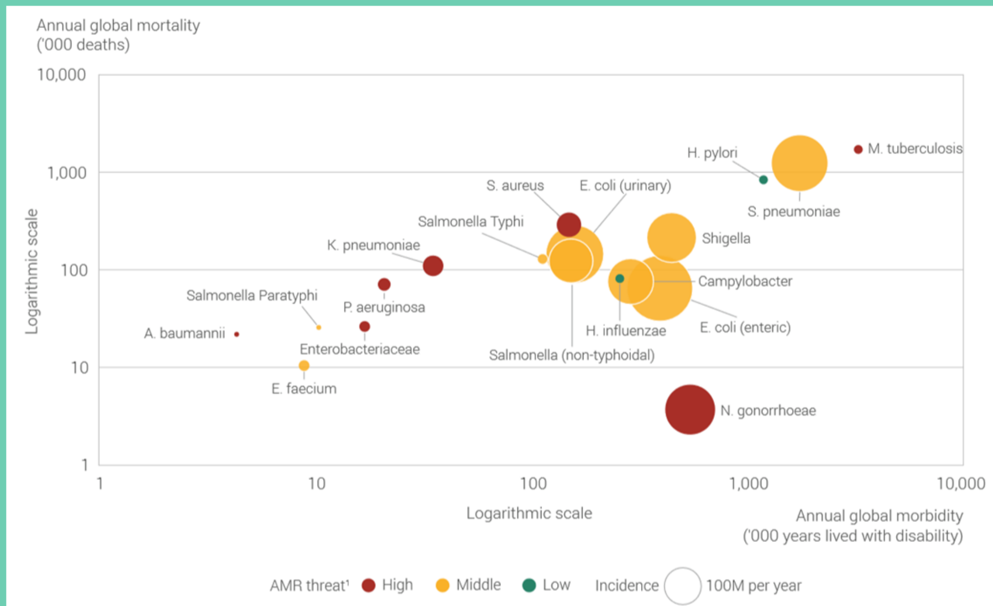
AMR threat on a global level by pathogen

Report by Wellcome Trust:



(taken from: https://vaccinesforamr.org/wp-content/uploads/2018/09/Vaccines_for_AMR.pdf)

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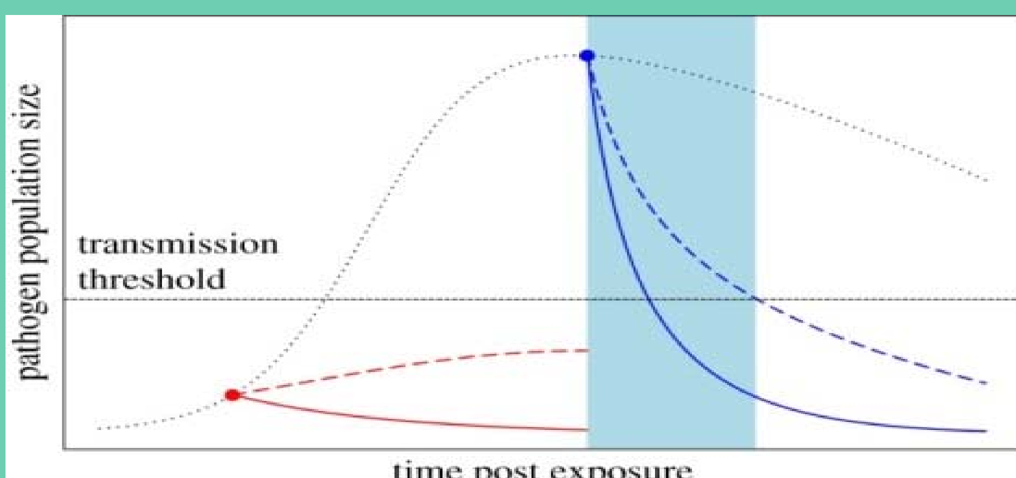
AMR evolution also depends on rate of transmission

- Drugs and vaccine-induced immunity impose selection for resistance at different times in an infection



(Kennedy DA & Read AF 2017 Proc. Biol. Sci.)

