ESTABLISHING THE IMPORTANCE OF HUMAN AND ANIMAL VACCINES IN PREVENTING ANTIMICROBIAL RESISTANCE (AMR)

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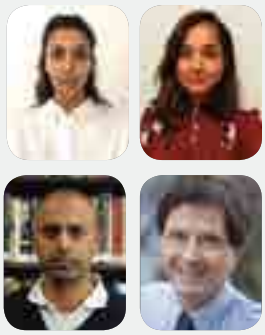

There is an urgent need to consider and develop long-term, sustainable solutions that take into account the complex drivers of AMR cross-cutting the human, animal and environmental sectors. Vaccines represent one of these solutions, but remain largely under-explored in terms of the potential health and economic benefits.

In 2017, the Centre on Global Health Security at Chatham House convened a meeting to review current knowledge and action on the role of vaccines in combating AMR, and to consider the issues involved in modelling how their value for this purpose could be established. A second meeting is planned in 2018 to explore the potential role and impact of veterinary vaccines, specifically, in reducing the global burden of AMR.

Antimicrobial resistance (AMR) – whereby a pathogen adapts in ways that render a drug used against it ineffective – is a natural process that has existed for as long as antimicrobials have been in use. A pathogen's ability to develop resistance evolved as a mechanism to survive environmental assaults, and is triggered in response to antimicrobial use and action *(1)*. The accelerated rate at which AMR has emerged and spread can be attributed to the inappropriate use of antimicrobial agents across the human, animal and environmental sectors *(2)*. The complexity of this global health issue, bridging disciplines, sectors and populations worldwide, has necessitated multi-pronged approaches and recommendations for combating AMR that have been increasingly at the fore of international policy discussions and global health agendas over the past decade *(3,4)*.

Although vaccines have been recognized as part of the solution – in the 2015 World Health Organization (WHO) Global Action Plan on AMR and the European Commission's 2017 One Health Action Plan against AMR for example – the extent to which vaccines can prevent AMR and have an impact on its global burden has been largely under-explored *(5,6)*.

There has been a strong focus, at the policy level, on optimizing the conditions for continued antibiotic use by enhancing awareness and surveillance measures, improving hygiene and sanitation practices, encouraging development of novel diagnostic tools and antibiotics, and shifting antimicrobial prescription and consumption behaviour in both the human and animal health sectors *(7,8)*. Maintaining this focus is of great importance, but should not frame the problem and the solution around antimicrobials such that the potential of alternative options for further research and development (R&D) are neglected. In 2016, around US$ 500 million in new funding was allocated to AMR from 13 existing or new initiatives whose primary purpose is to accelerate the development of new antibiotics *(9)*. New drugs face the same evolutionary process that led to resistance in current drugs, and the majority of those in the pipeline currently are simply modifications of existing drug classes and thus, "insufficient to mitigate the threat of AMR" *(10,11)*. There is a need to be innovative, not only in establishing best practice in antimicrobial use in human and animal health sectors, but in considering the breadth of practical, cost-effective R&D solutions that can reduce the reliance on antibiotics in both sectors. Vaccines are one of those potentially cost-effective solutions.

Vaccines in AMR control

The potential of vaccines in tackling AMR in humans is threefold: firstly, existing vaccines can prevent infections that would otherwise require antimicrobial medicines; secondly, existing vaccines can reduce the prevalence of primary viral infections often inappropriately treated with antibiotics and which can also give rise to secondary infections that require treatment with antimicrobials; and thirdly, the development and use of new or improved vaccines can prevent diseases that are becoming increasingly difficult to treat, or are in fact untreatable, owing to AMR *(7,12)*. Similarly in animals, antibacterial vaccines prevent infections that would otherwise require antimicrobial treatment; for antiviral vaccines, the positive effect on antimicrobial use is mediated through prevention of viral diseases and the associated risk of secondary bacterial infections. There are a number of mechanisms by which vaccines can reduce the burden of AMR in humans and animals, but all are based on the premise that an infection prevented by vaccination is "a case for which, by definition, the burden of AMR disease is reduced, the need for antibiotic therapy is eliminated, and the risk of poor outcomes is avoided" *(7)*.

