Vaccines Europe paper

The role of vaccination in reducing antimicrobial resistance (AMR)

Executive Summary

The frequency of antimicrobial resistance (AMR) is increasing in Europe and constitutes a serious danger to public health. Without policies and actions to prevent the spread of AMR, the current 25,000 annual deaths in Europe could grow to 390,000 per year by 2050 and could lead to an era in which common infections and minor injuries are no longer treatable.

Evidence has shown that existing vaccines have a positive impact in reducing AMR. In addition, new vaccines could play a critical role in preventing multi-drug resistant infections, such as from S. aureus, C. difficile and E. coli. To accelerate new vaccine research and development, private-public partnerships and multi stakeholder collaborations are needed for fundamental research and public authorities' engagement, to improve disease and AMR surveillance.

Recommended strategies for the reduction of AMR include the judicious use of antimicrobials and greater infection control measures, but EU and national AMR stewardship must include more comprehensive strategies in parallel that include effective prevention measures such as vaccination. Vaccination can play multiple roles in AMR reduction strategies, including: *reducing the use of antibiotics by preventing bacterial infections, e.g., conjugate pneumococcal vaccines; reducing the misuse of antibiotics by preventing viral diseases* for which antibiotics are inappropriately prescribed, e.g. influenza vaccines; and *preventing antimicrobial resistant infections from spreading; e.g. pertussis & Hib vaccines.* These strategies must strive a wider use of these existing vaccines to maximize their impact on AMR through a life-long approach of the National Immunisation programmes and by integrating vaccination planning into EU and national action plans to be developed for the fight against AMR.

Vaccines Europe's members are already engaged in the development of vaccines against AMR pathogens and Healthcare Associated Infections (HAI). However, there is a need to *engage all relevant stakeholders* to more clearly define the priorities for the development of new vaccines *against* AMR pathogens and to establish the necessary tools to support this development. This support ranges from setting *up robust and real-time disease and AMR surveillance* and database to ensure that vaccine developers select appropriate pathogens, as well as to *enhancing funding for early research* in epidemiology and immunology of AMR pathogens and HAI.

Introduction

Antimicrobial resistance (AMR) is the reduction or elimination of the effectiveness of antimicrobial agents to cure or prevent infectious diseases[1]. It occurs through mutations in microorganisms, or acquisition of genetic material from other bacteria, which neutralise or escape the effect of the antimicrobials.

New antimicrobial resistance mechanisms have been evolving rapidly. Bacteria producing extended-spectrum β-lactamases (ESBLs), enzymes that allow bacteria to resist several antimicrobials, first emerged in the 1980s but are now global in distribution[2]. They pose a major threat by limiting treatment options.

The frequency of antimicrobial resistance is increasing in Europe

In most countries across the European Union, antimicrobial resistance is occurring with increasing frequency but large inter-European variations occur [1,3,4,5,6]. There are both north-to-south and west-to-east gradient for AMR, with generally lower resistance percentages in the north and higher percentages in the south and east[3]. These can most likely be explained by different national practices and utilisation of healthcare.

The important vaccine-preventable AMR bacterium *Streptococcus pneumoniae* is no longer susceptible to both penicillins and macrolides in 0 – 37.8% of isolates from 28 European countries, and resistance rates are >5% in 14 of these countries[3].

Other AMR pathogens include carbapenem-resistant *Klebsiella pneumoniae* for which resistance rates had risen in some European countries to up to 33% by 2014[7]. Likewise, methicillin-resistant strains of *Staphylococcus aureus* (MRSA) infections account for more than 10% of *S. aureus* infections in 15 European countries, and several countries have resistance rates closer to 50%[8]. Antibiotic-resistant *Escherichia coli* strains are increasingly prevalent in Europe, reaching 12.0% for third generation cephalosporins and 22.4% for fluoroquinolones[3]. In the UK, between 1999 and 2011, *E. coli* antibiotic-resistant strains increased 7-fold[9].

Definition of Antimicrobial resistance (AMR): The ability of a microorganism to resist the action of an antimicrobial agent. Ref: ECDC[1]

Antibiotic resistance correlates with the use of outpatient antibiotics[10, 11, 12].

Antimicrobial resistance makes it more difficult to treat infectious diseases

The major cause of AMR in humans is the ecological pressure on microorganisms due to the widespread use of antimicrobials. AMR can arise from the misuse of antimicrobials in agriculture and in medicine. In veterinary use, several classes of antibiotics may be used in a rearing cycle, contributing to AMR for diseases that also affect humans. In medicine, auto-medication, or inappropriate use of antibiotics in viral infections (often because of the absence of a confirmatory or immediate diagnosis) contribute to the growing problem of AMR[1]. AMR makes some serious bacterial infections harder and more costly to treat and can lead to severe disease and deaths.