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Drivers of Antimicrobial Resistance (AMR)

- Drivers of AMR:

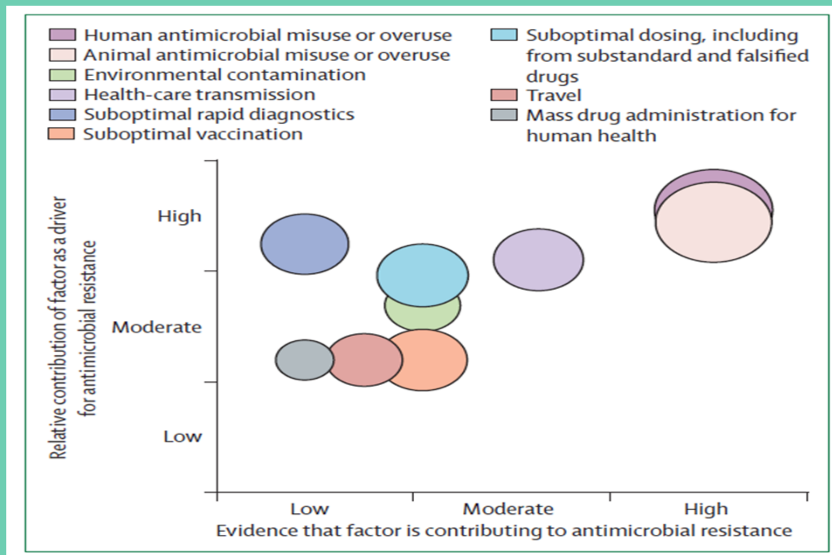
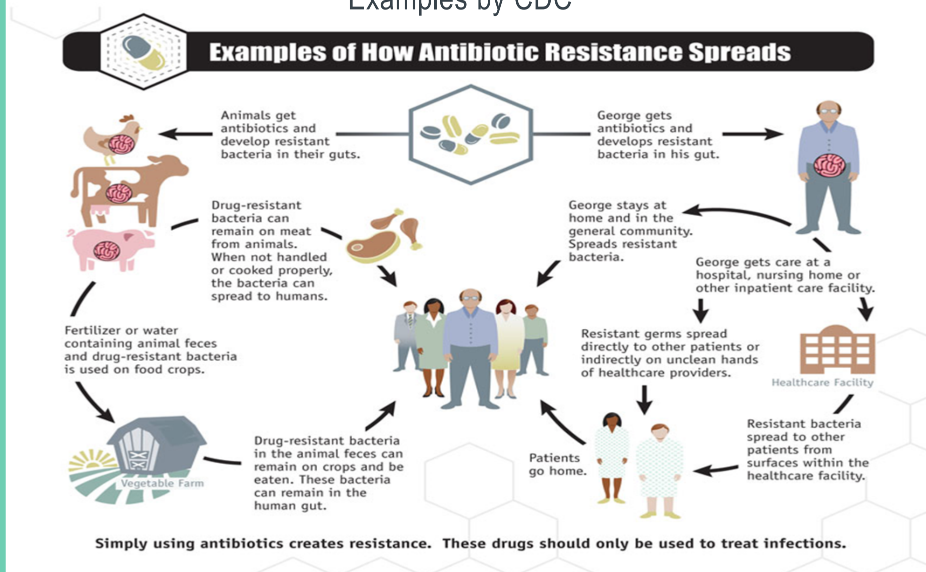


Figure 3: **Role of modifiable drivers for antimicrobial resistance: a conceptual framework**

11 (Holmes A et al. 2016 Lancet)

How does AMR spread?

Examples by CDC



12 https://www.cdc.gov/antibiotic-use/community/images/howAR-spreads.jpg

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Antibiotic use impacts on non-target bacteria

Proposed scenario for the emergence of Group B *streptococcal* neonatal infections

Before 1950: a diverse population of GBS teracycline sensitive (unknown)

1950: Extensive use of tetracycline

1. Selection of TcR isolates by gain of mobile genetic elements
2. Created a niche by eliminating TcS GBS and by altering the gut microbiota
3. Among TcR clones selection of those with higher colonization and dissemination properties
4. Worldwide dissemination of few TcR clones with higher virulence potential

(Da Cunha *et al*. Nature Communication 2014)

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Differences between vaccines and antimicrobial drugs with regards to AMR ?

- Vaccine effects are mediated through host immune responses while antimicrobial drug effects are mediated through chemical pathways with six consequences:

✓ – vaccines do not **interact** directly with pathogens, but instead act indirectly

✓ – vaccines induce systemic host responses that may **minimize spatial refugia** and spatial heterogeneity within hosts

✓ – immune responses are outside the control of individual patients, reducing opportunities for non-**compliance** that may create temporal heterogeneities and temporal refugia within hosts

✓ – vaccines are only active while pathogens are inside hosts, but drugs can remain active in environmental reservoirs, suggesting that the strength of **selection for resistance may differ for drug and vaccine resistance**

✓ – the immune system tends to be highly pathogen specific and so **vaccines** are in effect, **more-narrow spectrum** than most antimicrobial drugs

✓ – host immune systems have been shaped by **coevolution** between pathogens and hosts

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(Kennedy DA & Read AF 2017 Proc. Biol. Sci.)

