The Value of Vaccines in the Avoidance of Antimicrobial Resistance

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Centre on Global Health Security

• In order to bring understanding of global health issues to many sectors other than health - from foreign affairs to defence, trade, agriculture and industry – Chatham House established the Centre on Global Health Security in 2009.

• Health is an important foreign policy and diplomatic concern that has implications for security, economic wellbeing and international development.

• The Centre on Global Health Security seeks to generate new ideas for enhancing global health security, by stimulating discourse among the relevant communities in the internationally recognized, politically neutral forum of Chatham House.

• It pays attention to global health issues that have encountered, or could encounter, serious difficulties in bilateral relations, international organizations and diplomatic negotiations because of a divergence of political, economic or social interests.
Objectives of Chatham House Workshop

• Review current knowledge and activities on the role of vaccines in combatting AMR

• Consider the issues involved in modelling the value of vaccines in combatting AMR

• Consider how national and international policies on their use and support for R&D efforts could be influenced to properly recognize the contribution of vaccines in mitigating the growth of AMR.
Participants in Chatham House Workshop

Drugs for Neglected Diseases Initiative, Marshfield Clinic Research Foundation, GAVI, World Health Organization, Harvard University, Chicago University, Oxford University, Public Health England, Sanger Institute, AstraZeneca, London School of Hygiene and Tropical Medicine, BARDA, Pfizer, Public Health Foundation of India, Imperial College, Department of Health and Human Services, CDC, European Commission, Serum Institute, Bill & Melinda Gates Foundation, Fogarty Center, Sanofi, Centre for Disease Dynamics, Economics and Policy, University of Sydney, Janssen, Department of Health, UK, European Centre for Disease Prevention and Control, Hopitaux Universitaires Geneve, Seqirus, GSK, Merck, Medecins sans Frontieres, Nottingham University, Wellcome Trust.
The Health and Economic Burden of AMR

• The burden of AMR reflects past antibiotic use but also the absence of other preventative measures such as improved water and sanitation. In developed countries infection rates fell steeply well before antibiotics became available. High rates of antibiotic use in LMICs reflect that absence while many still cannot access antibiotics they need.

• In 2000-2010 antibiotic consumption rose by 36%, three quarters was in the BRICS countries. India is the largest consumer of antibiotics in the world, twice that of the US and 30% more than China.

• Those most at risk from AMR are the young (prone to infection) and the elderly (particularly if surgery is affected).

• The flu season is the key driver of antibiotic use throughout the world. Vaccines to reduce fevers, not just flu, could have a major impact on antibiotic use.

• Quantifying the economic impact of AMR needs a better understanding of health impact which has been hard to do. We need to estimate the value of expanding access to existing vaccines and the potential for new vaccines.
Specific Disease Presentations: Pneumococcus

• PCV7 vaccine reduced IPD very significantly, not only in vaccinated children but also the elderly
• But it contributed to expansion of new serotypes, notably 19A which is now covered by PCV13. But in the USA new resistant strains (35B, 15B and 23A)
• In Germany a cumulative reduction of 539000 in antibiotic prescriptions for pneumonia in 2007-14
• Need for vaccines that target all serotypes
Specific Disease Presentations: Influenza

- Influenza is an important cause of community acquired pneumonia – so antibiotics are used both appropriately and inappropriately for influenza
- Difficult to reduce usage without rapid point of care diagnostics
- But flu vaccination (live attenuated) of children has been shown also to reduce hospitalization in adults
- Challenges are that a) flu vaccine is not very effective and b) even in peak flu season less than 50% of ARIs are caused by flu
- Using RSV vaccines alongside flu vaccines could therefore have a much bigger effect on antibiotic usage in the flu season.
- We lack data on the burden of flu in LMICs which inhibits their expanded use.
Specific Disease Presentations: GBS

- GBS is responsible for a number of serious diseases and has become a major cause of neonatal sepsis, meningitis and death.
- In the US screening programmes result in 32% of pregnant women receiving antibiotics – the risk-based approach tried in the UK has been unsuccessful in reducing GBS.
- A vaccine for GBS could have a large impact in averting infections in mothers and children, antibiotic usage and AMR.
- There are only ten capsular serotypes for GBS and five are responsible for 95% of the disease (compare with pneumococcus).
- Serotype V shows macrolide resistance so vaccine must include it – otherwise could actually drive AMR as type V selected.
Specific Disease Presentations: Typhoid

• There is global resistance emerging and different types of pathogen are emerging as selection pressure is put on them

• Vaccination offers a way to stop this process and because it only resides in humans elimination of the disease is possible

• The Vi polysaccharide vaccine has limitations and the roll out of the Vli conjugate vaccine has been very slow but a study suggested 82% efficacy

• Nepal plans to ask GAVI to include vaccine in its portfolio, not because of AMR but the prevalence of typhoid
Specific Disease Presentations: Gonococcal Infection

• In the course of 100 years resistance has developed to each successive class of antibiotics and we are nearly back to zero treatments. The first dual therapy failure was recently recorded.

• There are few estimates of the health and economic costs of gonorrhoea – a crude 2005 estimate was $500 million globally.

