Regulatory and Scientific Strategies to Combat Antimicrobial Resistance in the EU

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List of Abbreviations

AAC	Antibody–antibiotic conjugate
AMG	*Arzneimittelgesetz*
AMP	Antimicrobial peptide
AMR	Antimicrobial Resistance
AST	Antimicrobial susceptibility testing
ASU	Antimicrobial Sales and Use
ATMP	Advanced Therapy Medicinal Product
ATC-Code	Anatomical Therapeutic Chemical-Code
AWaRe	Access, Watch and Reserve
BfArM	Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arznei-mittel und Medizinprodukte*)
BMG	*Bundesministerium für Gesundheit*
CDI	*C. difficile* infection
C. difficile	*Clostridium difficile*
CHMP	Committee for Medicinal Products for Human Use
CP	Central Procedure
CTD	Clinical Trials Directive
CTIS	Clinical Trials Information System
CTR	Clinical Trials Regulation
DG-SANTE	Directorate-General for Health and Food Safety
DSMB	Data and Safety Monitoring Board
EEA	European Environment Agency
EEA	European Economic Area
EAAD	European Antibiotic Awareness Day
EARS-Net	European Antimicrobial Resistance Surveillance Network
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
E. coli	*Escherichia coli*
ECHA	European Chemicals Agency
E. faecalis	*Enterococcus faecalis*
E. faecium	*Enterococcus faecium*
EFSA	European Food Safety Authority
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FAO	Food and Agricultural Organization
FDA	Food and Drug Administration
FTT	Faecal transplant treatment
G-BA	*Gemeinsamer Bundesausschuss*
GCP	Good Clinical Practice
GLASS	Global Antimicrobial Resistance and Use Surveillance System
GMP	Good Manufacturing Practice
HERA	Health Emergency Preparedness and Response Authority
HGT	Horizontal gene transfer
HTA	Health Technology Assessment
ICMRA	International Coalition of Medicines Regulatory Authorities

ITF	EMA's Innovation Task Force
IMI	Innovative Medicines Initiative
JPIAMR	Joint Programming Initiative on AMR
K. pneumoniae	*Klebsiella pneumoniae*
PD	Pharmacodynamic
PK	Pharmacokinetic
PMDA	Japanese Pharmaceuticals and Medical Devices Agency
PNAs	Peptide Nucleic Acids
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MDR	Multidrug-resistant
MGE	Mobile genetic elements
MIC	minimum inhibitory concentration
mRNA	messenger ribonucleic acid
MRSA	Methicillin-resistant *S. aureus*
M. tuberculosis	*Mycobacterium tuberculosis*
NCBI	National Cener for Biotechnology Information
ND4BB	New Drugs 4 Bad Bugs
NP	natural products
OECD	Organisation for Economic Cooperation and Development
OHHLEP	One Health High Level Expert Panel
OIE	World Organization for Animal Health (former abbreviation)
OH JPA	One Health Joint Plan of Action
PBP	Penicillin-binding proteins
PIP	Paediatric investigation plan
P. aeruginosa	*Pseudomonas aeruginosa*
PPP	Public-private partnership
RIR	Regulatory Intelligence Report
RKI	Robert Koch Institute
R&D	Research and Development
S. aureus	*Staphylococcus aureus*
SGB V	*Sozialgesetzbuch Fünftes Buch*
SMEs	Micro-, small- and medium-sized enterprises
SmPC	Summary of Product Characteristics
S. pneumoniae	*Streptococcus pneumoniae*
spp.	*species pluralis*
UNEP	United Nations Environment Programme
vfa	*Verband Forschender Arzneimittelhersteller*
VRE	Vancomycin-resistant enterococci
VRSA	Vancomycin-resistant *S. aureus*
WAAW	World AMR Awareness Week
WHA	World Health Assembly
WHO	World Health Organisation
WOAH	World Organisation for Animal Health
WHO GAP	WHO Global Action Plan on AMR

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1. Introduction

The European Commission (EC) called for urgent action on antimicrobial resistance (AMR) in November 2023. The fight against AMR was set as top priority for the Commission and defined as an integral part of many actions under the European Health Union [1]. This followed the adoption of the 'Council Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health Approach' in June 2023 [2].