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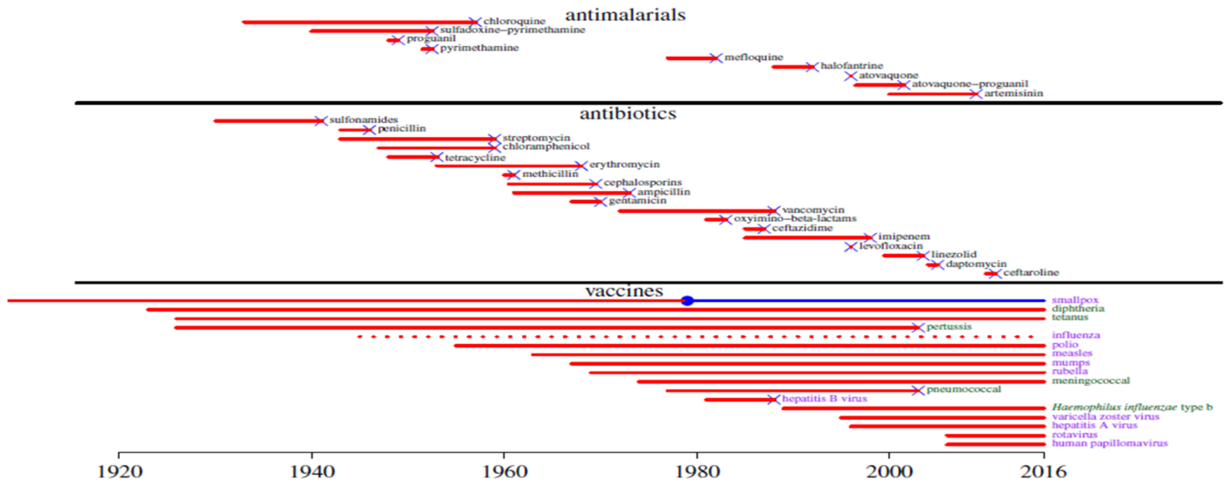
Pathogen evolution almost always undermines drugs but rarely undermines vaccines

- Resistance formation to a selective pressure onto a pathogen population:



(AF Read, ProcRSocB 2017)

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Evidence Base

Commonly Acquired Bacterial Infections

- **Hib conjugate vaccines:** [1]
  - Data from Italy: **50% decrease in resistance to ampicillin** and related antibiotics across all ages after universal introduction of the vaccine in 1999 – dataset spanning 10 years.[2]
  - Data from USA: **decrease in prevalence of antibiotic resistant *Haemophilus influenzae*** isolates from patients with respiratory tract infections across four national surveys between 1994 and 2003.[3]
  - Data from Spain: **reduction in the use of multiple antibiotics** due to Hib vaccination (1997 – 2007).[4]
  - Data from India: **evolution of antibiotic resistance** in the absence of primary prevention through vaccination.[5]

1. Jansen KU, Kinrsch C, Anderson AS. The role of vaccines in preventing bacterial antimicrobial resistance. Nat Med 2018;24:10–20.
2. Utt E, Wells C. The global response to the threat of antimicrobial resistance and the important role of vaccines. Pharm Policy Law 2016;18:179–97.
3. Heilmann KP, Rice CL, Miller AL, Miller NJ, Beekmann SE, Pfaller MA, et al. Decreasing prevalence of B-lactamase production among respiratory tract isolates of Haemophilus influenzae in the United States. Antimicrob Agents Chemother 2005;49:2561–4. doi:10.1128/AAC.49.6.2561-2564.2005.
4. García-Cobos S, Campos J, Cercenado E, Román F, Lázaro E, Pérez-Vázquez M, et al. Antibiotic resistance in Haemophilus influenzae decreased, except for β-lactamase-negative amoxicillin-resistant isolates, in parallel with community antibiotic consumption in spain from 1997 to 2007. Antimicrob Agents Chemother 2008;52:2760–6.
5. John J, Cherian T, Raghupathy P. Haemophilus influenzae disease in children in India: a hospital perspective. Pediatr Infect Dis J 1998;17:S169-171.