• Although it is on the WHO and CDC priority lists for needed antibiotics, the current R&D pipeline is not promising.

• Therefore a vaccine may in the end be the only way to control and even eliminate the disease.

• But there are major technical challenges in vaccine development, in spite of the discovery that meningococcal vaccine had an effect.
Specific Disease Presentations: Tuberculosis

• TB now kills more people than any other pathogen – 1.8 million in 2015.
• AMR, MDR and XDR are major problems. Treatment ranges from 6 months if not resistant to 18-20 months for XDR TB.
• Generating new antibiotics may never solve the problem
• There are now over a dozen vaccine candidates in trials (compared to none 14 years ago) but as with gonorrhoea many challenges in vaccine R&D
• Issues to do with what type of vaccines for which target population
• Prophylactic vaccines could be targeted at children and young people, the main group responsible for transmission
• Scope for post-exposure vaccines to prevent or eradicate latent infections and therapeutic vaccines in combination with chemotherapy, in particular to shorten treatment times
• More collaboration is required between drug and vaccine fields.
Modelling the Value of Vaccines: Mechanisms

• The most obvious way vaccines address AMR is by reducing the need for antibiotics to treat illnesses (eg PCV).
• But antibiotics can induce selection in the many bacteria residing in the body, not just those targeted – known as “bystander selection”
• This means estimating the reduction of AMR resulting from reduced antibiotic use is not simple
• Nevertheless “avoided use” may be the most feasible endpoint in valuing vaccine use.
• Vaccines could also be developed to target resistant strains but then selection can nullify this (cf PCV). Are there ways to develop vaccines that counteract selection for resistance?
Modelling the Value of Vaccines: Complications

• Models that assume resistant strains are otherwise identical to sensitive strains may be inaccurate.

• We do not fully understand what maintains resistance – we need to consider the vaccine’s impact on total antibiotic use given the bystander effect and the typical host/antibiotic environment experienced by each pathogen, not the prescription rate per pathogen.

• There are probably small but distinct possibilities that vaccines could increase resistance.

• Modelling the complex relationships in the AMR equation involves collaboration between three groups – those modelling antibiotic stewardship, vaccination modellers and those modelling health and economic outcomes.
Modelling the Value of Vaccines: Different Approaches

• Current modelling literature on the epidemiological impact of vaccination on AMR is limited in terms of pathways considered, geographical scope and pathogen/antibiotic combinations.

• Estimating the value of vaccination in preventing AMR will require integration of approaches used by the vaccine modelling, AMR modelling and economic evaluation communities.

• Potential modelling designs would ideally capture the dynamic nature of (i) the host-pathogen ecology in the presence of antibiotics and (ii) the health care system, antibiotic market and entire economic system.
Modelling the Value of Vaccines: Complexity

"Atkins et al. Lancet Infectious Diseases (in revision) [Academic in confidence]"
Modelling the Value of Vaccines: Simple Summary

• So getting from vaccine use just to estimates of reduced antibiotic use is not as simple as it might seem and would require some very strong assumptions concerning the relationships in the previous table.

• Then there is a no doubt equally complicated relationship between reduced antibiotic use and avoided AMR.

• And then what is the $ value of avoided AMR. There are reduced hospital costs, the societal value generated by better and faster treatment, the avoided cost of generating new antibiotics, or in the Doomsday scenario the avoided cost of many life-saving or life-enhancing operations becoming too risky to perform.
A Straw Poll

Participants were asked to prioritise 15 possible new vaccines in a straw poll. The results were in order:

- tuberculosis
- typhoid
- influenza
- RSV
- gonococcus
- GBS
- GAS
- staph aureus
- other (includes malaria)
- pseudomonas
- C.diff
- Klebsiella
- HIV
- chlamydia
- pneumococcus

• This list was very different from the WHO list of priorities for antibiotic development.
• But the criteria for prioritization were not defined.
• So pneumococcus may have come last because no extra incentives were considered necessary to stimulate R&D.
• The ability to treat (or growing inability) seemed to be a key factor in the prioritization.
Conclusions and Next Steps

Modellers emphasized the difficulties in valuation. Also given the inherent health and economic benefits of vaccines it is not clear that an AMR value, in most cases, would alter decisions on use or R&D. Nevertheless clear that vaccines could play a bigger role.

Four scenarios:

- Increase use of existing vaccines (such as PCV)
- Develop vaccines for diseases with high burden where antibiotic is primary treatment and resistance likely to increase (e.g. TB, typhoid)
- Develop vaccines for diseases with high burden where antibiotic use is extensive though resistance not yet impacting treatment (e.g. GBS, GAS)
- Develop vaccines for diseases with lower disease burden overall but resistance a major impact on treatment (e.g. gonorrhoea, S.aureus, E. coli)
Conclusions and Next Steps

Possible next steps:

• Modelling may be difficult but worth piloting for specific disease areas (e.g. gonorrhoea)

• How to develop a priority list for needed AMR vaccines like the list for needed antibiotics (role of WHO)

• Raise awareness in the scientific and decision making communities (Journal special issue? Chatham House meeting for decision makers? )

• Establish working group to take things forward

• Undertake similar steps for enhanced vaccine use in animals.