# EVM Briefing Sheet on the role of vaccination in reducing anti microbial 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. 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[1], the Council[2] and the European Centre for Disease prevention and Control (ECDC)[3].

*"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 promotion of the judicious use of antimicrobials and the prevention of the infections that would require antimicrobial treatment. There is, however, another strategy that could limit antimicrobial resistance. Several vaccines may contribute to fewer occasions to prescribe antibiotic treatments [1]. First, some effective vaccines inhibit bacterial colonization and transmission, thereby limiting exposure of bacteria to antimicrobials and reducing the spread of any antimicrobial resistant strains that do arise. Second, vaccination may prevent a bacterial infection before the infections leads to disease or spreads to others. Vaccination thereby could limit the development of antimicrobial resistance by decreasing the amounts of antimicrobial agents needed to treat infections.

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 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 resistance, vaccination campaigns and hygiene/infection control should be discussed and exchanged between Member States."***[4]

On December 1st 2009, the Council 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"***[5]

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

[1] Information about Commission initiatives available at http://ec.europa.eu/health/antimicrobial_resistance/policy/index_en.htm

[2] See for instance, Council Recommendation on patient safety, including the prevention and control of healthcare-associated infections (9 June 2009). Available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0001:0006:EN:PDF

[3] Information about ECDC activities available at http://ecdc.europa.eu/en/healthtopics/Pages/Antimicrobial_Resistance.aspx

[4] 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

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

European Vaccine Manufacturers

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

### 1.1 Antibacterial vaccine 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 colonization, infection, or both:

- Provide direct protection of individuals in the population from a disease due to a bacterium (regardless of whether the bacterium is sensitive to the antimicrobial),
- Inhibit carriage (decrease colonization) 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 (herd protection).

For example, widespread vaccination with a pneumococcal conjugate vaccine has been demonstrated to decrease the prevalence of antimicrobial resistance among colonizing 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, as well as tuberculosis.

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. diphtheriae* | Toxoid |
| Invasive pneumococcal disease | *S. pneumoniae* | Polysaccharide |
| Meningitis | *N. meningitidis* | Polysaccharide, conjugate |
| Meningitis, pneumonia, epiglottis | *H. influenzae type b* | Conjugate |
| Meningitis, bacteremia/sepsis, (pneumonia), otitis media | *S. pneumoniae* | Conjugate |
| Tetanus | *C. tetani* | Toxoid |
| Tuberculosis | *M. tuberculosis* | Live attenuated |
| 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 pneumoniae*

The introduction of the first pneumococcal conjugate vaccines had a significant impact in reducing antibiotic resistance, particularly in the background of programs in parallel intended to limit antibiotic usage [1-4][6]. Recent studies demonstrated a shift in serotype distribution with a greater proportion of carriage (colonization) 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

[6] More information available at http://www.evm-vaccines.org/pdfs/brief_sheet_Pneumococcal.pdf

than the seven-valent pneumococcal conjugate vaccine, including some of the non-vaccine serotypes that may acquire resistance.

***Vaccines under development against antimicrobial-resistant bacteria***

Other well-known resistant bacteria that cause nosocomial 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. 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

Influenza constitutes a major public health issues, 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* 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 successfully prevent any bacterial complications. Consequently, preventing influenza allows avoiding both misuse and limiting necessary use of antimicrobials to treat 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% [10] reduction in days of antibiotic use after influenza vaccination in healthy working adults.

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

### 2.1 Vaccination as a prevention of antimicrobial resistant infections in Hospitals and other Health Care Facilities

Hospitals constitute particular breeding grounds for antimicrobial-resistant bacteria. The high prevalence of resistant bacteria as a cause of disease in health care facilities can be explained by the presence of patients with weakened immune systems who tend to receive antimicrobials extensively, as well as the importance of cross-patient transmission.

Several infectious diseases have been identified as transmitted and/or acquired in healthcare settings and constitute healthcare associated infections (HAIs). Some of these diseases, such as bacterial pneumonia, pertussis, or the secondary complications of viral diseases (e.g., influenza), require treatment by antimicrobial agents. Therefore, ensuring that these diseases are effectively prevented would decrease their prevalence in health care settings and the resulting 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[7].

### 2.2 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.

**Recommendations:**

A programme to combat antimicrobial resistance will need to combine a number of different approaches including a rational use of antibiotics, the prevention of carriage or infection, and the discovery and development of new antimicrobial agents.

***Therefore, EVM calls on Public Authorities to:***

- ***Consider vaccination as a complementary measure to encourage the appropriate use of antimicrobial agents.***
- ***Allocate some funding to generate data on anti microbial resistance of vaccine preventable diseases to assess the potential of vaccination policies in reducing antimicrobial resistance.***

[7] 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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**2.** Dagan, R. and K. P. Klugman (2008). "Impact of conjugate pneumococcal vaccines on antibiotic resistance." The Lancet Infectious Diseases 8(12): 785-95.

**3.** Pilishvili, T., C. Lexau, et al. (2010). "Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine." Journal of Infectious Diseases 201(1): 32-41.

**4.** Coignard et al. (2008). "Recent trends in antimicrobial resistance among Streptococcus pneumoniae and Staphylococcus aureus isolates: the French experience". Eurosurveillance.13(46): Article 2.

**5.** Heikkinen T, et al.(2004) "Burden of Influenza in Children in the Community". Journal of Infectious Diseases 190:1369–73.

**6.** Kwong JC et al. (2009) "The Effect of Universal Influenza Immunization on Antibiotic Prescriptions: An Ecological Study" Clinical Infectious Diseases 49:750–756

**7.** Low, D. (2008) "Reducing antibiotic use in influenza: challenges and rewards". Clinical Microbiology and Infection14(4): 298-306

**8.** Tregoning J.S. and Schwarze J. (2010) "Respiratory Viral Infections in Infants: Causes, Clinical Symptoms, Virology, and Immunology." Clinical Microbiology Reviews 23(1): 74-98

**9.** Bridges CB, Thompson WW, Meltzer MI, et al. (2000) "Effectiveness and cost-benefit of influenza vaccination of healthy working adults: a randomized controlled trial". Journal of the American Medicine Association 284(13):1655–1663.

**10.** Nichol KL, Mendelman PM, Mallon KP, et al. (1999) "Effectiveness of live, attenuated intranasal influenza virus vaccine in healthy, working adults: a randomized controlled trial." Journal of the American Medicine Association 281:137–144.


***About EVM***

*EVM is a specialised group within the European Federation of Pharmaceutical Industries and Associations (EFPIA), the professional association of the European pharmaceutical industry. EVM 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.*

*EVM represents major European vaccine producers:*

- *Major worldwide vaccine producers representing 70% of global production*
- *Contribute to European industrial competitiveness with 90% of EVM Members production in the region*
- *Major partner in improving global public health by targeting all major vaccine preventable disease around the world*
- *Conduct research and development into new vaccines and technologies (around 60% of R&D projects are in Europe)*
- *Deliver vaccines to developing countries which account for 36% of their exports but only 3% of revenues*

*EVM members are: Baxter, Crucell, GlaxoSmithKline Biologicals, MedImmune, Novartis Vaccines, sanofi pasteur, sanofi pasteur* MSD, Solvay Biologicals, and Pfizer.

Please go to: http://www.evm-vaccines.org/.

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