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Evidence Base

Commonly Acquired Bacterial Infections

- ***Streptococcus pneumoniae***
- The most commonly cited pathogen when demonstrating a vaccines impact on AMR by, ….
  - reducing overall burden of disease (including herd immunity),
  - targeting the most resistant serotypes,
  - and decreasing antibiotic use.[3]

  - Data from the USA (2011): **64% reduction in antibiotic-resistant pneumococcal infections in children** and a **45% decrease in adults over the age of 65 due to use of PCV7 (1998-2008)**.[1]

  - CDC data: **93% and 86% reduction** of isolates that were resistant to either single or multiple antibiotics respectively.[2]

1. Hampton LM, Farley MM, Schaffner W, Thomas A, Reingold A, Harrison LH, et al. Prevention of antibiotic-nonsusceptible streptococcus pneumoniae with conjugate vaccines. J Infect Dis 2012;205:401–11
2. Tomczyk S, Lynfield R, Schaffner W, Reingold A, Miller L, Petit S, et al. Prevention of Antibiotic-Nonsusceptible Invasive Pneumococcal Disease with the 13-Valent Pneumococcal Conjugate Vaccine. Clin Infect Dis 2016;62:1119–25. 3.
3. Lipsitch M, Siber GR. How can vaccines contribute to solving the antimicrobial resistance problem? MBio 2016;7:1–8.

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Evidence Base and Outlook

Commonly Acquired Bacterial Infections

Streptococcus pneumoniae

- Potential future and observed impacts:
  - Predictions from the USA (2003): Use of PCV7 could potentially **prevent 1.4 million antibiotic prescriptions** annually.[1]

  - Universal coverage with a pneumococcal conjugate vaccine could avert up to **11.4 million days per year of antibiotic use for pneumonia caused by *S. pneumonia* in children under-five**, a **47% reduction** in days on antibiotics.[2]

  - Introduction of PCVs have a direct effect on antibiotic purchases:
    - Data from Finland: **8% reduction in antibiotic purchases** after introduction of PhiD-CV10.[3]

1. Fireman B, Black S, Shinefield H, Lee J, Lewis E, Ray P. Impact of the pneumococcal conjugate vaccine on otitis media. Pediatr Infect Dis 2003;22.
2. Laxminarayan R, Matsoso P, Pant S, Brower C, Røttingen JA, Klugman K, et al. Access to effective antimicrobials: A worldwide challenge. Lancet 2016;387:168–75.
3. Palmu A, Jokinen J, Nieminen H, Syrjanen R. Vaccine effectiveness of the pneumococcal Haemophilus influenzae protein D conjugate vaccine (PHiD-CV10) against clinically suspected invasive pneumococcal disease: a cluster-randomised trial. Lancet Respir Med 2014;2:717–27.

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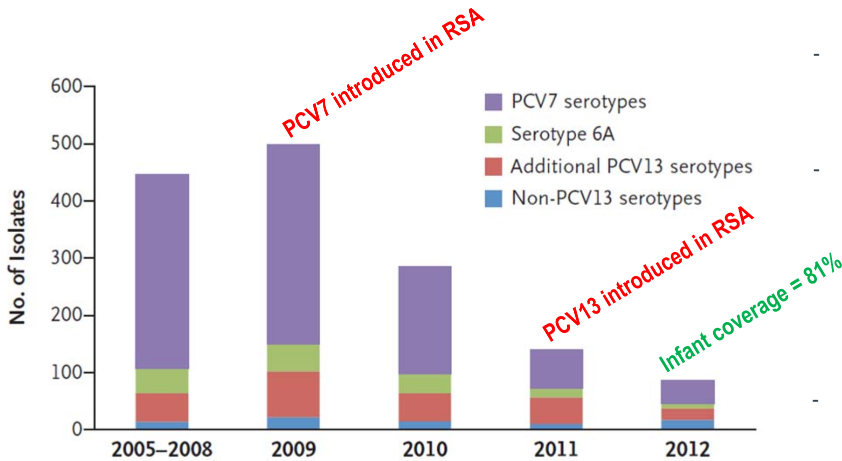
PCVs use impact on Invasive Pneumococcal Disease in South Africa



- Prior to vaccination, 83% of multidrug-resistant pneumococcal disease isolates were serotypes contained in PCV7
- 2009 – 2012 among children younger than 2 years of age, IPD caused by resistant pneumococci declined by:
  - 82% for penicillin resistant isolates
  - 85 % for ceftriaxone res. isolates
  - 84% for multidrug res. isolates
- Additional impact of vaccine programs in children on capsular types infecting adults

Number of Penicillin-Nonsusceptible Isolates Causing IPD among Children Younger then 2 Years of Age, According to Serotype.

