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Role of vaccination in reducing antimicrobial resistance

Antimicrobial resistance is the reduced susceptibility of pathogenic bacteria to one or more of the antimicrobial agents administered in clinical medicine. Antimicrobial resistance is on the rise in most countries across the European Union[1]. The result is that some serious bacterial infections are becoming harder to treat and are therefore causing more disease, more prolonged disease and more severe disease, which in turn leads to higher healthcare costs and reduced quality of life. In addition, antimicrobial-resistant strains of some previously rare infections are becoming more frequently reported. As a result, antimicrobial resistance constitutes a serious danger to public health, which has been acknowledged by the European Commission[2], the Council[3] and the European Centre for Disease Prevention and Control (ECDC).

"Anti microbial resistance constitutes a serious danger to public health"

Considering that acquired-resistance is mainly driven by the exposure of bacteria to widely used antimicrobial agents, pragmatic responses to this problem are the promotion of judicious use of antimicrobials and the prevention of the infections that would require antimicrobial treatment. Therefore any strategies which can reduce the use of antibiotics should be considered as part of a long term strategy to combat this global health issue. Both viral and bacterial vaccines have the potential to reduce community reliance on antibiotics. Contrary to antibiotics, vaccines have the benefit of working with the immune system of a patient to enhance the natural tool needed to fight infections. First, some effective vaccines inhibit bacterial colonisation and, limit exposure of bacteria to antimicrobials and thereby reduce transmission, reducing the spread of antimicrobial resistant strains. Second, vaccination may prevent a bacterial infection before the infections leads to disease or spreads to others. Several vaccines may contribute to fewer occasions to prescribe antibiotic treatments [1]. Therefore, by reducing the prevalence of infection through vaccination the number of patients visiting medical facilities are also minimised, which in the majority of cases avoids the indiscriminate use of antibiotics.

Recent evidence suggests that antibiotic use can decrease in association with the initiation of immunisation programmes or increased uptake of available vaccines (e.g. pneumococcal and influenza immunisation programmes)[4]. This enable not only to protect the vaccine from the pathogen but this benefit is amplified by herd protection effects. Vaccination, therefore, could limit the development of antimicrobial resistance by decreasing the likelihood that bacteria targeted by certain vaccines would be exposed to antimicrobial agents. Public authorities are increasingly acknowledging the role of vaccination in the fight against antimicrobial resistance and considering it as a key intervention within their antimicrobial resistance programmes:

"The trends observed in France confirm that the fight against antimicrobial resistance is a long and demanding challenge and suggest that the dissemination of recommendations for a rational use of antibiotics, infection control and vaccination should be actively pursued."[4]

The European Commission also acknowledged that vaccination constituted an entire part of the fight against antimicrobial resistance:

"EU-wide exchange of best practice of all relevant issues should be promoted. Examples of good practice concerning antimicrobial

[1] ECDC (2010), Strategies for disease-specific programmes 2010-2013. Available at: http://ecdc.europa.eu/en/publications/Publications/100714_COR_Strategies_for_disease-specific_programmes_2010-2013.pdf
[2] Information about Commission initiatives available at http://ec.europa.eu/health/antimicrobial_resistance/policy/index_en.htm
[3] See for instance, Council Recommendation on patient safety, including the prevention and control of healthcare associated infections (9 June 2009). Available at: http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0001:0006:EN:PDF

[4] Kyle J. Wilby, Denise Werry (2012), A review of the effect of immunization programs on antimicrobial utilization, Vaccine 30 (2012) 6509– 6514.

resistance, vaccination campaigns and hygiene/infection control should be discussed and exchanged between Member States[5]."

In 2010 several Member States were reported to have **"issued recommendations on vaccination against *Streptococcus pneumoniae* infections, addressing both children and the elderly in most cases"**, as part of their action to prevent and control healthcare associated infections[6].
On December 1st 2009, the Council had already 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[7]".***

The purpose of this document is to provide a series of examples where vaccination proves its role in limiting antimicrobial resistance.

1. Existing evidence of the impact of vaccination on the reduction of antimicrobial prescriptions and prevention of antimicrobial resistant diseases

1.1 Antibacterial vaccines impact on antimicrobial prescriptions and prevention of antimicrobial resistant diseases

Concept

Vaccines targeting bacterial pathogens can have multiple beneficial effects because their induced immune response may prevent bacterial acquisition, colonisation and infection:

- Provide direct protection of individuals in the population from a bacterial disease (regardless of whether the bacterium is sensitive to the antimicrobials),
- Inhibit carriage (decrease acquisition and colonisation) of bacteria particularly targeted by the vaccine, consequently decreasing the likelihood that they might be exposed to antimicrobials and become antimicrobial resistant; or,
- Prevent transmission of bacteria leading to less likelihood of infection among unvaccinated members of the population (indirect herd) protection).

For example, widespread vaccination with pneumococcal conjugate vaccine has been demonstrated to decrease the prevalence of antimicrobial resistance among colonising pneumococcal isolates or disease causing clinical isolates [1-4].

