Vaccines Europe
An industry for healthy lives

Vaccines Europe White Paper on the role of vaccination in the fight against antimicrobial resistance

November 2023

EXECUTIVE SUMMARY

Antimicrobial resistance (AMR) represents a major challenge of our times. It is considered a global public health issue and a societal issue in the context of the United Nations' Sustainable Development Goals (SDG) (1). **At global level, 4.91 million deaths were associated with bacterial AMR in 2019. By 2050, that number could rise to 10 million deaths per year globally, generating costs from $300 billion to more than $1 trillion annually** (2)**,** (3)**.** In the EU/EEA region, the health burden of infections due to AMR is comparable to that of influenza, tuberculosis and HIV/AIDS combined and it is estimated that by 2050, AMR will result in over 569 million extra hospital days annually (4).

AMR is an inherent natural process occurring in microorganisms, which can be enhanced by multiple drivers, the most significant being the overuse and misuse of antibiotics both in humans and animals.

Despite several global, European and national initiatives that aim to address AMR through a One Health approach, the impact of AMR on patients, public health, the global economy and equity remains significant. This is exacerbated by inadequate infection control, and limited available treatment alternatives in both children and adults. **Vaccination is now recognised to be a cost-effective tool in the fight against AMR. It has the capacity to address AMR-related health consequences by preventing deaths and complications, decreasing the prevalence and transmission of resistant pathogens, and reducing the misuse and overuse of antimicrobials. In so doing, vaccination can diminish the healthcare costs associated with AMR, including costly hospitalisations and care related to long-term sequelae.**

Developing vaccines that address resistant pathogens remains a challenging task due to the scientific hurdles, long development times, high failure rates, high costs, inability to account for market failures, prolonged licensure review process and lack of recommendations regarding use. Numerous vaccines on the market have demonstrated significant effectiveness against AMR. These include pneumococcal vaccines, *Haemophilus influenzae* type B vaccine (Hib), rotavirus vaccine, measles vaccines and influenza vaccines. Unfortunately, their coverage at global level remains low due to varying recommendations and/or access. Based on the Vaccines Europe pipeline review (5), more vaccines are expected to become available against a variety of pathogens and will also play a role in reducing AMR in the near future.

To fully harness the benefits of vaccines in addressing the unmet medical needs associated with infectious diseases and AMR (6), comprehensive efforts are required across the entire value chain – from research and development to market availability and widespread vaccination of populations, encompassing both existing and future products. Therefore, this paper aims to provide recommendations for an end-to-end approach to ensure the development, availability and use of vaccines to address AMR, in synergy with other available tools.

AMR cannot be solved with treatments alone. The solution resides in the complementarity of prevention and other tools (such as therapy), with prevention contributing to preserving the benefit and value of antimicrobials. To tackle AMR, it is crucial to maintain dialogue and commitment among all relevant stakeholders to accelerating the development of new vaccines, as well as improving access and coverage of existing vaccines that address antibiotic-resistant pathogens.

The revision of the European General Pharmaceutical Legislation represents a great opportunity to foster an innovative ecosystem that will further advance the development of valuable products to address AMR. The value of vaccines in addressing this challenge should be reflected in the upcoming legislation (7) in line with the *Council Recommendations on stepping up EU actions to combat antimicrobial resistance in a One Health approach* (8). Additionally, and in line with this Council Recommendation, the AMR national action plans should be updated to promote the use of vaccination, as well as the development of, the availability of and the access to vaccines.

STRATEGIES FOR EXISTING VACCINES

To reduce the burden of AMR on public health, it is vital to support the uptake of licensed vaccines through:

AWARENESS

- Enhance public awareness of the importance of vaccination in the fight against AMR to improve vaccine confidence, uptake, and coverage.
- Support education and incentives to healthcare professionals and those involved in animal farming.

IMMUNISATION UPTAKE

Improve human vaccination coverage in all age groups in all EU Member States, through a life-long approach, with an emphasis of including adult immunisation in national immunisation plans (NIP) and implementing targeted vaccination of at-risk populations (e.g., healthcare workers, patients with chronic illnesses, pregnant women).

POLICIES

- Develop policies to integrate and support prevention in the fight against AMR.
- Align AMR National Action Plans with national immunisation programmes (NIP), setting clear and defined vaccine uptake targets, increased vaccination budget, horizon scanning to ensure sustainable immunisation financing, and timely monitoring of vaccination programmes.
- Invest in data systems across the EU to collect quality data and drive public health decision-making.

REAL-WORLD EVIDENCE

Improve generation and utilisation of real-world healthcare data and develop surveillance systems to monitor the impact of both new and established vaccines on AMR.

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STRATEGIES FOR UPCOMING VACCINES

Create an ecosystem that supports innovation and promotes the development of future vaccines through:

SURVEILLANCE

Ensure availability of surveillance platforms assessing the use and misuse of antibiotics for vaccine-preventable infections.

PRIORITY PATHOGENS

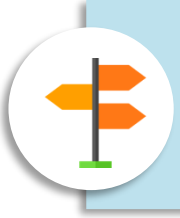
Increase awareness of global and regional priority pathogens lists developed by relevant stakeholders, such as WHO, ECDC, DG HERA, U.S. CDC.

INCENTIVES

Develop innovative financing mechanisms and appropriate incentives for early- and late-stage research for specific vaccines, tailored to each case's unique needs.

FUNDING AND PARTNERSHIPS

Increase public funding and incentivise public-private partnerships in R&D that support the role of vaccines in the fight against AMR.



REGULATORY GUIDANCE

Ensure that the regulatory framework provides guidelines and supports streamlined development and authorisation of vaccines against AMR. This includes offering guidance on potential AMR clinical endpoints and utilising real-world evidence following (conditional) approval.