Antimicrobial resistance constitutes a serious danger to public health

In May of 2014, the World Health Assembly requested (in resolution WHA67.25[13]) that a global action plan on antimicrobial resistance be developed. This in light of a global consensus that antimicrobial resistance poses a profound threat to human health[14].

The European Commission[15], the European Council[16], and the European Centre for Disease Prevention and Control (ECDC)[1], all agree that antimicrobial resistance constitutes a serious danger to public health in Europe, the ECDC reporting that the continuous

spread of carbapenemase-producing *Enterobacteriacea*e (CPE), (including E. coli, *K. pneumoniae and Enterobacter species, etc.*), "*presents a serious threat to healthcare and patient safety in European hospitals*"[3].

It is estimated that 25,000 deaths from AMR occurred in EU countries in 2011[17]. Without policies and actions to halt the spread of AMR, the 25,000 deaths in Europe could grow to 390,000 every year by 2050[18], and cost $ 2.9 trillion in OECD countries[17] (as much as $ 100 trillion globally by 2050 in lost global productivity[19]). The WHO warns that AMR could lead to a post-antibiotic era in which common infections and minor injuries are no longer treatable[2].

Limiting the misuse of antimicrobials and preventing infections can contribute to a reduction in antimicrobial resistance

Recommended strategies for the reduction of AMR include the judicious use of antimicrobials and infection control measures. But these strategies alone are not sufficient. *More comprehensive approaches to combatting AMR, such as through the use of other available and under-utilised tools, like vaccination, are needed.* Longer-term strategies include research and development of better diagnostics, novel antimicrobials and vaccines against additional infectious diseases[14, 19].

Vaccination plays multiple roles in strategies aimed at preventing the direct health consequences of AMR infections as well as reducing antimicrobial resistance

Vaccination can prevent the direct health consequences of serious vaccine-preventable infectious diseases, prevent deaths and complications, and reduce healthcare costs, including costly hospitalisations.

Vaccination can reduce AMR by reducing the number of infectious cases in the population, through direct protection of vaccinated individuals, and by reducing the carriage (the colonisation of an individual in the absence of disease), whereby limiting the spread of infections within a community (herd immunity).

The reduction in the number of infections from vaccination is a result of both direct and herd protection. In the US, for instance, after the introduction of 13-valent conjugate pneumococcal vaccine (PCV 13) in children, AMR invasive pneumococcal disease declined in both the vaccinated and some unvaccinated age groups (herd immunity)[20]. A similar phenomenon was noted after the earlier introduction of PCV 7, and the implementation of PCV10[21, 22], when herd immunity decreased acute otitis media-related health care utilization in unvaccinated young children[23].

Reducing bacterial infections: Vaccination can reduce the prevalence of AMR by reducing the total number of cases of infectious disease (though direct and indirect protection - herd effect), by reducing the number of circulating AMR strains, and by reducing the need for antimicrobial use. AMR was becoming a problem before *Haemophilus influenzae* type b (Hib), *S. pneumoniae*, and *Neisseria meningitidis* vaccines were introduced, but these vaccines have reduced or nearly eliminated circulation of AMR for strains covered by the vaccines[24]. Following widespread use of pneumococcal vaccines, the incidence of AMR related invasive pneumococcal diseases was largely reduced in all ages in the US and Europe[25, 26, 27, 28, 29]. Hib vaccine has virtually eliminated the ampicillin-resistant infection caused by *H. influenzae* type b[24].

Reducing viral infections: Viral infections often lead to secondary infections (bacterial infections that occur on top of viral infections). In persons with laboratory confirmed influenza, reported rates of bacterial secondary infection range from 2%

(in newborns) to 65% (in adults)[30]. The most common bacterial secondary infections in influenza were found to be *S. pneumoniae* and *S. aureus*, 35% and 28% of infections, respectively[30].

Reducing the number of viral infections, through vaccination, can in turn reduce the total number of cases of bacterial secondary infections, and therefore reduce the use of antimicrobials. Conjugate pneumococcal vaccination, in turn, can reduce the incidence of viral respiratory infections[31].