Antimicrobials are substances that kill or inhibit the growths of microorganisms, i.e. bacteria, parasites or fungi. Microorganisms that are able to grow in the presence of an antimicrobial are referred to as resistant to that substance [3]. Antibiotics are specifically used for the treatment of bacterial infections and were originally defined as antibacterial substances produced by a microorganism. However, since antibiotics have also been produced (semi)-synthetically, this strict definition was broadened [4].

After the discovery of the first antibiotic agents by Alexander Fleming in 1929 (penicillin) and Selman A. Waksman in 1941 (streptomycin), clinical relevance was rapidly explored [3]. The selective toxicity of antibiotics is of great importance as they act on specific target structures of certain microorganisms (e.g. plasma membrane, protein synthesis) [5]. The success of antibiotics in treating infectious diseases has been accompanied by their overuse. In addition, antibiotics have not only been used to treat bacterial infections in humans and animals, they have also been used in agriculture to stimulate growth and prevent infections. Massive antibiotic overuse and misuse contributed to selection of bacterial strains which have acquired strategies to evade susceptibility to these agents, making them resistant [3, 4]. New antimicrobial agents need to be developed to counteract evolving AMR to combat microbial infections in the future. This need is further exacerbated by the evolution of multidrug-resistant (MDR) bacteria [6].

AMR is a major issue for the public health. According to the European Centre for Disease Prevention and Control (ECDC) report on the health burden of infections with antibiotic-resistant bacteria in the EU/EEA, 35,000 deaths per year are associated with infections with resistant bacteria [7]. Globally, 4.29 million deaths per year are associated with resistant bacteria, of which 1.27 million deaths are directly attributed to resistant bacteria [8]. The Health Emergency Preparedness and Response Authority (HERA) identified AMR as one of three high impact health threats [9]. The relevance of AMR and the need to combat it is

highlighted by the WHO (World Health Organisation) initiative 'World AMR Awareness Week' (WAAW) which is held from 18th to 24th November every year [10]. The ECDC supports this event, holding the annual 'European Antibiotic Awareness Day' (EAAD) on 18th November [11]. The International Coalition of Medicines Regulatory Authorities (ICMRA) emphasises that a 'One Health' approach is required to combat AMR, considering public and animal health and the environment [12]. In view of this, the topics of the EU strategy to tackle AMR are: 1. More restrictive use of antimicrobial agents; 2. Ensuring the availability of antibiotics; 3. Addressing AMR globally; and 4. Funding of research and technological innovation into AMR [13].

This thesis analyses the implications of AMR, focusing on bacterial resistance to antibiotics. It also shows, with a focus on trends at EU level, how the need for new antibacterial substances can be met in the future. Two main topics are evaluated: First, current research and development (R&D) of new antibiotic substances or novel alternatives are described. This includes recent marketing authorisations (MAs), marketing authorisation applications (MAAs) and preclinical and clinical development stages. Data analysis was limited to developments from 2017 onwards, i.e. the implementation of the 'European One Health Action Plan against Antimicrobial Resistance (AMR)'. Second, regulatory measures which help to address the issue of AMR in a One Health approach are elucidated. Both topics are intertwined and must be observed hand in hand. Pharmaceutical R&D are costly and ultimately the costs of drug development are intended to be disbursed by sales of that pharmaceutical after obtaining a MA. However, for antimicrobials sales are limited since the use of these substances is restricted by prescription. Moreover, the use will be restricted even further in the future to prevent overuse and misuse [13]. Additionally, sales expectations of antibiotics are limited by the fact that antibiotics at best lead to the healing of an infection after a relatively short treatment period of only days to weeks [14]. Hence, research and development need to be more attractive for all stakeholders, including the pharmaceutical industry, smaller companies, foundations and academia. This can be achieved, for example, by providing incentives and regulatory guidance not only during drug R&D, but also during the processes of obtaining and maintaining a MA. Of note, the access and supply of traditional effective antibiotics is just as important. Overall, prudent use of antibiotics, infection prevention and control measures, and global collaboration to address AMR in a One Health approach will be critical to the overall goal of combating AMR.

2. Methods

2.1. Literature Search

The main resources used for the literature research were the PubMed Database of the National Library of Medicine of the National Cener for Biotechnology Information (NCBI), EUR-Lex, the library, webpage and PharmNet.Bund portal of the Federal Institute of Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte*, BfArM), webpages of EMA (European Medicines Agency), ECDC, WHO, EC (European Commission), and RKI (Robert Koch Institute).