VALUE OF VACCINATION

- Developing vaccine-specific HTA methodologies that recognise the broad value of vaccination, including their impact on AMR.
- Enhance vaccine assessment and decision-making pathways to accelerate access to innovative vaccines (31).

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1. INTRODUCTION

Antimicrobial resistance (AMR) occurs when bacteria, viruses, fungi and parasites change over time and no longer respond to medicines, making infections harder to treat and increasing the risk of disease spread, severe illness and death (8)**.** This paper will focus mainly on AMR in bacteria and viruses.

AMR represents a major challenge of our times. It is both a global public health issue and a societal issue in the context of the United Nations' Sustainable Development Goals (SDG): Nine out of the 17 SDGs are impacted by AMR (1). Recently, two specific indicators for AMR (3.d.2, 3.d.3) were included under SDG 3 (Good Health and Wellbeing) (9). *More information about the UN SDGs can be found in Annex I.*

Antimicrobial resistance is an inherent process occurring in microorganisms. However, there are multiple drivers that enhance this phenomenon, notably the overuse and misuse of antibiotics, with important variability in prescribing being observed across different health systems. In a systematic evaluation of antibiotic consumption across 76 countries for a period of 15 years (2000-2015), the WHO AWaRe[1] Classification Database recorded an increase in the overall use of antibiotics per capita of both *Access* (first- and second-line therapies) and *Watch* (for use only with specific indications). The increase in Watch antibiotic consumption was greater in LMICs[2] than HICs[3], showcasing challenges in antibiotic stewardship[4] (10). Both self-medication and the inappropriate use of antibiotics to treat viral and bacterial infections (often because of the absence of a confirmatory or immediate diagnosis) may contribute to the growing problem of AMR (11).

When it comes to **veterinary use**, vaccines should be considered a first line of defence against bacterial and viral diseases. By preventing diseases, vaccines can help minimise the need for antibiotics. It is encouraging to observe that recent data indicate a decrease in antibiotic use in the veterinary field both at European and global level (12), (13) thanks to improved vaccination practices and the use of technical solutions such as improved monitoring systems and precision livestock farming.

Other **social and economic practices with important effects on AMR** are the misuse and overuse of antimicrobials in agriculture, underutilisation of vaccines, inadequate diagnostics, lack of access to clean water, poor sanitation and low health expenditure (14), (15), (16)**.**

The COVID-19 pandemic also had a negative impact on AMR. While the prevention efforts and improved antimicrobial use in the U.S. led to an 18% overall decrease in deaths from AMR between 2012 and 2017, resistant hospital-onset infections and deaths both increased at least 15% in 2020. After years of steady reductions in healthcare-associated infections (HAIs), U.S. hospitals saw significantly higher rates for four out of six types of HAIs in 2020, many of those being resistant to antibiotics or antifungals (17).

At the microbiological level, **AMR appears either through mutations in chromosomal genes or acquisition of resistant genetic material from other bacteria**, which neutralises or escapes the effect of the antimicrobials (18). There are four main categories of resistance to antimicrobials: limiting the uptake of a drug, modifying a drug target, inactivating a drug or removing the drug from the bacterial cell (19). Resistance to antivirals has also been observed in several viruses, such as hepatitis C virus, influenza A virus, *Herpes simplex* virus, human cytomegalovirus, HIV and hepatitis B virus (20). Therefore, there is a risk that in the future antivirals will be less and less efficient in combatting viral diseases (21).

[1] *WHO Access, Watch, and Reserve (AWaRe) antibiotic classification framework*
[2] *Low- and Middle-Income Countries*
[3] *High-Income Countries*
[4] *Antibiotic stewardship is described with U.S. CDC as the effort to measure and improve how antibiotics are prescribed by clinicians and used by patients.*

In 2017, WHO[5] published its first **list of antibiotic-resistant priority pathogens.** The list includes 12 families of bacteria that were considered to pose the greatest threat to human health. The publication aimed at guiding and promoting the R&D of new antibiotics (22). In 2019, U.S. CDC[6] published a report that classifies 18 microorganisms (bacteria and fungi) in 3 categories: *urgent, serious and concerning* (23). In the same report, CDC compiled a watch list that includes microorganisms that are currently responsible for few infections in the U.S., but either cause infections in other countries, have the potential for rapid spread or remain insufficiently understood (23). In 2022, WHO and ECDC[7] released a joint report on *AMR Surveillance in Europe* that includes surveillance data for eight bacterial species of highest concern in Europe (24). The list of microorganisms mentioned in these three documents, along with their antimicrobial resistance, are summarised in *Annex II.*

The increasing trend towards AMR highlights the increased need for new antimicrobials. Yet, the threat of resistance, even to the new-generation antibiotics, will persist unless we implement effective preventive measures to reduce disease and pathogen spread. These measures include ensuring the judicious use of antimicrobials, as well as implementing disease and infection control measures such as life-course vaccination. **Vaccination has been shown to prevent the health consequences of infectious diseases, prevent deaths and complications, reduce pathogen prevalence and transmission, and to reduce healthcare costs, including costly hospitalisations, as well as reducing the use of antimicrobials** (25), (2). Higher vaccination coverage rates and policies supporting prevention of infections could help to ensure an appropriate and judicious use of existing antibiotics.