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(2014, Von Gottberg NEJM)

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PCV13 use impacts on AMR in Invasive Pneumococcal Disease (US)

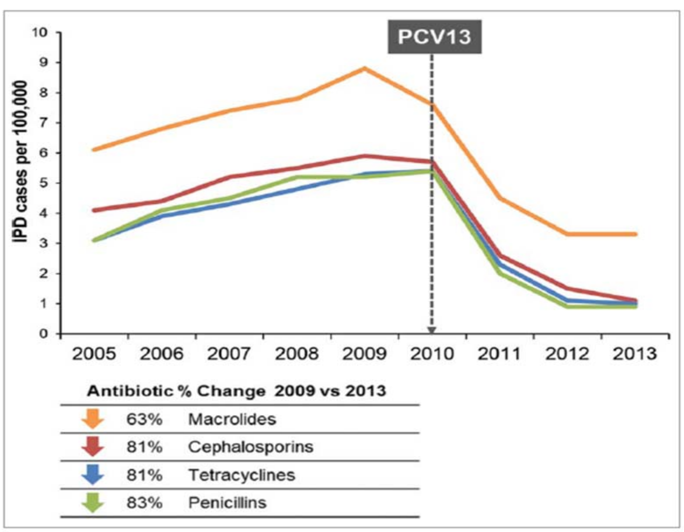

Figure 2. Rates of antibiotic non-susceptible invasive pneumococcal disease (<5 years) 2005–2013.[28]

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(2018, Jansen, Human Vaccines & Immunotherapeitics)

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Pneumococcal strains identified from middle ear fluid – French data

- 6883 AOM middle ear fluid samples taken between 2001 – 2011
- 1694 S. pneumoniae strains in 2001 compared to 560 strains in 2011

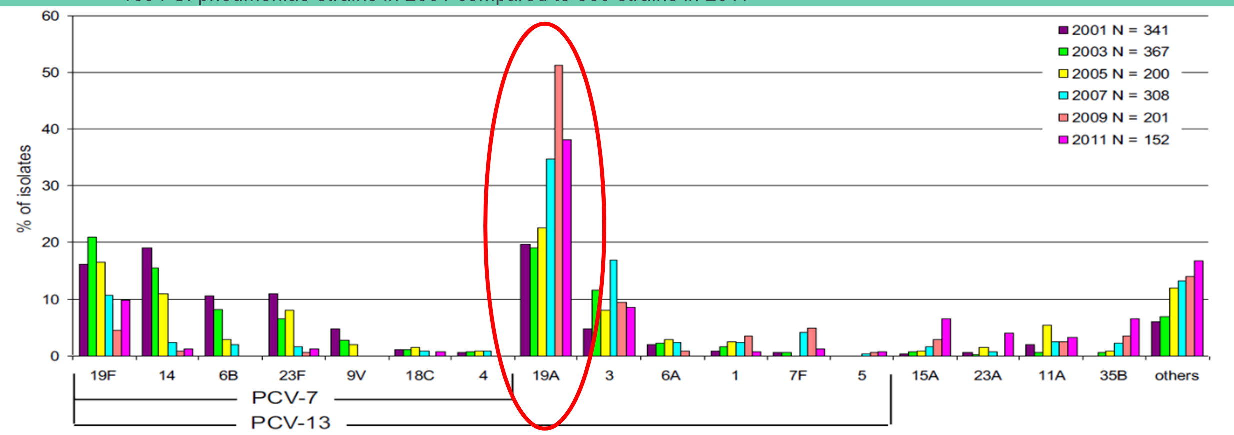

FIG. 1. Trends in *Streptococcus pneumoniae* serotypes isolated from middle ear fluid of French children with acute otitis media between 2001 and 2011.