2.2. New Marketing Authorisation (MA) Applications (MAA) for Antibacterials and Bacterial Vaccines (2017-2024)

2.2.1. MAs: Cortellis Clarivate

Data on new MAs approved by the EMA via the centralised procedure (CP) since 2017, was obtained using the Cortellis Regulatory Intelligence Report (RIR). The data was extracted to Excel and the following filters were applied:

- "Therapeutic Area" = "Infections";
- "EC Opinion" = "from 2017";
- Excluding the term "virus" in "Indication";
- Excluding the term "COVID" in "Indication".

Filtering for the term "antibacterial" in indication only resulted in incomplete results since this automatically excluded bacterial vaccines and antimycobacterial agents. To circumvent the problem that filtering in Excel is only possible for two terms per column, indications for antiviral agents and agents against COVID were excluded using the filtering tool in Excel. Antifungals were then manually excluded from the results lists. The remaining datasets were manually screened for indications associated with antibiotic treatments for bacterial infections or vaccines against bacterial infections. Duplicate data was eliminated.

2.2.2. MAs: EMA

Information on new MAs authorised by the EMA via CP obtained from Cortellis was verified using the EMA webpage search (Link) [15]. The following filters were applied: "human", "medicines", "marketing authorisation date: from 01/01/2017 to 15/02/2024". Additional

filters “antibacterials for systemic use” or “vaccines” or “antimycobacterials” or “pneumococcus” or “other antibacterials” or “immune sera and immunoglobins” were applied. Since these search criteria did not yield identical results to the Cortellis search, further searches with the exact name of the medicinal product or active substances were conducted to verify the Cortellis results in the EMA database. All MAs identified by Cortellis were ultimately identified in the EMA database. Additional information, such as ATC (Anatomical Therapeutic Chemical) Code was obtained from product information texts provided in the EMA database.

2.2.3. MAs: Germany

The national medicinal product database of Germany (AMIce) was screened for new MAs from January 2017 until February 2024. No MAs authorised via MRP/DCP/purely national procedure with ATC Code J01/J04/J06/J07 containing new active substances were identified (Link) [16].

2.2.4. MAAs: EMA

Information on ‘Applications for new human medicines under evaluation by the CHMP’ was retrieved from the EMA webpage (Link) [17].

2.3. Clinical Trials with Antibiotics

2.3.1. CTIS

CTIS (Clinical Trials Information System) was searched for trials conducted under the Clinical Trials Regulation (CTR) (EU) No 536/2014. The database can be accessed via Link [18]. The following filter was applied: “Diseases [C] – bacterial infections and mycoses [C01]”.

2.3.2. EU Clinical Trials Register

The EU Clinical Trials Register was searched for trials under the Clinical Trials Directive 2001/20/EC. The database can be accesses via Link [19].

2.4. Shortages

2.4.1. EMA (EU/EEA)

Information on supply shortages for the EU were obtained from EMA shortages catalogue (Link). Results were filtered for ongoing shortages for antibiotics [20].

2.4.2. PharmNet.Bund (BfArM, Germany)

Information on supply shortages (excluding vaccines) on a national level for Germany were retrieved from PharmNet.Bund Portal which is hosted by BfArM (Link) [21]. Results were filtered for ongoing shortages with ATC Code J01xx.

3. Antibiotics and Antimicrobial Resistance (AMR) – Now and Then

3.1. Antibiotics

3.1.1. History and Discovery

According to historical evidence, the usefulness of antimicrobial substances was already known in ancient cultures, even though the underlying microbiological principles behind it were not [22, 23]. The antibiotic era began in the 19th century when Louis Pasteur and later Robert Koch described the causal relationship between a certain microorganism and a corresponding disease [24]. This principle was further confirmed by Paul Ehrlich in 1909 who discovered Salvarsan, and later Neosalvarsan, the first antibacterials against *Treponema pallidum*, the causative agent of syphilis [22]. Due to risks associated with the presence of arsenic in these drugs, they were superseded by Prontosil, containing the broad-spectrum antibacterial substance sulfonamide, discovered by Gerhard Domagk in 1930 [22, 24]. In 1929 Alexander Fleming was the first to discover that a substance produced by the fungus *Penicillium notatum* (i.e. penicillin) limited the growth of colonies of the bacterium *Staphylococcus aureus* (*S. aureus*) [3, 4]. In contrast to the previously identified antimicrobial agents, which were chemically synthesised, penicillin was the first true antibiotic in a strict sense, i.e. an antibacterial substance produced by a microorganism. However, the clinical relevance of penicillin was only discovered in 1940 when Florey, Chain and Heatley identified and isolated penicillin and studied the therapeutic effects, such as treatment of *Streptococcus pyogenes* infected wounds [4]. Penicillin was the first industrially manufactured