[5] *World Health Organisation*
[6] *Centers for Disease Control and Prevention*
[7] *European Centre for Disease Prevention and Control*

2. THE AMR BURDEN ON PUBLIC HEALTH REMAINS SIGNIFICANT DESPITE INITIATIVES AIMING TO ADDRESS IT

AMR represents a significant medical, economic and societal burden at global level with major impacts on patients and public health.

a) Impact of AMR infections on patients

Bacteria can become resistant to multiple antimicrobial agents, resulting in limited available treatment options for children and adults (25). This can be exacerbated by the misuse or overuse of antibiotics that could lead to broader resistance to efficient therapies. The propensity for resistance to develop against new treatments remains considerable in the absence of preventive measures aimed at reducing disease incidence and limiting pathogen transmission. Without enough effective treatment options, common infections could become life-threatening resulting in a significant impact on human and animal health. In addition, performing common surgical procedures such as orthopaedic surgeries, as well as organ transplants and treatments for HIV, cancer, liver and kidney disease would be more challenging without having effective antimicrobials available (26).

b) Impact of AMR on public health

In a recent study (26), it was estimated that 541,000 deaths were associated with bacterial AMR in the WHO European region in 2019. The largest fatal burden was attributed to bloodstream infections, followed by intra-abdominal and respiratory infections associated with resistance to antibiotics. About 457,000 deaths were attributable to seven pathogens: *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterococcus faecium, Streptococcus pneumoniae,* and *Acinetobacter baumannii.* Another study estimates that at the global level 4.91 million deaths were associated with bacterial AMR in 2019 (27) and the number could rise to 10 million deaths per year globally by 2050 (2). The OECD[8] and the ECDC have stated that the health burden of infections due to AMR in the EU/EEA region is comparable to that of influenza, tuberculosis and HIV/AIDS combined (4). Additionally, it is estimated that by 2050, AMR will result in over 569 million extra hospital days annually across countries in the EU/EEA region (4).

AMR also poses significant challenges to healthcare systems, including increased treatment costs, additional infection control interventions and prolonged length of hospital stay (28). As clinical decisions are often made in the absence of a microbiological test result, ineffective treatments may be given to patients with resistant infections. This leads to wasted resource and delays to the commencement of an effective therapy (29).

c) Impact of AMR on global economy and equity

AMR also poses a considerable economic burden at the global level. It is projected that AMR could cost from $300 billion to more than $1 trillion annually by 2050 worldwide (3). In the EU/EEA region, the OECD has estimated that up to 1.1 billion Euro could be spent yearly between 2015 and 2050 due to AMR if no action is taken (4). Additionally, increasing life expectancy means a rising risk of catching infectious diseases, considering the decline of the immune system with age. This highlights the need for more healthcare interventions in adults and older adults, which could lead to a greater economic burden of AMR in the long-term.

AMR also raises equity concerns. The second- or third-line drugs used to replace the first-choice antibiotics are less accessible to people living in LMICs because the use of these agents is often restricted to hospital settings (30). This is particularly dangerous considering that large populations living in areas with high levels of infectious diseases provide opportunities for resistant pathogens to emerge and propagate. Even in the EU, access to vaccination is not equal across Members States, resulting in citizens of some European countries having to wait

[8] *Organisation for Economic Co-operation and Development*

significantly longer in order to benefit from new vaccines than their counterparts elsewhere in the European Union (31).

Sustainable food and feed production will also be at risk with the emergence of drug resistant pathogens, forcing up to 24 million people into extreme poverty by 2030, mainly in LMICs (32).

There are numerous global, European and national initiatives to address AMR.

Several global initiatives aim to raise awareness of the dangers of AMR and to promote hygiene measures, proper use of antibiotics in humans and animals, and adequate disposal of antimicrobials. One such initiative is the **WHO Global Action Plan on AMR** adopted at the World Health Assembly in 2015. It aims to ensure that the treatment and prevention of infectious diseases with quality-assured, safe and effective medicinal products is achievable. The Action Plan covers multiple measures, ranging from education, training, surveillance and research to the importance of developing sustainable investments in new medicines, diagnostic tools, vaccines and other interventions (25). The Action Plan also emphasises the need for an effective **One Health**[9] approach and highlights the value of coordination between international actors, including those representing human and veterinary medicine, finance, the environment and consumers (25). The fight against AMR represents a shared responsibility between WHO, FAO, UNEP[10] and WOAH[11]. Together, they have established the **AMR Quadripartite organisation** with the aim to advance a One Health response to AMR (33).

Many actions are also taking place at EU level, such as the **2017 EU One Health Action Plan against AMR** (34), the funding provided by the **EU4Health programme** for projects that reduce antimicrobial-resistant infections and improve vaccination rates (35), and various public-private partnerships.

Of note is the creation of **DG HERA**[12] in September 2021 to prevent, detect and rapidly respond to health emergencies, through intelligence gathering and building the necessary response capacities. AMR is one of the key topics targeted by HERA in its 2022 and 2023 Work Plans (36), (37), and the issue has been identified as one of the top three serious cross-border health threats (38).

The recently published *Council Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach* (8) acknowledge the potential of vaccination to curb the spread of infections and reduce the use of antimicrobials. The Recommendation encourage the Member States to promote the use of vaccination, as well as the development of, the availability of and the access to vaccines. More specifically, it invites Member States to fully develop and implement national immunisation programmes and take measures to progressively eliminate vaccine preventable diseases.

More initiatives and public-private partnerships are presented in *Annex III.*

[9] *One Health is an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals and ecosystems. It recognizes the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are closely linked and inter-dependent* (82).
[10] *United Nations Environment Programme*
[11] *World Organisation for Animal Health*
[12] *Health Emergency Preparedness and Response Authority*

3. VACCINATION: AN UNDERESTIMATED TOOL IN THE FIGHT AGAINST AMR

Vaccination represents an indispensable tool in tackling AMR, as recognised by many key actors in healthcare. In its 2015 Global Action Plan (25), **WHO notes the cost-effectiveness of prevention** and, more recently, in July 2022, it released an **urgent call for better use of existing vaccines and development of new vaccines to tackle AMR.** The report points out the **need to accelerate trials for AMR-related vaccines in late-stage development and the importance of maximising the use of existing vaccines** (39). The urgency of developing new prophylactic vaccines to prevent antibiotic-resistant pathogens is also mentioned in the EU Action Plan (34), the U.S CARB[13] (40) and the recent joint report of WHO and ECDC (24).