The human vaccine landscape

The 2016 O'Neill Report made three recommendations pertaining to the development and use of vaccines: (i) to use existing products more widely in both human and animal populations, (ii) to renew impetus for early research and (iii) to sustain a viable market for needed products.

There are human vaccines currently in use against a number of microbial diseases commonly acquired in the general population, including diphtheria, tetanus, pertussis, *Haemophilus influenzae* type B (Hib) and *Streptococcus pneumoniae*, which are referred to as community-acquired infections (CAIs) *(7,8)*. Conjugate vaccines targeting these diseases, particularly Hib and *S. pneumoniae*, have dramatically reduced the global prevalence of invasive bacterial diseases most associated with mortality and in doing so, have removed the need for their antimicrobial treatment *(13)*. If the pneumococcal vaccine is universally rolled out, it has been estimated that approximately 11.4 million days of antimicrobial use in children under five years of age would be eliminated in 75 low- and middle-income countries (LMICs), in addition to the prevention of unnecessary childhood mortality *(6,14)*. Universal coverage of these vaccines, however, remains a challenge and varies from low-income to high-income countries. At present, the pneumococcal vaccine is included in 128 national immunization programmes, however global coverage for the three doses reached just 42% in 2016 with significant disparities across the economic spectrum; in low-income countries (LICs), coverage is 68% while in middle-income countries (MICs), it is 24%.

Global coverage of the diphtheria-tetanus-pertussis (DTP) vaccine, defined as children who have received a full three doses of DTP, was 86% in 2016. However, a number of low-income countries, such as the Congo, Guatemala and Iraq, have fallen short of their vaccination targets for several reasons, ranging from under-investment and conflict and civil unrest, to disease outbreaks and generally weakened health systems (World Health Organization, 2016). The DTP and Hib vaccines are typically used in combination, which helps to achieve similar levels of coverage in countries with routine national immunization programmes, although global coverage of the Hib vaccine still lags at 64%.

In the case of higher-income countries such as Romania, Italy and France, there has been a recent drop in immunization rates of vaccine-preventable diseases due to "anti-vaccination" lobbying, which has caused a surge in measles and tetanus cases and led to mandatory vaccination laws for upwards of ten diseases *(15)*.

The 2016 Review identifies three other categories of vaccines with the potential to prevent AMR: vaccines to prevent hospital-acquired infections, which frequently result in fatalities and for which there is a current lack of licensed vaccines, vaccines to prevent viral infections and associated secondary infections, and vaccines to prevent infections in animals. There is a recognized need to develop an evidence-based vaccine priority list for humans that weighs the value of vaccines against the burden and cost of AMR in different geographic and socioeconomic contexts (Heymann & Omaar, 2016) *(14)*. There are several challenges to this task. Firstly, how to define and accurately measure such an impact from a health and economic perspective, taking into consideration the direct and indirect mechanisms by which vaccination can have an effect on AMR *(9)*. A number of key principles were adopted to facilitate prioritization of vaccine R&D for animals based on identifying the most prevalent and important bacterial and non-bacterial infections associated with antibiotic use, patterns of antibiotic use in response to syndromic indication or diagnosed disease, the availability of vaccines (and their effectiveness), and the potential for new or improved vaccines to reduce the need for antimicrobial treatment. These principles, and the process of arriving at a priority vaccine list, provide a model and opportunity for the human health sector to adopt.