antibiotic which obtained great importance in the treatment of infectious diseases [3]. The findings on penicillin led Selman A. Waksman to intensify his research on soil bacteria which resulted in the discovery of more antibiotic agents, namely actinomycin produced by *Actinomycetes* species and streptomycin produced by *Streptomyces griseus*. The latter compound was the first effective agent against *Mycobacterium tuberculosis (M. tuberculosis)*, the causative agent of tuberculosis [4]. Later, Waksman discovered chloramphenicol, tetracycline, and erythromycin in soil samples [25]. Figure 1 displays a timeline of the discovery of various antibiotic substances, their origin and the occurrence of bacterial resistances. The time between ~1940 and ~1970 is considered as 'Golden Age' of the antibiotic era. Over twenty antibiotic classes were discovered during this time [24]. Antibiotics have been derived from several different sources, such as from *Actinomycetes*, other bacteria, or fungi. Moreover, (semi)-synthetic production has also been used [22, 26]. The quick and relatively easy discovery of numerous antibiotic substances resulted in excessive use of these drugs and first bacterial resistances towards these agents were soon observed [22, 24]. The decrease in identification of new antibiotic substances after the end of the golden antibiotic age in combination with increasing emergence of resistances highlight the need for action: New effective antibacterials are required, but the factors that lead to increased occurrence of resistance must also be addressed.