Both viral and bacterial vaccines have the potential to reduce community reliance on antimicrobials. Influenza vaccination has been demonstrated to reduce use of antibiotics by as much as 64% in vaccinated individuals, by reducing the incidence of disease, thereby reducing the number of associated antimicrobial prescriptions (for secondary bacterial infections or for misdiagnosed influenza)[32]. The role of vaccination in strategies to reduce antimicrobial resistance is threefold[19]:

1. *Reduce the use of antibiotics by preventing bacterial infections* (*S. pneumoniae*, *H. influenzae* type b, *Neisseria meningitides*, *Bordetella pertussis*, *Mycobacterium tuberculosis*, etc.) *and prevent viral infections* (such as influenza and varicella) *for which bacterial secondary infections are common* (every year *S. aureus* causes an estimated 150,000 bacterial infections secondary to varicella[33]).

2. *Reduce the misuse of antibiotics, by preventing viral diseases for which antibiotics are inappropriately prescribed*.

   Antimicrobials are often *inappropriately prescribed* for influenza or other upper respiratory tract viral infections (usually in the absence of a confirmatory or immediate diagnosis)[34]. A review from Western Europe found that antibiotics were prescribed to children with influenza in 28% to 55% of cases[35]. The inappropriate prescription of antibiotics increases the exposure of bacteria to widely used antimicrobial agents, and leads to the development of antimicrobial resistance.

   For influenza, the most appropriate strategy for reducing the inappropriate use of antibiotics is vaccination. Several studies have demonstrated that antibiotic use for influenza related illnesses may decline by as much as 64% after influenza vaccination is introduced[1,33, 36].

3. *Prevent antimicrobial resistant infections from spreading*.

   With approximately 35 million elderly admitted to hospital per year in the US and EU (a group especially at-risk of antimicrobial-resistant infections), vaccines could significantly reduce the current risks of AMR spread in institutional settings[19].

   In adults, hospitalisation rates for pertussis substantially increase with age, so wider implementation of dTap boosters in adults and older adults could reduce hospitalisation rates and limit exposure to AMR pathogens in the hospital[37].

   In infants and young children, rotavirus vaccination substantially reduces hospitalisation and the rate of hospital acquired infections and so can likewise limit the risks of exposure to AMR pathogens in hospitals[38].

Public health and scientific bodies have recommended vaccination be included in strategies aimed at reducing antimicrobial resistance

Because vaccination directly or indirectly reduces the use of antibiotics, limiting the opportunity for antimicrobial resistance to arise, scientific bodies and public health authorities consider vaccination a key intervention in the fight against antimicrobial resistance.

The WHO recognizes the importance of vaccination as one of the most cost-effective public health interventions, and the important role of vaccination in reducing AMR[39]. And the Review on Antimicrobial Resistance recently concluded that "a much more robust pipeline of new vaccines" is needed to help contain growing AMR[40].

Vaccination strategies recommended to combat AMR include[14, 19]:

1. wider use of vaccination in humans and animals to maximise coverage with available vaccines;
2. more vaccine research, especially for diseases where scientific barriers exist; and,
3. creating the conditions for a viable and sustainable vaccine market[17].

The EU Commission and Member States are called to develop sound antimicrobial resistance policies and an action plan by mid-2017

In 2009, the EU Council conclusions on innovative incentives for effective antibiotics recognised that "*a wide range of measures is needed to ensure that currently available antibiotics remain effective for as long as possible, such as effective vaccines to prevent infections*"[41]. In June 2016, the EU Council on the next steps under a One Health approach to combat antimicrobial resistance, called on Member States to "*encourage the use of alternative treatment and prevention options including vaccines*"[42]. Scientific bodies have endorsed or echoed these recommendations[43]. The Council has called on Member States to have national action plans against Antimicrobial Resistance in place before mid-2017, and on the EU Commission to develop a new and comprehensive EU Action Plan on Antimicrobial Resistance, based on the One Health approach.

In view of the ongoing development of national and EU policies to combat AMR, this paper highlights some of the major challenges and needed policies for better implementation of vaccination programs and vaccine research, in support of the fight against antimicrobial resistance.

Vaccines can help to address the current challenges posed by AMR if vaccination programs in EU Member States are strengthened

Childhood vaccination programs have been enormously successful, having a huge impact on human health over the last 50 years, from the control of both viral and bacterial diseases[40], and often saving society more than 10 times their cost[44]. However, vaccine-preventable diseases also have a significant impact on adult mortality, health and quality of life. Adult vaccination has been given less emphasis than other health priorities and its benefits to society are not well recognised.