An additional challenge to developing new vaccines is the heterogeneity of pathogen interactions with the human body, as well as in response to actual and potential vaccines and antimicrobials. The introduction of the conjugate pneumococcal vaccine, PCV7, in 2000 in the United States

brought the incidence of invasive pneumococcal disease in vaccinated children and elderly populations down significantly, however, it simultaneously contributed to the emergence of new serotypes that PCV7 did not protected against *(14)*. These interactions need to be understood and appropriately targeted, for example by considering all pneumococcal serotypes in novel vaccine R&D, in order to make a sustainable impact on AMR *(14)*. Using vaccines more routinely would benefit from reliable, fast and inexpensive point-of-care diagnostic tools that permit rapid identification of population groups at risk *(9)*. Additionally, there are a number of stakeholders involved across multiple sectors of the health system who need to be engaged and committed to vaccine R&D. These complexities necessitate greater evidence-based research to inform policy makers and engage key stakeholders in a discussion on the value of vaccines for AMR.

The animal vaccine landscape

AMR is a cross-sectoral threat with severe implications for the health and welfare of animal populations, as well as the safety and security of global food systems. In the United States, for example, "70% of antimicrobials that are medically important are used in agriculture" *(8,16)*. There is sufficient evidence linking the consumption of antibiotics in animals to AMR in humans to recommend the immediate "curtailing the quantities of antimicrobials used in agriculture" *(8)*.

It is well understood that veterinary vaccines play an important role in protecting animal health, public health, animal welfare and food production *(17)*. The World Organization for Animal Health (OIE) is strongly aligned with the strategic goals and objectives of the WHO's Global Action Plan on AMR, and has argued that veterinary vaccines represent the single most cost-effective medical countermeasure that can be used to confront the threat of AMR *(18)*. The OIE ad hoc Group on Prioritization of Diseases for which Vaccines Could Reduce Antimicrobial Use in Animals has prioritized diseases in chickens, swine and fish where a new or improved vaccine could have the maximum effect on reducing antibiotic use (Table 1) *(18)*.

Commercial veterinary vaccines exist for the majority of pathogens listed in Table 1, albeit with major challenges to their widespread adoption and use; the most common identified by the OIE ad hoc Group across animal populations is the limited pathogen strain coverage and degree of cross-protection. Additionally, there are vaccine-specific and animal-specific issues, for example the limited efficacy of the Swine Influenza Virus (SIV) vaccine in piglets and the practical challenges of vaccinating some of the major fish species in mass due to the complications of bringing fish out of the water, which requires handling and in some instances, anesthesia, skilled staff, dedicated equipment and application costs. The vaccination strategies in the Norwegian salmon and Japanese yellowtail industries are examples of the effective reduction of antibiotic use due to increased uptake of vaccines in fish production (World Health Organization, 2015). In cattle, the highest antimicrobial use is in treating mastitis and viral diseases in veal production, although new (or re-emerging) pathogens such as *Mycoplasma bovis* demand further vaccine research *(17)*. A second convening of the OIE *ad hoc* Group is planned in late 2018 to discuss high priority vaccines for large livestock. The Group noted a number of data gaps when prioritizing areas for further vaccine research, for example the lack of a current list of all market-authorized available vaccines, the quantities of antibiotics used for different infections and the relative incidence of different infections worldwide. Thus, the Group relied mainly on available expert opinion and not on an evidence base supported by epidemiological modelling of the cost-benefit and cost-effectiveness of vaccine strategies.