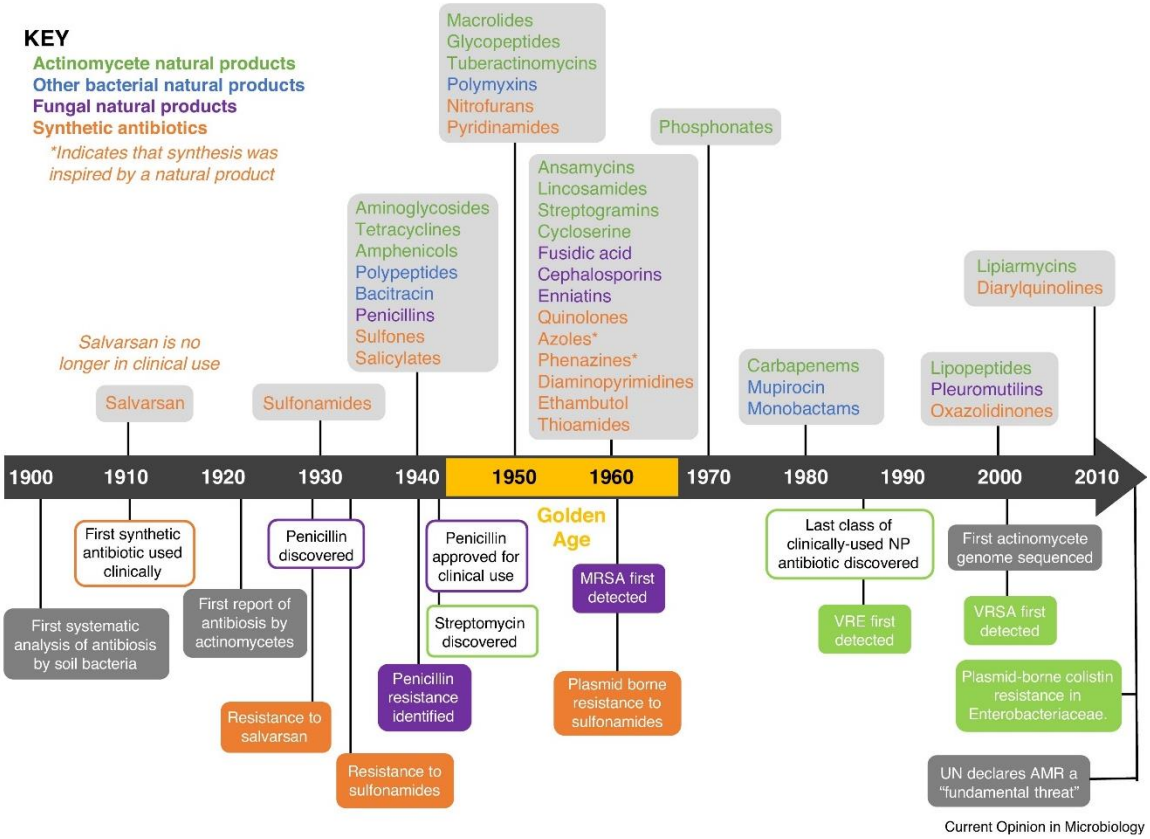


Figure 1 - Discovery of Antibiotics of different Origin and related AMR; Timeline from 1900 to 2010.

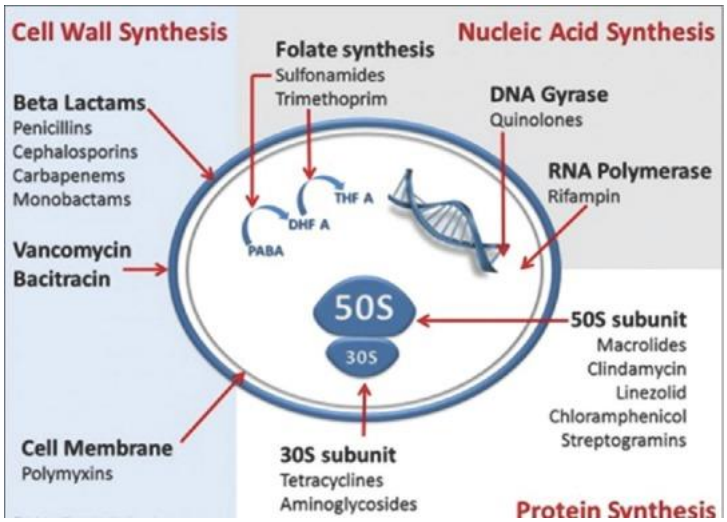
Legend: MRSA: methicillin-resistant S. aureus; NP: natural product; VRE: vancomycin-resistant enterococci; VRSA: vancomycin-resistant S. aureus. Source [22]

3.1.2. Mode of Action

Antibiotics belong to the class of antiinfective agents, i.e. medicinal products used to treat infectious diseases. Infections can be caused by several different pathogenic microorganisms, i.e. bacteria, viruses, fungi and parasites [27]. Antibiotics are specifically used for the treatment of bacterial infections. They kill bacteria or inhibit their growth by, e.g. (1) interference with cell wall synthesis, (2) disturbance of plasma membrane integrity, (3) inhibition of nucleic acid synthesis (DNA/RNA), (4) interference with ribosomal function/ protein biosynthesis, or (5) inhibition of metabolic pathways (e.g. folate synthesis) [5, 24, 25]. Antibiotics are classified according to their mode of action. Figure 2 presents examples of selected antibiotic substances and their bacterial targets. Examples for antibiotics which act on cell wall synthesis are β-lactams (e.g. penicillin, cephalosporins). The protein biosynthesis is targeted by tetracyclines, macrolides, and chloramphenicol; Nucleic acid synthesis is inhibited by quinolones, and rifampin; And folate synthesis is targeted by sulfonamides [28].

Figure 2 - Mechanism of Action of specific Antibiotics.

Adapted from [28]



Depending on the antibiotic *per se*, the bacterial target and the concentration, the effects of an antibiotic can be bactericidal or bacteriostatic [5]. Antibiotics acting on the protein synthesis machinery of a bacterium tend to exert bacteriostatic effects (e.g. tetracyclines). On the other hand, if cell wall synthesis or membrane integrity is attacked, antibiotics are more likely to act bactericidal (e.g. β-lactams) [29]. Antibiotics can exert their effects on a narrow- or broad-spectrum of target microorganisms. The latter being effective against Gram-positive and Gram-negative bacteria. Due to fundamental differences in the structure of eukaryotic (e.g. human) cells *versus* prokaryotic (e.g. bacteria) cells, antibiotics are able to specifically target structures which are only present in bacterial cells [5]. Nevertheless, adverse effects are not excluded and they can be classified into to the following categories: (1) hypersensitivity reaction; (2) direct toxic effects; (3) change in microbial flora; (4) microbial lysis [30]. These effects can be dose-related , but have also been observed to be idiosyncratic [26].