21 (Kempf M, CMI, 2015)

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Evidence Base

Viral Infections

- **Influenza** is the most commonly cited viral vaccine that demonstrates the ability to reduce AMR. Vaccination for influenza not only prevents infection / disease, but it also displays two mechanisms to decrease antibiotic use: (1) prevents inappropriate antibiotic use, and (2) decreases the likelihood of secondary bacterial infections requiring antibiotics.
  - In the US, **half of all antibiotic prescriptions** are inappropriately written for acute respiratory illnesses associated with viral pathogens.[1]
  - Data from USA: **43% - 47% reduction in inappropriate antibiotic use** after influenza vaccination in healthy working adults.[2]
  - Data from Turkey: **51% reduction in the incidence of otitis media** in children who had been vaccinated against influenza compared to unvaccinated controls. By inference, **antibiotic use was similarly reduced** in vaccinated children.[3]
  - Data from Canada: universal influenza vaccination program in Ontario resulted in a **64% decrease in influenza-associated respiratory antibiotic prescriptions** over one year. This translated to roughly **144,000 antibiotic prescriptions prevented** across all ages by universal introduction of the vaccine compared to other Canadian provinces that limited vaccine use to high-risk situations.[4]

1. Chatham House - The Royal Institute of International Affairs. The Value of Vaccines in the Avoidance of Antimicrobial Resistance. vol. 44. London, England: 2017.
2. OMS. Guide pratique sur la prevention des infections nosocomiales, Chaptire X. 2008.
3. Ozgur S, Beyazova U, Kemaloglu Y, Maral I, Sahin F. Effectiveness of Inactivated Influenza Vaccine for Prevention of Otitis Media in Children. Pediatr Infect Dis J 2006;25:401–4.
4. Kwong JC, Maaten S, Upshur REG, Patrick DM, Marra F. The Effect of Universal Influenza Immunization on Antibiotic Prescriptions: An Ecological Study. Clin Infect Dis 2009;49:750–6.

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How can vaccines impact on AMR ? Selected mechanisms

- **Direct reduction** of target disease with vaccine induced protection
  - (examples: infant routine vaccination, all vaccines)
- **Direct protection** of immunocompromised subjects including HIV positive population
  - (example: PCV use in RSA with 30% of pregnant women being HIV positive)
- **Reduction of opportunistic infections** which follow the target disease
  - (examples: influenza vaccine preventing pneumonia following influenza infection)
- **Reduction of target disease in unvaccinated** age groups due to reduction of prevalence in target age group
  - (examples: Infant PCV vaccination programs reduce adult/elderly pneumonia)
- Reduction of diseases due to **cross-protection**
  - (potential example: MenB Vaccines potential protection against gonococcal disease)
- **Reduction of unspecific use of antimicrobial agents** in diseases without fast diagnostics
  - (example: Use of Ebola vaccine prevents use of antimicrobials in emergency situation with diagnostic uncertainty)
- **Animal health:** Vaccines reduce the use of antimicrobial agents

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The situation in Animal Health

- O'Neill Report introduced 50mg/kg target for agriculture in 2015
- DEFRA endorsed the target and challenged the agricultural industry through The Responsible Use of Medicines in Agriculture Alliance (RUMA) to meet this target by 2019.
- RUMA established the RUMA Targets Taskforce.
- A 27% reduction in antibiotic use has been achieved in the last 2 years and the 50mg/kg target achieved 2 years early. 2016 data shows usage rate at 46mg/kg
- New targets have now been set for continued reduction

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Animal Health needs to increase use of vaccines

- New targets introduced in October 2017 include reduction in antibiotics and increase in vaccination.
- MSD Animal Health is working with many stakeholders to increase vaccination levels in UK agriculture, in improved animal health, reduce disease burden and reduce antimicrobial use.
- Current vaccination use in agriculture is varied:
  - Aquaculture and poultry – over 95% vaccinated
  - Pigs – high vaccination for PCV2 (95%) and PRRS (60%). Low vaccination for other diseases including APP, Glässer's disease and Streptococcus suis.

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Animal Health – Example from Aquaculture

- Impact of vaccines on use of antimicrobial agents (1981 – 2004)