A recent study estimated that 510,000 global deaths and 28 million disability-adjusted life-years (DALYs) associated with bacterial AMR could have been averted in a baseline scenario for vaccination of primary age groups against 15 pathogens. In the same scenario, 150,000 deaths and 7.6 million DALYs attributable to AMR could have been avoided in 2019 (41).

A strategy to emphasise the role of vaccines against AMR has been developed by WHO as a technical annex to the Immunization Agenda 2030 (30). **The action framework describes a vision for vaccines to contribute fully, sustainably and equitably to the prevention and control of AMR and** identifies a series of priority actions to be taken by different stakeholders in the fields of immunisation and AMR. It focuses on three areas:

- Expanding the use of licensed vaccines to maximise impact on AMR;
- Developing new vaccines that contribute to the prevention and control of AMR;
- Expanding and sharing knowledge on the impact of vaccines on AMR.

Vaccination strategies and the AMR challenge

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

There are 3 main strategies:

a) ***Preventing the serious outcomes of bacterial infections with resistant strains through direct protection of vaccinated individuals.***

b) ***Prevention of pathogen prevalence and transmission, mitigating the spread of resistant strains***

Vaccination also reduces carriage (the colonisation of an individual in the absence of disease) and shedding of bacteria, thus limiting the spread of infections within a community (herd protection).

The reduction in the number of infections from vaccination is a result of both direct and herd protection:

- Preventing primary and secondary[14] bacterial infections
- Preventing viral infections and secondary bacterial infections
- Reducing the mortality and morbidity (e.g., severity of the disease), and decreasing length of hospitalisation.

c) ***Reduction of antibiotic overuse and misuse***

- Reducing erroneous prescriptions of antibiotics and therefore their overall consumption.

[13] *U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria 2020-2025*
[14] *A secondary infection occurs when a different infection, known as a primary infection, has made a person more susceptible to disease.*

Example: Pneumococcal vaccines in children offering broader protection
The introduction of the 13-valent conjugate pneumococcal vaccine (PCV13) in children in the U.S. has shown the impact of vaccination on the incidence of infectious disease. Antibiotic-resistant invasive pneumococcal disease declined in both the vaccinated and unvaccinated populations (herd protection) (42). A similar phenomenon was noted after the earlier introduction of PCV7, and the implementation of PCV10 (43), (44) when acute otitis media-related health care utilisation decreased in both vaccinated and unvaccinated young children (45).

Example: Hib vaccines reduces disease
The effectiveness in reducing AMR has also been proven by vaccination against *Haemophilus influenzae* type b (Hib). Before the introduction of the Hib conjugate vaccines, 16.6% of all Hib strains worldwide were beta-lactamase positive which reduced drastically the treatment options. With the routine use of Hib conjugate vaccines, disease cases have dropped significantly together with the number of beta-lactamase positive strains (46).

Vaccination against viruses has also been shown to reduce the number of people susceptible to secondary bacterial infections that could potentially require antibiotic treatment (47)**.** For example, vaccination against rotavirus is estimated to prevent 13.6 million antibiotic-treated disease episodes in children under the age of 5 in LMICs every year (48). Vaccination against influenza, varicella and dengue also have been shown to reduce antibiotic use (49), (50), (51), (52). A similar trend is expected for COVID-19 and Respiratory Syncytial Virus (RSV). For example, recent findings show that the administration of an RSV vaccine to pregnant mothers would reduce antimicrobial prescribing among their infants by 12.9% over the first 3 months of life (53).

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 (54). Erroneous prescription of antibiotics is an important factor in the unwanted exposure of bacteria to widely used antimicrobial agents which can leads to the development of resistance (55). For example, evidence shows that during the pandemic, antibiotics were used in 75% of the patients suffering from severe COVID-19 in Europe, while only 15% of those patients actually developed bacterial superinfections (56). Another review from western Europe conducted in 2012 found that antibiotics were prescribed to children with influenza in 28% to 55% of cases (57). More recent data from the U.S. showed that a 10% increase in the influenza vaccination rate led to a 6.5% decrease in antibiotic use, notably in the paediatric and elderly populations (58).

4. DEVELOPING VACCINES AGAINST AMR IS A CHALLENGING PROCESS

While existing vaccines reduce the need to use antibiotics for the infections that they prevent, new vaccines could play a critical role in preventing high-threat bacterial infections associated with AMR. By the end of July 2022, there were 11 vaccines aiming to address AMR in the pipelines of Vaccines Europe member companies, targeting 6 high-threat microorganisms, at different stages of development and tested in various populations (5) (*Fig 1*).

Microorganism	Number of vaccines in the pipeline	Status	Trial population	Technology Platform
C. difficile	3	Phase I (1) Phase II (1) Phase III (1)	Adults, Older Adults	Toxoid vaccine Protein subunit
***E. coli* (ExPEC)**[15]	1	Phase III	Older Adults	Glycoconjugate vaccine
K. pneumoniae	1	Phase I	Adults, Older Adults	Glycoconjugate vaccine
Shigella spp.	1	Phase II	Paediatric, Adults	Glycoconjugate vaccine
S. aureus	1	Phase II	Adults	Glycoconjugate vaccine
S. pneumoniae	4	Phase II (3) Phase III (1)	Paediatric, Adults, Older Adults	Protein subunit Glycoconjugate vaccine

Fig 1 – Vaccines under development tackling AMR

However, the development of vaccines tackling microorganisms predisposed to develop resistance to antimicrobials remains a very challenging task for vaccine manufacturers, for the following reasons:

a) Vaccine R&D is limited by the state of scientific knowledge and rapidly evolving resistance

For many of the AMR pathogens, scientific challenges inhibit vaccine development (2). These challenges include the lack of immunological correlates of protection for some diseases, the complexity and high costs of target validation and proof of concept, and the absence of good animal models for research. Insufficient bacterial genotype and serotype surveillance may limit knowledge for vaccine development (59), (60), (61).