Other theoretical examples could be typhoid fever or cholera, for which safe and effective vaccines are available.

Therefore, the preventive use of antibacterial vaccines could potentially protect individuals and communities against infectious disease, including those caused by resistant bacterial strains. Vaccines could also potentially prevent bacterial acquisition of resistance due to decreased exposure to antimicrobial agents.

Table 1 A non-exhaustive list of existing vaccines targeting potentially antimicrobial resistant bacteria

Diseases	Pathogen	Vaccine type(s)
Cholera	*V. cholerae*	Inactivated, recombinant toxin subunit
Diphtheria	*C. diphtheria*	Toxoid
Invasive pneumococcal disease	*S. pneumoniae*	Polysaccharide
Meningitis	*N. meningitidis*	Polysaccharide, conjugate
Meningitis, pneumonia, epiglottis	*H. influenzae type B*	Conjugate
Tetanus	*C. tetani*	Toxoid
Meningitis, bacteremia/sepsis, (pneumonia), otitis media	*S. pneumoniae*	Conjugate
Typhoid fever	*S. typhi*	Polysaccharide, Live attenuated
Whooping cough	*B. pertussis*	Inactivated, sub-unit, toxoid

New and future vaccines targeting antimicrobial-resistant bacteria

The research, development and introduction of new vaccines will play a critical role in the fight against the main antimicrobial-resistant bacteria.

Streptococcus pneumonia

[5] European Commission. Report from the Commission to the Council on the basis of member states' reports on the implementation of the Council Recommendation (2002/77/EC) on the prudent use of antimicrobial agents in Human Medicine. 2005. Available at: http://ec.europa.eu/health/ph_threats/com/mic_res/com684_en.pdf

[6] European Commission (2010), Second Report from the EC to the Council on the basis of Member States' reports on the implementation of the Council Recommendation (2002/77/EC) on the prudent use of antimicrobial agents in human medicine. Available at: http://ec.europa.eu/health/antimicrobial_resistance/docs/amr_report2_en.pdf

[7] Council Conclusions on innovative incentives for effective antibiotics, 2980th EPSCO Council meeting Brussels, 1 December 2009. Available at http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:302:0010:0011:EN:PDF

The introduction of the first pneumococcal conjugate vaccine, seven-valent, had a significant impact in reducing antibiotic resistance, particularly in the background of programs in parallel intended to limit antibiotic usage [1-4][8]. Recent studies demonstrated a shift in serotype distribution with a greater proportion of carriage (colonisation) by the non-vaccine serotypes consequent to a decrease in carriage in the vaccine-serotypes. In the setting of non-judicious antibiotic use, however, these non-vaccine serotypes may acquire antimicrobial resistance.

"The introduction of the first pneumococcal conjugate vaccines had a significant impact in reducing antibiotic resistance"

The newly developed pneumococcal conjugate vaccines cover a broader number of serotypes than the seven-valent pneumococcal conjugate vaccine, including some serotypes that already acquired or may acquire resistance.

Vaccines under development against antimicrobial-resistant bacteria

Other well-known resistant bacteria that cause healthcare associated infections are the target of vaccines under active clinical development such as *Staphylococcus aureus* and *Clostridium difficile*.

"New vaccines will play a critical role in the fight against the main antimicrobial-resistant bacteria"

Such vaccines could play a critical role in preventing the spread of existing infections caused by such multi-drug resistant pathogens[9]. In addition, research and development is gearing up in order to find a more effective vaccine against tuberculosis, which is now characterized by a heavy level of antimicrobial resistance.

1.2 Antiviral vaccination's impact on antimicrobial prescriptions

In the case of viral vaccines, protection from a virus will reduce the number of viral infections which in some cases are mistakenly diagnosed as a bacterial infection and thus treated with antibiotics. An example of this situation is influenza, which is associated with excess rates of hospitalisation and mortality, in various groups including children. For instance, in Finland, 39.7% of children with *acute otitis media* during the winter months had evidence of an influenza virus infection [5].

Although the significant burden that influenza represents is well documented, there is little awareness about the disease amongst the general population. In particular, people tend to ignore that the influenza burden is mainly comprised of secondary complications arising from the primary infection. Viral infection leads to an alteration of the physical barriers but also to a reduced the immune response, which results in secondary complications. Most of these complications are bacterial infections, which account for substantial numbers of all antibiotic consumption [6-8]. Common pathogens associated with influenza include *Streptococcus pneumoniae* and *Staphylococcus aureus*.

Although it is perfectly legitimate to use antibiotics to treat secondary bacterial infections, there is extensive evidence in Europe of antimicrobial prescriptions given for primary viral infections such as influenza [7]. For instance, in Finland, 42% of children suffering from seasonal influenza are getting antimicrobials [5]. Inappropriate prescription of antibiotics is extremely problematic as it increases exposure of bacteria to widely used antimicrobial agents, hence leading to development of anti microbial resistance.