3.2. The Rise of Antimicrobial Resistances

3.2.1. History and Discovery

AMR is defined as the ability of microorganisms or cells to grow in the presence of antimicrobials [3]. The ability of the microorganism to do so can either be innate or acquired. Innate resistance of bacteria to antibiotics is achieved by specific features of the bacterium which prevent the antibiotic from exerting its toxic effect. Examples include the composition of the outer membrane of Gram-negative bacteria which prevents certain antibiotics

from entering the bacterial cell and ultimately reaching its intracellular target. On the other hand, acquired AMR describes the implication that a bacterium previously susceptible to an antibiotic substance develops the ability to evade the toxic effects [26]. If resistance is acquired in the presence of an antibiotic, this is referred to as inducible resistance. Chloramphenicol can trigger certain Gram-positive bacteria to produce chloramphenicol acetyltransferase which leads to inactivation of the antibiotic [5]. As depicted in Figure 1, acquired resistances were detected soon after clinical introduction of the first antibiotic substances. Shortly after the discovery of penicillin and sulfonamides, first resistances were observed [22]. Over time, more resistant bacteria were discovered, including multidrug-resistant bacteria such as MRSA and VRE [6].

3.2.2. Bacterial Mechanisms to Evade Susceptibility to Antimicrobials

The bacterial mechanism of adaption to a toxic environment by either mutation or acquisition of new genetic material is a natural process [30]. The presence of vast amounts of antibiotics in the environment increases the genetic selection pressure on bacteria, accelerating the emergence of AMR [4]. As depicted in Figure 3, bacterial resistance against antibiotics can be achieved via several different mechanisms, i.e. (1) reduced permeability; (2) active transport of antibiotics; (3) target alteration, modification and protection; (4) inactivation and modification of the drug, and (5) target bypass [31].

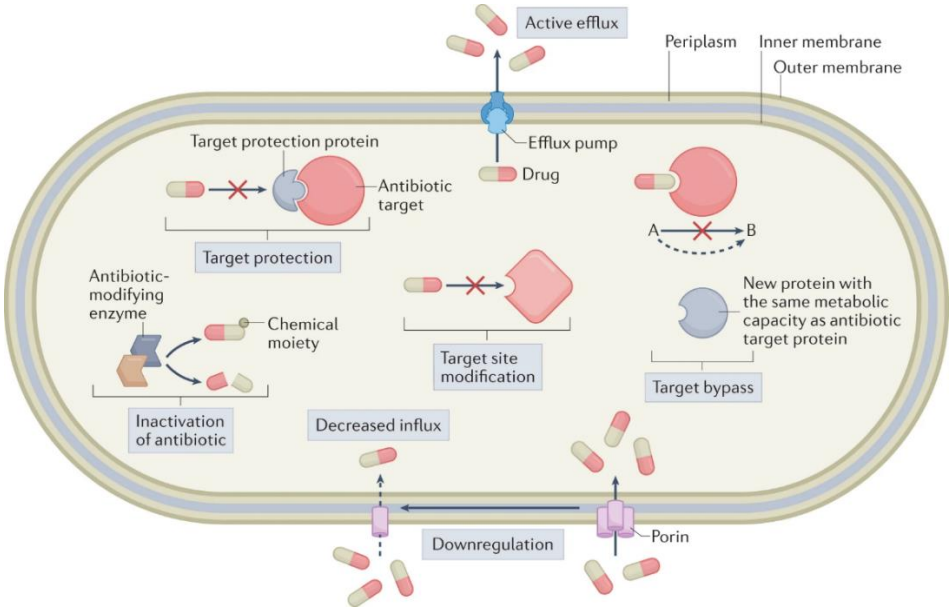


Figure 3 – Overview on selected Mechanisms of Bacterial Resistance against Antibiotics.