The above-mentioned challenges need to be tackled to enable manufacturers develop candidate vaccines with high purity, stable shelf-life, acceptable safety and efficacy profile, as well as ensure market viability. Some pathogens, such as *S. aureus*, pose significant challenges in the development of vaccines. The specific antigen targets needed to provide protection against infections remain unclear, there are no established markers to indicate protection, and it is uncertain whether a vaccine can effectively safeguard against all clinical syndromes (58).

Progress in basic immunology, such as for the development of reference assays, with special attention to the immune responses in specific populations, is needed to advance vaccine R&D.

Finally, new AMR resistant strains are emerging constantly, complicating the development of multivalent vaccines that could provide long-term protection against AMR.

[15] *Extraintestinal Pathogenic E. coli*

b) R&D for vaccines is long, complex and carries high investments and risks, while market demand is sometimes limited

The average development timeline of a vaccine is approximately 11 years from the preclinical phase (62), although shorter timelines have been observed for vaccines using newer technologies. Additionally, the vaccine development process can require investments of US$ 0.5 – 1 billion (63). This challenge is amplified for the pathogens listed in *Annex I*, as generating a sustainable market for AMR vaccines becomes even more complex. The demand for some of these vaccines may be limited to specific populations or regions.

Furthermore, there is no regulatory or policy precedent for hospital-acquired infections and there is a limited market for at-risk vaccines, underscoring the need for potential vaccine-tailored 'pull' market incentives.

c) Clinical research is challenging for diseases that occur in specific risk groups or environments

Vaccine development poses unique challenges in specific populations, particularly among the hospitalised elderly and immunocompromised individuals. In these groups, factors such as compromised overall health, poor immune responses, limited documentation of epidemiology, and the need for a large number of study participants can significantly hinder successful vaccine development efforts. Additionally, recruitment into clinical trials can be challenged by issues surrounding informed consent, the role of caregivers, and high morbidity and mortality in this population (64).

Another major challenge for manufacturers is related to the development of maternal immunisation to help protect both mothers and their new-borns, despite the high burden of several infectious diseases in neonates, such as those caused by *K. pneumoniae. E. coli* and Group B *Streptococcus.* Conducting clinical trials in neonates is a complicated process.

Additionally, sometimes there is a lack of clarity on the target population. For example, in HICs, *K. pneumoniae* is more likely to affect older and immunocompromised people, while in LMICs, it is neonates who are more likely to be affected by this infection (61).

d) The technical, regulatory and HTA requirements are complex and contribute to higher investment needs and risks

Vaccines have a profound impact in various ways, especially due to their broad ranging effects on public health, the economy and society at large. However, regulatory and HTA requirements do not yet consider AMR community impact or the potential impact on AMR reduction in the assessment of new vaccine applications. There is a need for the wider acknowledgment of the value of vaccines in preventing AMR and providing guidance on the necessary data generation to support claims of impact on AMR.

These challenges underscore the need for incentives tailored for AMR vaccines to provide adequate support for all development stages and to ensure market attractiveness. R&D investments and market viability are closely connected, highlighting the importance of defining 'push' and 'pull' incentives[16].

[16] *Push incentives refer to strategies aiming to support financially innovation, research, and development of new products from early stages to clinical trials. Pull incentive refers to strategies to reward successful development of a new product and ensure access to it.*

5. AN ATTRACTIVE EU ECOSYSTEM IS REQUIRED TO PROMOTE INNOVATION AND ENCOURAGE THE DEVELOPMENT AND UPTAKE OF VACCINES THAT ADDRESS AMR

Strategies for existing vaccines

Evidence shows that there are already several vaccines on the market with significantly positive effects on AMR, such as PCV, Hib vaccine, rotavirus vaccine, measles vaccines and influenza vaccines. However, the coverage remains low, especially in certain areas of the globe. A crucial part of the Global Action Plan on AMR is to achieve ambitious uptake coverage. An important step in this direction would be for Member States to define national action plans with vaccine-related recommendations. The Immunization Agenda 2030 will play a vital role in ensuring that everyone, regardless of age or location, benefits fully from vaccines in the prevention and control of AMR (30).

While childhood vaccination is relatively well established, more work needs to be done regarding vaccination in adult populations, especially considering the ageing population of Europe (65). It is well known that with age, people become more susceptible to infectious diseases and related complications. Despite being proven to help combat AMR in adults (66) and the substantial economic, social and health advantages associated with vaccination, vaccines are still underused and undervalued as a tool against AMR. For example, it is estimated that 77% of the countries in the EU spend less than 0.5% of their healthcare budget on immunisation (67). Ensuring a sustainable immunisation programme across the lifespan would be a key tool in the fight against AMR. This could only be achieved through policies that prioritise and embed adult vaccination in national immunisation plans and ensure sufficient funding to improve access and uptake of existing vaccines and faster inclusion of new vaccines (68).

The real impact of vaccines on AMR can be measured by collecting and analysing a wide range of data (27). While some data is currently available in the U.S., it is very limited in the European space. To inform decision-makers and vaccine manufacturers about the value of vaccines in tackling AMR and allow them to prioritise resources in this field, data need to be collected, analysed and made publicly available at regular intervals.

Additionally, the current narrow HTA framework systematically undervalues the benefits of vaccines by not considering, among others, their impact on AMR, enablement value[17] or productivity (69). A new, value-based methodology for assessing vaccines is needed to account for and recognise the broad value of vaccination – not only as a high-value public health investment, but also as an economically and socially beneficial healthcare intervention. The implementation of EU Regulation on HTA can play a role in that respect. A framework that considers the Full Value of Vaccines Assessments (FVVA) has been proposed, aiming to guide the assessment and communication of the full value of vaccines and improve decision-making regarding investment in vaccine development, policy, procurement and introduction of vaccines (70). Through this type of assessments, aspects that are often neglected could be considered – such as the added health and socio-economic impact of preventing AMR in the context of different vaccines.