The joint European Medicines Agency (EMA) and European Food Safety Authority (EFSA) review of measures taken in the EU to reduce the need for and use of antibiotics outlined more general challenges with existing, commercially available veterinary vaccines. Major limitations of the live and modified live vaccines relate to the risk of potential reversion to virulence, which can be overcome using DNA technology to add more than one attenuating modification, for example the most recent modified live virus vaccine for BVD virus II that has two separate modifications. Autogenous vaccines, primarily used in swine, poultry and fish, are derived from the specific pathogens that infect an individual herd or flock and are used when no registered vaccines for the pathogen (or serotype) exists, or existing ones are deemed ineffective. Despite their widespread use in the European Union, Member States differ considerably on the regulatory terms of production and use of autogenous vaccines; conflicts arise between good manufacturing practice requirements, which specify only one batch of vaccines can be produced at any one time in a facility, and the individual production of herd-specific vaccines. If regulations cannot be harmonized across the EU, there is an increased risk of uncontrolled (and illegal) feeding of faeces and/or intestines from infected to healthy animals in the same herd, so-called "back feeding", a practice that is widely and controversially used in the United States to control enteric infections in swine *(17)*. On the other hand, DIVA vaccines – vaccines that differentiate infected from vaccinated animals (DIVA) – provide an example of innovative vaccine development that meet regulatory standards without impairing the sanitary status of the infected herd and have been key to eradication strategies, for example Aujeszky's disease in Germany, the Netherlands, Italy, Spain, Portugal and Ireland *(17)*.

Table 1: **A list of primary pathogens for which new or improved vaccines would significantly reduce the need for antibiotic use, as identified by the OIE *ad hoc* Group**

Animal	Key syndrome	Pathogen
Chicken	Systemic (broilers)	*Escherichia coli* (yolk sac infection, airsacculitis, cellulitis)
	Systemic (breeders, layers)	*Escherichia coli* (airsacculitis, cellulitis, salpingitis and peritonitis)
	Enteric (broilers, breeders, layers)	Coccidiosis *Clostridium perfringens*
Swine	Systemic (respiratory) Respiratory	*Streptococcus suis* *Pasteurella multocida* (for pneumonic disease) *Actinobacillus pleuropneumoniae* Porcine Reproductive and Respiratory Syndrome virus (secondary bacterial infections) Swine Influenza Virus (secondary bacterial infections)
	Enteric (weaners / finishers)	*Escherichia coli* *Lawsonia intracellularis* Rotaviruses (secondary bacterial infections)
Fish	Systemic bacterioses Dermal bacterioses / red spot disease	*Aeromonas hydrophila* and other species *Pseudomonas spp.*

Conclusion

Despite the number of existing veterinary vaccines, rigorous studies to assess and document the effect of vaccination on antimicrobial use have rarely been conducted, let alone what measurable impact this could potentially have on the global burden of AMR *(17)*. A similar gap in the literature exists in the human health sector, in addition to persisting challenges to the universal coverage of vaccines against CAIs. Demonstrating the cost-benefit of human and veterinary vaccines remains one of the most critical parameters for achieving successful uptake in human health and agricultural systems. This is a particularly crucial element that guides the uptake of vaccines in LMICs where a strong regulatory system is often not in place to support controls over the use and sales of antibiotics, which often makes them less costly, and therefore more favourable than vaccines.

Technological advances can be inconsequential given the expense, time and difficulty of authorizing and registering a new or improved vaccine. This inevitably allows many of the "old" vaccines, with their limitations, to remain on the market for many years. Due to these costs (financial or otherwise), maintaining an economic perspective in the argument for increased vaccine use can help assign values to the contribution of human and veterinary vaccines in AMR avoidance and is critical in providing policy incentives for their R&D and support for their use. Gavi, the Vaccine Alliance's, innovative financing mechanism – Advance Market Commitment (AMC) – has accelerated the global roll out of pneumococcal vaccine and provides an example of alternative approaches to incentivizing vaccine development and production. Global and regional collaborations, such as the EMA and its partners in the European Medicines Regulatory Network who are currently implementing a joint action plan that aims to increase the availability of veterinary vaccines in the European Union, and partnerships with the private sector are needed more and more to address challenges that are exacerbated by sectoral silos and contextual differences.

Tackling AMR will require a concerted global effort to fill gaps in the current knowledge and evidence base, maximize existing resources and identify the most appropriate areas for further investment. A key step towards these goals is realizing the full potential of human and veterinary vaccines in reducing the global burden of AMR. ■

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