Source [31]

There are two processes which lead to generation of resistant bacteria: Mutation and horizontal gene transfer (HGT) between different bacterial cells. Bacteria which have acquired traits and characteristics to withstand a hostile environment are favoured in their growth due to natural selection. Since bacteria have a rather short generation time, random, but effective, mutations are likely to occur. Point mutations resulting in target alteration can already reduce the binding affinity of an antibiotic to its bacterial target, thereby conferring resistance [32]. Mutations in penicillin-binding proteins (PBP) in *Escherichia coli* (*E. coli*) are associated with decreased susceptibility to β-lactam antibiotics [31]. Via HGT, genetic information can be transferred between different bacterial cells. This can be achieved by conjugation, natural transformation (integration of naked DNA) and phage-mediated transduction [32]. During conjugation close cell-to-cell contact is formed and genetic information (mobile genetic elements (MGE): plasmids, transposons, integrons) is shared between two bacterial cells [33]. These mechanisms are highly effective in transferring resistance genes and thereby play a crucial role in bacterial defence evolution [32]. In addition to these genetic mechanisms, bacteria also use cellular mechanisms for the protection against antibiotics. These include the formation of biofilms and persister cells that reside and rest within a biofilm [31]. This principle has been observed for tuberculosis and leprae [29]. MDR bacteria often utilise a combination of several resistance mechanisms [31].

3.2.3. EUCAST (European Committee on Antimicrobial Susceptibility Testing)

Categorisation of a certain microorganism as susceptible or resistant to a specific antibiotic is determined using clinical breakpoints defined by EUCAST. Antimicrobial susceptibility testing (AST) determines the minimum inhibitory concentrations (MIC) of an antibiotic required for the inhibition of bacterial growth. EUCAST clinical MIC breakpoint tables are updated annually und published online on the EUCAST webpage [33]. This information is also provided in the SmPC (Summary of Product Characteristics) of antibacterial medicinal products.

3.3. AMR – The Silent Pandemic

AMR is a major issue for the public health and is often referred to as 'silent pandemic'. However, increasing numbers of AMR-associated deaths and the emergence of AMR raise awareness on this important health issue. The EC called for 'urgent action on AMR' and set AMR as top priority for the Commission in connection with the campaign on the European Antibiotic Awareness Day (EAAD) [1]. As depicted in Figure 4, globally 4.29 million deaths per year are associated with resistant bacteria, of which 1.27 million deaths are directly attributed to resistant bacteria [8]. AMR was recognised by HERA as one of three high impact health threats [9].