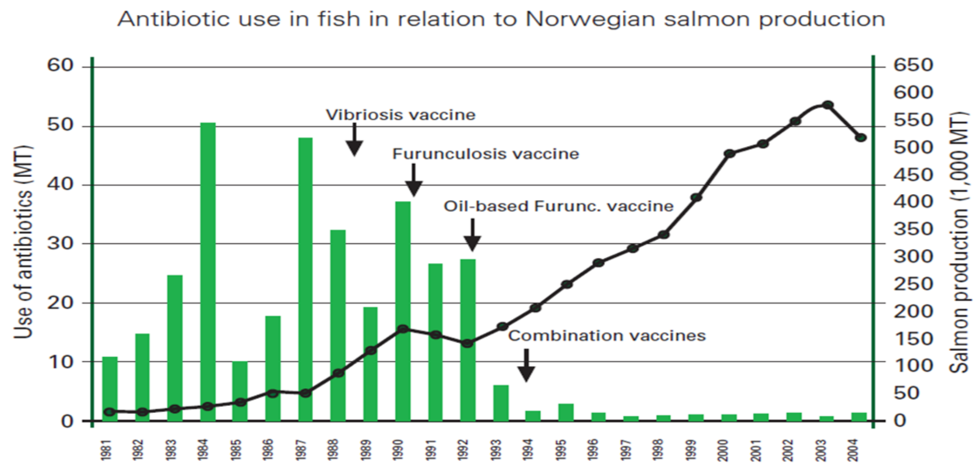

Fig. 1. Antibiotic use in fish (green bars) in relation to Norwegian salmon production (black line), 1981–2004. Note the dramatic drop in antibiotic use following the introduction of oil-based vaccines in 1992. These vaccines offered high protection against vibriosis caused by *Listonella (Vibrio) anguillarum* and furunculosis caused by *Aeromonas salmonicida* (Håstein et al., 2005).

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Animal Health needs to increase use of vaccines

- The majority of cattle and sheep are not vaccinated.
- Cattle vaccination rates:
  - BVD – 27%, BRD – 17%, Neonatal Scour – 13%,
    IBR – 22%
- Sheep Vaccination rates:
  – Lameness – 16%, Enzootic abortion – 36%, Toxoplasmosis – 22%, Clostridial diseases and pasteurellosis – 42%

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How can Vaccines impact on AMR ? Mechanisms:

- Reducing the need for antimicrobial use
- Reducing the total number of cases
- Reducing the number of pathogens that may be responsible for a particular clinical syndrome – use of narrow spectrum Abx is feasible for empiric therapy
- Effects may be increased by herd immunity
- Reducing pressure for AMR development in bystander commensals in the normal flora
  – Thereby reducing the prevalence of AMR genes which could be transferred to potential pathogens.

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(Siber & Lipsitch 2016 mBio)

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Global and local activities around AMR

- Global efforts:
  - United Nations Political Declaration on AMR (2016)
  - WHO Global Action Plan on AMR (2015)
    - Subsequently adopted by: World Animal Health Organization (OIE)
    - Food and Agriculture Organization (FOA)
  - Action item on the agenda of G7 and G20 Meetings.

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Antibiotic Resistance Threats in the USA and what to do about it

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives. Protecting People™

Four core actions that will help fight deadly infections:

- preventing infections and preventing the spread of resistance
- tracking resistant bacteria (surveillance)
- improving the use of today's antibiotics (stewardship boards)
- promoting the development of new antibiotics and developing new diagnostic tests for resistant bacteria

Bacteria will inevitably find ways of resisting the antibiotics we develop, which is why aggressive action is needed now to keep new resistance from developing and to prevent the resistance that already exists from spreading.

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(ANTIBIOTIC RESISTANCE THREATS in the United States, 2013; CDC 2013)

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Global Guidance Documents Acknowledging the Role of Vaccines

Guiding Document	Description / Reference to Vaccines
The Review on Antimicrobial Resistance (Jim O'Neill)	• Considers impact of vaccines in tackling infections and drug resistance • Acknowledges that strategies to prevent and treat infections should run in parallel to antimicrobial stewardship activities • Proposes a three pronged approach to incentivize **innovation and uptake of vaccines**: 1. **Use existing products** more widely in humans and animals 2. **Renew impetus for early-stage scientific research** (e.g. Global Innovation Fund) 3. **Sustain a viable market** for needed products through pull incentives (e.g. Advanced Market Entry Rewards)
WHO Global Action Plan on Antimicrobial Resistance	• Looks at AMR through a **one-health approach** considering human health, animal health, agriculture, and environmental aspects • Defines five strategic objectives • **Strategic Objective #5**: **Develop economic case for sustainable** investment that takes account of the needs of all countries, and **increases investment** in new medicines, diagnostic tools, **vaccines**, and other interventions
2016 UN declaration on antimicrobial resistance	• Reaffirms that the blueprint for tackling AMR is the WHO Global Action Plan • Provides the mandate of the UN Interagency Coordinating Group (IACG) • Recognizes that one of the keys to tackling AMR is **prevention and control of infections**, including **immunization**, monitoring and surveillance of AMR • Calls for: **affordability and access to existing and new** medicines, **vaccines**, and diagnostics, as well as to the broader health services and food, clean water and environment
UN IACG Framework For Action	• Builds on WHO Global Action Plan, UNGA political declaration, and Sustainable Development Goals • Provides a comprehensive approach to capture (1) all 14 content areas, (2) relevant levers to address them, and (3) underlying enablers • Allows identification of progress and gaps in key content areas • **Content area #13: Vaccine development and access** 1. Develop or improve **vaccines for human and animal** pathogens 2. Improve human **routine immunization** coverage in all geographies 3. Improve **access to animal vaccines** in farm worldwide