[17] *Enablement value is defined as the value of vaccination generated by enabling other cost-effective interventions, starting from the idea that vaccines should not be evaluated in isolation because they enhance the effectiveness of other non-vaccine interventions.*

STRATEGIES FOR EXISTING VACCINES

To reduce the burden of AMR on public health, it is vital to support the uptake of licensed vaccines through:

AWARENESS

- Enhance public awareness of the importance of vaccination in the fight against AMR to improve vaccine confidence, uptake, and coverage.
- Support education and incentives to healthcare professionals and those involved in animal farming.

IMMUNISATION UPTAKE

Improve human vaccination coverage in all age groups in all EU Member States, through a life-long approach, with an emphasis of including adult immunisation in national immunisation plans (NIP) and implementing targeted vaccination of at-risk populations (e.g., healthcare workers, patients with chronic illnesses, pregnant women).

POLICIES

- Develop policies to integrate and support prevention in the fight against AMR.
- Align AMR National Action Plans with national immunisation programmes (NIP), setting clear and defined vaccine uptake targets, increased vaccination budget, horizon scanning to ensure sustainable immunisation financing, and timely monitoring of vaccination programmes.
- Invest in data systems across the EU to collect quality data and drive public health decision-making.

REAL-WORLD EVIDENCE

Improve generation and utilisation of real-world healthcare data and develop surveillance systems to monitor the impact of both new and established vaccines on AMR.

Strategies for upcoming vaccines

In a recent study conducted by DG HERA on *Bringing Antimicrobial Resistance Medical Countermeasures to the Market* (71), prevention is recognised as a scientifically feasible tool in the fight against AMR that should be financially supported. The report recognises the differences between vaccines and antibiotics at market level (stewardship policies), but also regarding the mode of action. **It recognises that incentive-based policies, especially push incentives, might be needed for some vaccines**, but their type, timing and mechanism would be different than those proposed for antibiotics.

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The numerous challenges encountered in the development of vaccines to counter AMR contribute to these being a complex or even not feasible business investment. This is due to the scientific hurdles, long development times, high failure rates, high costs, inability to account for market failures, prolonged licensure review process and lack of recommendations regarding use. To overcome these hurdles, both market and financial incentives would be needed, on a case-by-case basis. Initiatives such as those mentioned for existing vaccines that would increase the awareness of the value of vaccination, improve access and ensure uptake would encourage the development of new products. Additionally, the research and development of new vaccines that address AMR needs to be supported with innovative financing mechanisms, through channelling investments from both private and public sectors (30). It is crucial for all relevant stakeholders to co-create the right 'push' and 'pull' incentives that would further support the development of vaccines against priority pathogens.

Public-private partnerships (PPPs) are also a critical aspect for AMR vaccine R&D. Collaborations between academic researchers, pharmaceutical companies, and government agencies would lead to more efficient vaccine development. These PPPs should cover:

- **Fundamental research for understanding immunology and pathogenesis:** funding for research in fundamental immunology and related sciences is critical for identifying appropriate target epitopes, immunological correlates of protection for AMR pathogens, and new technologies for developing novel vaccine design concepts.
- **Strong and reliable disease surveillance where good databases 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 those conducted under the Innovative Medicines Initiative (IMI) and Innovative Health Initiative (IHI) are highly valuable.

Accelerated regulatory pathways for vaccines targeting priority AMR-related pathogens could also be of use both to incentivise vaccine manufacturers to develop vaccines against these microorganisms and to ensure faster availability of the products to the population. Vaccines Europe welcome the recent project on AMR best practices adopted by the International Coalition of Medicines Regulatory Authorities (ICMRA) and the report presenting several successful or promising regulatory and non-regulatory interventions used to address AMR and provide timely access to safe critical products (73). We believe it would be important to further assess how the regulatory agilities implemented during COVID-19 could be applied in the challenge of AMR. For example, we would like to make sure that Conditional Marketing Authorisation (CMA) could be applicable for vaccines with an AMR indication and that PRIME would include AMR vaccines within its scope. This way, key vaccine candidates could receive enhanced support during development and the possibility of accelerated assessment.

Additionally, appropriate regulatory guidance and frameworks would be necessary to guide manufacturers regarding possible AMR endpoints or use of real-world evidence following (conditional) approval. Clinical trials particularly for vaccines targeting low incidence infections in hospital settings, for example, could be challenging for development. Therefore, further guidance would be valuable to assist the measurement of the impact of vaccines in preventing AMR-induced diseases and in reducing antibiotic overconsumption via more targeted data generation to accelerate licensure.

STRATEGIES FOR UPCOMING VACCINES

Create an ecosystem that supports innovation and promotes the development of future vaccines through:

SURVEILLANCE

Ensure availability of surveillance platforms assessing the use and misuse of antibiotics for vaccine-preventable infections.

PRIORITY PATHOGENS

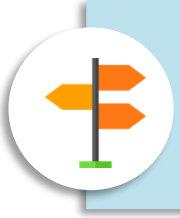
Increase awareness of global and regional priority pathogens lists developed by relevant stakeholders, such as WHO, ECDC, DG HERA, U.S. CDC.

INCENTIVES

Develop innovative financing mechanisms and appropriate incentives for early- and late-stage research for specific vaccines, tailored to each case's unique needs.

FUNDING AND PARTNERSHIPS

Increase public funding and incentivise public-private partnerships in R&D that support the role of vaccines in the fight against AMR.



REGULATORY GUIDANCE

Ensure that the regulatory framework provides guidelines and supports streamlined development and authorisation of vaccines against AMR. This includes offering guidance on potential AMR clinical endpoints and utilising real-world evidence following (conditional) approval.