With the EU population ageing, and the incidence of non-communicable diseases rising (increasing the risk of serious complications from infectious diseases), better preventive measures against infectious diseases are urgently needed. Groups such as the ESCMID Vaccine Study Group (EVASG), the European Geriatric Medicine Society (EUGMS), the World Association for Infectious Diseases and Immunological Disorders (WAidid)[45], and the European Federation of

Internal Medicine[46], now recommend a life-long approach to vaccination, where the emphasis on vaccines for children is extended to include better health through vaccination of working-age adults and the elderly.

Very few countries in the EU have a comprehensive strategy for adult vaccination and few have good vaccination coverage data for working age adults and the elderly, with the exception of influenza[47].

The reasons are multiple:

- lack of recommendations for some newer vaccines;
- lack of reimbursement for recommended vaccines;
- limited information of vaccination for working age adults and the elderly and some high-risk groups;
- lack of knowledge and complacency amongst healthcare workers and the public;
- vaccine hesitancy.

Far more infections could be prevented in Europe by establishing programmes with a life-long approach to vaccination and appropriate implementation of these programmes. For influenza alone, it is estimated that, each year, Member States fall short of the coverage target of 75% by almost 60 million persons, resulting in around 2 million additional cases of influenza[48]. Only two member states reached the 75% influenza vaccination coverage target in the 2012–13 influenza season. A majority of countries had less than 50% coverage, and almost half of the countries had lower coverage than in the previous influenza season[1]. Reducing influenza cases can reduce the use of antimicrobials by up to 64%[33, 36, 50].

In spite of the observed herd immunity and reduction of antimicrobial use from pneumococcal conjugate vaccination[20, 21], childhood and elderly pneumococcal vaccination coverages are sub-optimal in several EU Member States[47, 51].

Vaccination coverage in infants in some countries is decreasing[52], and measles outbreaks continue to occur where vaccination coverage in children is not optimal, either because of non-completion of vaccination boosters, or because of delayed or refused vaccination[53].

Tetanus and diphtheria, virtually eliminated in childhood, now occur predominantly in adults in Europe, due to low vaccination coverage with booster vaccines[51, 54].

To better contribute to AMR reduction strategies, comprehensive life-long vaccination programs are needed, and countries should take practical actions towards their implementation, in particular for working age adults and the elderly.

Importance of improving vaccination in healthcare workers

Several bacterial infectious diseases (like pertussis or the secondary bacterial infections of viral diseases) are more easily transmitted and/or acquired in healthcare settings. Healthcare associated infections (infections acquired by patients receiving healthcare) are among the leading causes of preventable deaths and are associated with a substantial increase in health care costs each year. Because of the extensive use of antimicrobials, the healthcare environment acts as a breeding ground for *Clostridium difficile,* and antimicrobial-resistant bacteria like *Pseudomonas aeruginosa* and *E. coli*. The later carries a very high risk of mortality, at approximately 10 %[19]. Mortality from Carbapenem-resistant *Enterobacteriaceae* (CRE) infections, which mostly occur in healthcare settings[7], may be as high as 75%, likely because of limited treatment options[55].

Due to their contacts with multiple patients, healthcare workers play a major role in cross-patient disease transmission. For influenza, vaccination of healthcare workers is critical for preventing the spread of the disease. Preventing disease, in turn, can curtail the use

of antibiotics and limit the opportunities for antimicrobial-resistant bacteria to arise. The World Health Organisation recommends vaccination for healthcare workers against several diseases[56].

Vaccines in development against nosocomial infections could prove very useful for high-risk groups, for instance those scheduled for elective surgeries, or at risk of urinary tract, skin, and respiratory infections.

The challenges of new vaccine development to address AMR pathogens

While existing vaccines reduce the use of antibiotics for the infections that they prevent, new vaccines could play a critical role in preventing multi-drug resistant infections, such as from *S. aureus* and extra-intestinal pathogenic *E. coli* [55, 57].

While the EU has not ranked the AMR pathogens of greatest concern, for example the US has done so to prioritise its research efforts[58]:

- *E. coli*: resistance to 3rd generation cephalosporins and to fluoroquinolones;
- *K. pneumoniae*: resistance to 3rd generation cephalosporins and to carbapenems;
- *S. aureus*: methicillin resistance, or MRSA;
- *S. pneumoniae*: resistance (non-susceptibility) to penicillin ;
- Non-Typhoidal *Salmonella* (NTS): resistance to fluoroquinolones ;
- *Shigella* species: resistance to fluoroquinolones ;
- *Neisseria gonorrhoeae*: reduced susceptibility to 3rd generation cephalosporins.

Other pathogens, such as multidrug resistant tuberculosis and Group B *Streptococcus*, are included in the list of national concerns[58].