This justifies policies targeting a more judicious use of antimicrobial agents. Indeed, the inappropriate prescription of antibiotics for influenza is mainly due to the complexity of making a reliable diagnosis of the disease [7]. But influenza vaccination itself is the most appropriate strategy: by providing protection against the primary viral infection, the seasonal vaccination can often

[8] More information available at http://www.evm-vaccines.org/pdfs/brief_sheet_Pneumococcal.pdf
[9] European Commission (2011). Action Plan against the risising threats from antimicrobial resistance COM (2011) 748. Available at: http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf and ECDC (2011). Report from the Transatlantic Taskforce on Antimicrobial Resistance. Recommendations for future collaboration between the U.S. and EU. Available at: http://ecdc.europa.eu/en/activities/diseaseprogrammes/tatfar/documents/210911_tatfar_report.pdf

successfully prevent any bacterial complications. Consequently, by preventing influenza one avoids both misuse and limits antimicrobial use to necessary treatment of influenza-related bacteria complications. In a recent study, Kwong et al. showed some evidence that would support this strategy. In the province of Ontario, Canada, the increase in influenza vaccination rate, which followed the introduction of universal influenza vaccination, resulted in a 64% decrease in influenza associated respiratory disease antimicrobial prescriptions [6].

"In the province of Ontario, (…) the introduction of universal influenza vaccination, resulted in a 64% decrease in influenza associated respiratory disease antimicrobial prescriptions"

Other studies reported a 25% [9] reduction in antibiotic use for influenza-associated illnesses and a 42.9% to 47.0% [10] reduction in days of antibiotic use after influenza vaccination in healthy working adults.

Another example is chickenpox which is one of the most common agents of secondary infection is Staphylococcus aureus which causes an estimated 150,000 infectious every year [10]

2. Additional opportunities offered by vaccination for preventing the emergence and the spread of anti microbial resistance

Healthcare associated infections (HAIs)

HAIs are infections that patients get while receiving treatment for medical or surgical conditions. They are among the leading causes of preventable deaths and are associated with a substantial increase in health care costs each year. Hospitals constitute particular breeding grounds for antimicrobial-resistant bacteria. The high prevalence of resistant bacteria as a cause of disease in healthcare facilities can be explained by extensive antimicrobial use due to the presence of elderly patients with weakened immune systems who rely heavily on drugs to fight infections, as well as the importance of cross-patient transmission.

Several infectious diseases have been identified as transmitted and/or acquired in healthcare settings such as bacterial pneumonia, pertusis or the secondary complications of viral diseases (e.g. influenza).

Therefore, ensuring that these diseases are effectively prevented would decrease their prevalence in health care settings and support a resulting decline in the use of antimicrobials. Given that the extensive use of antimicrobial agents is contributing to development of resistance, vaccination has a critical role to play.

Health care workers constitute a major factor of cross-patients transmission due to their contacts with multiple patients. Therefore, health care workers' immunisation could play a critical role in preventing the spread of antimicrobial-resistant bacteria from patient to patient, and perhaps the use of antimicrobial agents. The World Health Organisation recommends health care workers' vaccination against several of these diseases[10].

2.1 Vaccination against antimicrobial resistant travel-related infectious diseases

The globalisation of travel and trade increases the likelihood of spread of travel-related diseases, which may already be marked by antimicrobial resistance, as it is the case for *Salmonella typhi* or *Vibrio cholera*. Some of these diseases are vaccine preventable, and for others, vaccines are under development.

Vaccination has a role to play in the fight against antibiotic resistance. This is a global issue and as such should be addressed in a comprehensive and holistic way, including renewed research efforts. In this respect, industry is largely investing in new generation of vaccines capable of targeting hospital associated infections (E.coli, S. aureus...). This should also be accompanied by public research in future innovative vaccines targeting antibiotic resistant bacteria.

[10] OMS, Guide pratique sur la prévention des infections nosocomiales, Chapitre X. 2008. WHO/CDS/CSR/EPH/2002.12 Available at: http://www.who.int/publications/list/WHO_CDS_CSR_EPH_2002.12/fr/index.html

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11. Kock et al 2010

About Vaccines Europe

Vaccines Europe is a specialised group within the European Federation of Pharmaceutical Industries and Associations (EFPIA), the professional association of the European pharmaceutical industry. Vaccines Europe was created in 1991 as the voice of the vaccine industry to create a supportive environment for improved vaccine protection and coverage in the interest of individuals and the community and to promote vaccine R & D to meet new challenges for innovative vaccine applications against infectious and other types of diseases.

Vaccines Europe represents major European vaccine producers:

- *Contributing to European industrial competitiveness with 79% of their production in the region*
- *Major partners in improving global public health by targeting all major vaccine preventable disease around the world*
- *Conducting research and development into new vaccines and technologies (around 50% of R&D projects and 60% of their total R&D investment are in Europe)*
- *Delivering vaccines to developing countries and specific/humanitarian groups which account for 44% of their exports but only 4% of revenues*

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