VALUE OF VACCINATION

- Developing vaccine-specific HTA methodologies that recognise the broad value of vaccination, including their impact on AMR.
- Enhance vaccine assessment and decision-making pathways to accelerate access to innovative vaccines (31).

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Other strategies

As demonstrated earlier in this paper, the high burden of AMR cannot be solved by any stakeholder alone. All global actors in the health field should join forces, align on strategies and ensure their implementation. To win the AMR battle, collaboration is key.

To tackle AMR, it is crucial to maintain dialogue and commitment among all relevant stakeholders to accelerating the development of new vaccines, as well as improving access and coverage of existing vaccines that address antibiotic-resistant pathogens.

The Pharmaceutical Strategy for Europe published in November 2020 and the European Commission's proposal on the General Pharmaceutical Legislation placed AMR high on the political agenda, as a critical unmet medical need with serious health and economic consequences (74). Unfortunately, vaccines are not mentioned in these documents as valuable tools in the fight against AMR that should be further incentivised.

The revision of the European General Pharmaceutical Legislation represents a great opportunity to foster an innovative ecosystem that will further advance the development of valuable tools to address AMR. As recognised by many relevant global actors, and the recent EU Council recommendation (8), **the value of vaccines should be reflected in the upcoming legislation** (7).

6. CONCLUSION

The significant role and value of vaccines in the fight against AMR is widely recognised in the scientific community, by international organisations such as the European Union, and by public health NGOs. However, additional efforts are needed to facilitate the development and introduction of new vaccines targeting resistant pathogens. Simultaneously, it is crucial to promote the appropriate use of existing vaccines while ongoing work focuses on the development of new antibiotic therapies.

Due to the numerous challenges encountered in the research and development of vaccines that have the potential to address AMR, appropriate support is needed from the private and public sectors. Innovative financing mechanisms and public-private partnerships would lead to more efficient vaccine development. Developing regulatory guidance and frameworks to support the value of vaccines in addressing AMR would be of tremendous help in accelerating the availability and use of those products. It is crucial to integrate the impact of vaccines on antimicrobial resistance (AMR) control into decision-making strategies of regulatory agencies, health technology assessment (HTA), and national policies.

Healthcare professionals play a pivotal role in administering vaccines and in educating patients about the importance of vaccination in preventing infections and reducing the need for antibiotics. Ensuring that healthcare professionals are aware of the benefits of vaccines and their role in combating AMR is vital. This should be supported by public awareness programmes and the integration of life-course immunisation into national vaccination strategies. To accomplish these goals, there is a need for policies and systems that facilitate the generation of robust real-world data for measuring the impact of vaccines in Europe.

By investing in the development and widespread adoption of existing and future vaccines, we can better protect public health, reduce the risk of antibiotic resistance, and ultimately address the unmet medical needs associated with infectious diseases and AMR.

ANNEX I – Sustainable Development Goals

AMR is considered both a global public health and societal issue in the context of the United Nations' Sustainable Development Goals (SDG). Nine out of the 17 SDGs are impacted by AMR (1). The SDGs were published in 2015 as an urgent call for action at global level to ensure a more sustainable life on the planet (75). Most of the SDGs have the target of 2030.

The goals discussed in the context of AMR are the following (1):

- Goal 1: No Poverty
- Goal 2: Zero Hunger
- Goal 3: Good Health and Well-Being
- Goal 6: Clear Water in Sanitation
- Goal 8: Decent Work and Economic Growth
- Goal 10: Reduced Inequalities
- Goal 12: Responsible Consumption and Production
- Goal 13: Climate Action
- Goal 17: Partnership for the Goals

Recently, two specific indicators for AMR were included under SDG 3 (9):

- SDG indicator 3.d.2: Percentage of bloodstream infections due to selected antimicrobial-resistant organisms; and
- SDG indicator 3.d.3: Proportion of health facilities that have a core set of relevant essential medicines available and affordable on a sustainable basis (where antibiotics will be disaggregated from the core set of data used in the metadata).

ANNEX II – Bacterial species of highest concern

The table below summarises the microorganisms mentioned in the 2017 WHO list of antibiotic-resistant priority pathogens, the 2019 U.S. CDC report classifying key microorganisms as *urgent, serious and concerning* (23), and the 2022 WHO and ECDC[18] joint report on *Antimicrobial resistance surveillance in Europe* that includes surveillance data for bacterial species of highest concern (24).

Microorganism	Antimicrobial group/agent	WHO (2017)	CDC (2019)	WHO-ECDC (2022)
Acinetobacter baumannii	Carbapenems Fluoroquinolones Aminoglycosides	CRITICAL	URGENT	✓[19] ✓ ✓
Aspergillus fumigatus	Azoles		WATCH LIST	
Bordetella pertussis	Azithromycin, Erythromycin		WATCH LIST	
Campylobacter spp.	Fluroquinolones	HIGH	SERIOUS	
Candida auris	Antifungals		URGENT	
Candida sp.	Antifungals		SERIOUS	

[18] *European Centre for Disease Prevention and Control*
[19] *✓means that the joint WHO-ECDC report considers the bacterial species as of highest concern in Europe*