New vaccines for *C. difficile*, *P. aeruginosa, S. aureus*[59], and extra-intestinal *E. coli* are projected to become available in the next 3 to 6 years.

R&D for vaccines is long, complex, and carries high risks

Vaccine development is lengthy (between 8 and 18.5 years, on average). The risks are considerable: for every 5000 – 10,000 drug and vaccine candidates that enter early research, about 250 will make it to preclinical testing, only about 5 will make it into clinical testing, and only one will make it to market[60].

The technical and regulatory requirements are complex and contribute to the increased investment needs and risks in this type of industry[61].

For example, the requirements for extensive post-marketing pharmacovigilance on newly licensed vaccines increase manufacturers' requirements for resources[60].

Vaccine R&D is limited by the state of scientific knowledge

For many of the AMR pathogens, scientific challenges inhibit vaccine development[19]. These challenges include the lack of immunological correlates of protection for some diseases, or the absence of good animal models for research. Additionally, insufficient bacterial genotype and serotype surveillance may limit knowledge for vaccine development. And progress in basic immunology, such as for the development of reference assays, with special attention to the immune responses of the elderly, is needed to advance vaccine R&D.

Vaccine R&D is challenging for diseases that occur in specific risk groups or environments

Vaccine development is especially challenging in some specific populations, such as the hospitalised elderly, and immunocompromised, where poor immune responses, poorly documented epidemiology

and a requirement for a large number of subjects may all challenge successful vaccine development. And recruitment into clinical trials may additionally be challenged by issues surrounding informed consent, the role of caregivers, and high morbidity and mortality in this population[62].

Public-private partnerships (PPPs) are critical for future vaccine R&D

These PPPs should cover:

Fundamental research for understanding immunology and pathogenesis

Funding for research in fundamental immunology and related sciences, are critical for identifying appropriate target epitopes and new technologies for developing novel vaccine design concepts.

Strong and reliable disease surveillance where good database and networks are key

Robust disease and AMR surveillance, and the creation of national and supranational healthcare databases, are necessary to ensure that appropriate pathogens are selected for vaccine development. Projects that aim to evaluate disease burden, such as the Innovative Medicines Initiative (IMI) project on *C. difficile* infection (a partnership between the European Union and the European pharmaceutical industry) are highly valuable[63].

Table 1. List of vaccines in the pipeline against pathogens for which AMR is a serious concern[64, 65].

Vaccine	Clinical stage of development			Total number in pipeline
	Phase I	Phase II	Phase III	
Clostridium difficile		2	1	3
Carbapenem-resistant *Escherichia coli*	2			2
Extra-intestinal *Escherichia coli*		1		1
Moraxella catarrhalis* + Non-typable *Haemophilus influenzae		1		1
Mycobacterium tuberculosis	1	4		5
Pseudomonas aeruginosa		1		1
Staphylococcus aureus		2		2
Group B *Streptococcus*		1		1
Streptococcus pneumoniae		1		1

Engage in continuous dialogue with all relevant stakeholders to accelerate vaccine development for new vaccines that address AMR

A recently published paper by the UK independent Review on Antimicrobial Resistance highlights that many vaccines that are not on the market or even in early stages of development could play a crucial role in tackling drug resistance[40]. The report concludes that there is a need for a much more robust pipeline of new vaccines to help contain rising drug resistance.

Early and continuous dialogue throughout development could be established with all relevant stakeholders (regulators, HTA / NITAGs' bodies, payers) to optimise development plans and speed up the evaluation of regulatory files so that these vaccines could reach patients earlier.

Call for action to maximise the impact of vaccination on AMR

To be successful, AMR reduction strategies must include vaccines as a complementary approach, and to maximise the benefits they must strive to:

Wider use of existing vaccines to maximize their impact on AMR

- *Encourage EU Member States to improve vaccination coverage in all age groups*, through a life-long approach, in order to reduce the use and misuse of antibiotics, and integrate vaccination planning into national plans for the fight against AMR.

Implement additional measures to facilitate new vaccine development against AMR pathogens

- *Set up robust disease and AMR surveillance* and database to ensure that vaccine developers select appropriate pathogens and monitor their evolution.
- *Enhance funding for early research* in epidemiology and immunology of AMR pathogens and HAI, for instance, to define mechanism of immunity and correlates of protection against AMR bacteria, particularly in the elderly population.
- *Engage in continuous dialogue with all relevant stakeholders* (regulators, HTA bodies, and payers) to accelerate vaccine development for AMR pathogens and HAI.

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