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Global Guidance Documents Acknowledging the Role of Vaccines

Guiding Document	Description / Reference to Vaccines
Davos Declaration	• **Joint declaration** issued at the World Economic Forum; signed by >100 companies and trade associations across 21 countries • Declaration lays out a common set of principles for global action to support antibiotic conservation and **development of new drugs, diagnostic, and vaccines** that enhance conservation for new and existing treatments; it also calls for coordinated action to improve infection prevention, hygiene, stewardship, and conservation methods • Signatory companies call on governments to work with them to develop **new and alternative market structures** that provide more dependable and sustainable market models
Industry Roadmap for Progress	• **Builds on the Declaration** by setting out four detailed commitments by the pharmaceutical industry to address AMR • Declares commitment to work to **reduce development of AMR**, **invest in R&D**, and **improve access** to high quality antibiotics and **vaccines** • **Commitment #3**: Support **mechanisms to facilitate affordable access** to high quality new and existing antibiotics, diagnostics, and **vaccines** to all patients who need them, in all parts of the world, and at all income levels • Work with stakeholders to **establish new business models** to improve access to new antibiotics, diagnostics, and **vaccines** globally • **Commitment #4**: Explore new opportunities for **open collaboration** between industry and public sector to **address challenges in R&D** of new antibiotics, **vaccines**, and diagnostics, **recognizing value** they bring to society
Berlin Declaration of the G20 Health Ministers	• Calls on UN Secretary General, WHO, FAO, and OIE to provide strong leadership for combatting AMR • Commits to support the work of the IACG • Recognizes that infection prevention and control, sanitation, and **vaccination** needs to be **prioritized across health systems** to prevent emergence and contain spread of AMR • Highlights importance of **fostering R&D** for new antimicrobials, alternative therapies, **vaccines**, and rapid-point-of-care diagnostics • Acknowledges importance of **reactivating the R&D pipeline** through push and pull incentive mechanisms, as well as **affordable access** to existing antimicrobials, diagnostic tools, alternative therapies, and **vaccines**

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Organizations Supporting Vaccines in Addressing AMR

- In March 2017**, the Centre on Global Health Security at Chatham House** held an invite only meeting for vaccine experts, representative of international / regional organizations, economists, modelers, and scientists from the industry to (1) review current knowledge on the role of vaccines in combatting AMR and (2) consider issues for modelling their value for this purpose.
- **The Bill & Melinda Gates Foundation; Gavi, the Vaccine Alliance; Wellcome Trust; Sabin Vaccine Institute,** advocate for vaccine development and higher rates of vaccination globally, not only to prevent disease, but also as an essential intervention in tackling AMR.[1]
  - **Bill & Melinda Gates Foundation** has expressed interest in funding work to determine the impact AMR has on mortality in low and middle-income countries. The core of the Foundation's strategy on AMR is to support the development of vaccines that have a major impact on global mortality.[2]
    - Major programs for HIV, TB, and malaria
    - Supports the only phase III trial for RSV and development of a vaccine for GBS
  - **Gavi, the Vaccine Alliance** has embarked on a new vaccine investment strategy that requires valuing the impact of different vaccines on AMR, in addition to the usual health and economic indicators, to influence ranking of vaccines (mechanism still being established).[2]
  - **Wellcome Trust** has identified both vaccines and AMR as a priority area for the next five years.[2]
  - **Sabin Vaccine Institute** advocates for vaccines to be part of the solution to the emerging crisis of antibiotic resistance.[3]

1. Access to Medicine Foundation. Antimicrobial Resistance Benchmark 2018: Methodology 2017. Amsterdam, The Netherlands: 2018.
2. Chatham House - The Royal Institute of International Affairs. The Value of Vaccines in the Avoidance of Antimicrobial Resistance. London, England: 2017.
3. Gellin B. Vaccines are part of the solution to the emerging crisis of antibiotic resistance. Stat 2017. https://www.statnews.com/2017/08/01/antibiotic-resistance-vaccines/.

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Hopes for the future ?

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