Clostridioides difficile			URGENT	
Enterobacteriaceae	Carbapenems ESBL-producing	CRITICAL	URGENT SERIOUS	
****Escherichia coli***	Aminopenicillins 3rd gen cephalosporins Carbapenems Fluoroquinolones Aminoglycosides			✓ ✓ ✓ ✓ ✓
****Klebsiella pneumoniae***	3rd gen cephalosporins Carbapenems Fluoroquinolones Aminoglycosides			✓ ✓ ✓ ✓
Enterococci ****Enterococcus faecium***	Vancomycin Aminopenicillins Aminoglycosides	HIGH	SERIOUS	✓ ✓ ✓
****Enterococcus faecalis***	Aminoglycosides			✓
Group A streptococcus	Erythromycin		CONCERNING	
Group B streptococcus	Clindamycin		CONCERNING	
Haemophilus influenzae	Ampicillin	MEDIUM		
Helicobacter pylori	Clarithromycin	HIGH		
Mycobacterium tuberculosis	First- and second-line antibiotics		SERIOUS	
Mycoplasma genitalium	Azithromycin		WATCH LIST	
Neisseria gonorrhoeae	Cephalosporins, Fluroquinolones	HIGH	URGENT	
Pseudomonas aeruginosa	Carbapenems Multi-drug	CRITICAL	SERIOUS	✓
Salmonella spp.	Fluroquinolones	HIGH	SERIOUS	
Shigella spp.	Fluroquinolones	MEDIUM	SERIOUS	
Staphylococcus aureus	Methicillin, Vancomycin Fluoroquinolones Rifampicin	HIGH	SERIOUS	✓ ✓ ✓
Streptococcus pneumoniae	Penicillin	MEDIUM	SERIOUS	

ANNEX III – Global, European and national initiatives

Global and U.S. initiatives

In addition to the **WHO Global Action Plan on AMR** adopted at the World Health Assembly in 2015, more recent initiatives have been developed. In 2021, the FAO[20] released its revised AMR Action Plan 2021-2025, built around five main objectives (76). Combatting AMR is a shared responsibility between WHO, FAO, UNEP[21] and WOAH[22] that established the **AMR Quadripartite organisation** aiming to advance a One Health response to AMR (33).

In the U.S., a **2020-2025 National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB***)* was established to guide government activities and action by public health, healthcare, and veterinary partners in a common effort to address urgent and serious antimicrobial-resistant threats (40).

European initiatives

In June 2017, the European Commission adopted the **EU One Health Action Plan against AMR** that focuses on three main pillars: make the EU a best practice region; invest in research, development and innovation; and shape the global agenda. The plan provides concrete actions to reduce the emergence and spread of AMR and to increase the development and availability of new effective antimicrobials (34). The environmental piece of the EU Action Plan is supported by several actions included in **the Strategic Approach to Pharmaceuticals in the Environment (PiE)** released in 2019 (77).

DG HERA[23] was created in September 2021 to prevent, detect and rapidly respond to health emergencies, through intelligence gathering and building the necessary response capacities. AMR is one of the key topics targeted by HERA in their 2022 and 2023 Work Plans (36), (37), after being identified as one of the top three serious cross-border health threats in June 2022 (38).

The **EU4Health programme** (2021-2027) is a source of funding for EU countries, health organisations and NGOs addressing the reduction of antimicrobial-resistant infections and improving vaccination rates (35).

Public-private partnerships represent a great tool in Europe's AMR battle. The IMI ND4BB (New Drugs for Bad Bugs) series of programmes is one of the biggest AMR research partnerships, aiming to directly address some of the scientific challenges associated with antibacterial drug discovery and development (78). Another positive example of a PPP is PRIMAVERA, an IMI2 project that started in 2021 with the aim of developing mathematical models and an open access epidemiological repository to facilitate the assessment of the AMR impact of different vaccines and monoclonal antibodies (79).

National initiatives

The EU Member States (MSs) were encouraged to put in place **National Action Plans (NAPs) against AMR** (80), based on the One Health approach, being supported in the implementation stage by EU-JAMRAI[24]. In 2022, DG SANTE[25] published a review of the NAPs (81). The findings show that all MSs have NAPs in place, but many of them still need to work more on the One Health dimension, notably in the environmental area. Additionally, most NAPs contain a strategic component, but the implementation aspect (operational, monitoring, evaluation and budget) are not as well developed. The report notes the negative effect the COVID-19 pandemic had on the AMR challenge by diverting necessary resources at the Member State level.

[20] *Food and Agriculture Organisation of the United Nations*
[21] *United Nations Environment Programme*
[22] *World Organisation for Animal Health*
[23] *Health Emergency Preparedness and Response Authority*
[24] *European Union Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections*
[25] *European Commission's Directorate-General for Health and Food Safety*

ACRONYMS

AMR = Antimicrobial Resistance
CMA = Conditional Marketing Authorisation
ECDC = European Centre for Disease Prevention and Control
EEA = European Economic Area
EU = European Union
EU-JAMRAI = European Union Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections
DG HERA = European Health Emergency Preparedness and Response Authority
DG SANTE = European Commission's Directorate-General for Health and Food Safety
ExPEC = Extraintestinal Pathogenic *E. coli*
FAO = Food and Agriculture Organisation of the United Nations
FVVA = Full Value of Vaccines Assessments
HAI = healthcare-associated infections
Hib = *Haemophilus influenzae* type b
HIC = High-Income Countries
HIV = human immunodeficiency virus
HTA = Health Technology Assessment
ICMRA = International Coalition of Medicines Regulatory Authorities
IHI = Innovative Health Initiative
IMI = Innovative Medicines Initiative
LMIC = Low- and Middle-Income Countries
MS = Member State
NAP = National Action Plans
NIP = National Immunisation Program
OECD = Organisation for Economic Co-operation and Development
PCV = pneumococcal conjugate vaccine
PPP = Public-private partnership
PRIME = PRIority MEdicines scheme
R&D = Research & Development
RWD = Real World Data
RWE = Real World Evidence
UN SDG = United Nations' Sustainable Development Goals
UNEP = United Nations Environment Programme
U.S. CARB = United States National Action Plan for Combating Antibiotic-Resistant Bacteria
U.S. CDC = United States Centers for Disease Control and Prevention
WHO = World Health Organisation
WHO AWaRe = WHO Access, Watch, and Reserve (AWaRe) antibiotic classification framework
WOAH = World Organisation for Animal Health

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