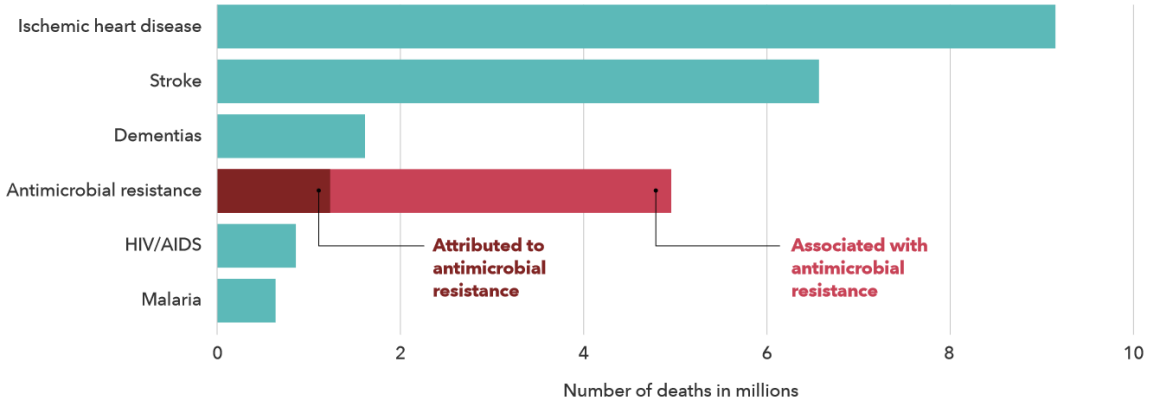


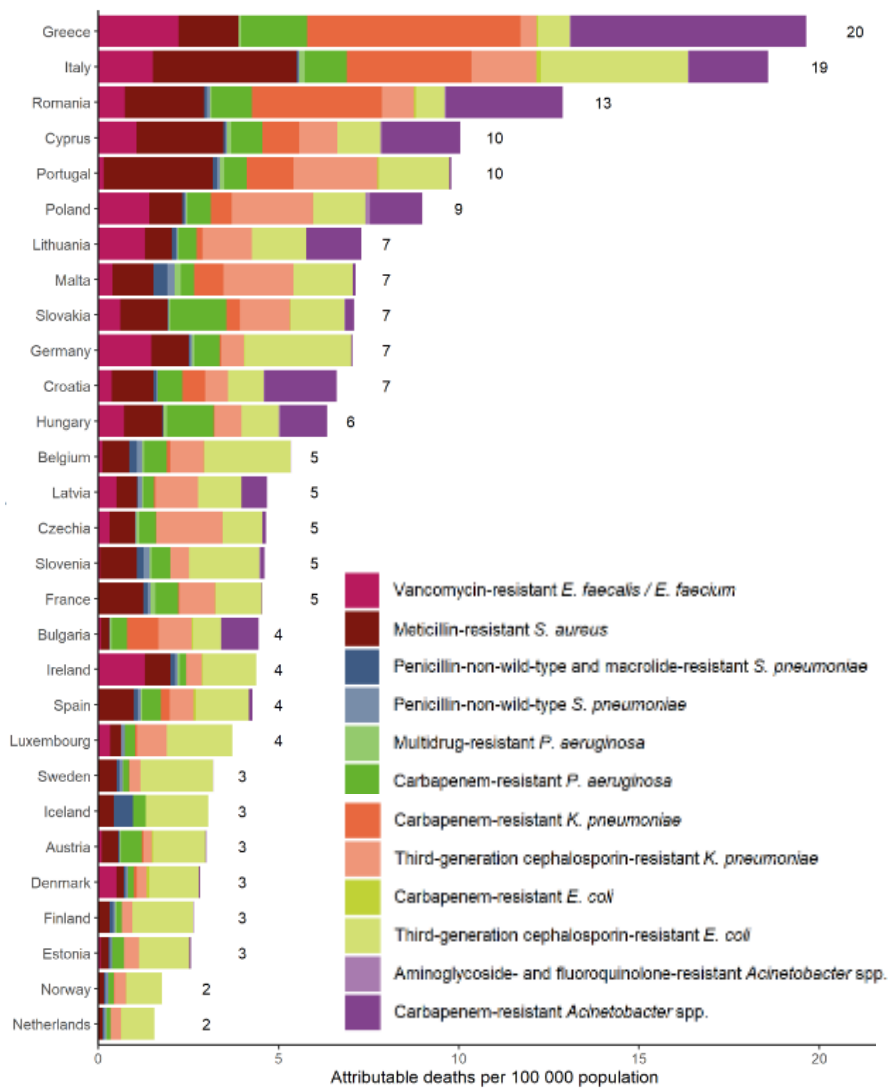
Figure 4 - Global AMR-attributable and -associated deaths compared to other deaths in 2019.

Source [34]

According to an ECDC report on the health burden of infections with antibiotic-resistant bacteria in the EU/EEA, every year 35,000 deaths are associated with infections by resistant bacteria [7]. The AMR-associated costs for the healthcare system of the EU/EEA are estimated at €1.5 billion per year [13]. The ECDC report on 'Assessing the health burden of infections with antibiotic-resistant bacteria in the EU/EEA, 2016-2020' estimates the burden of infection of certain antibiotic-resistant bacteria by linking the infection caused by these pathogens to attributable deaths per 100,000 population by country in the EU/EEA. Figure 5 presents the data from the report for the year 2020 [7]. The number of attributable deaths varies greatly among pathogens and among countries, indicating that the topic of AMR is very diverse. Therefore, national measures against AMR are required to be specifically tailored to the needs of each country. However, the overall target of fighting AMR is still to be considered on an international One Health approach.

Figure 5 - Estimations of the burden of infections with antibiotic-resistant bacteria per country in the EU/EEA in 2020 [attributable deaths per 100 000 population].

Source [7]



The unavailability of traditional antibiotics due to supply shortages, especially for the treatment of infections in children, brings further attention to the fragile system of antimicrobials, and more specifically antibiotics.

Most recently, the review of the pharmaceutical legislation in the EU was communicated. The topic of AMR is specifically addressed in the communication from the EC on the 'Reform of the pharmaceutical legislation and measures addressing antimicrobial resistance' and the 'Council Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach' [2, 35]. The main topics of the EU pharmaceutical strategy to tackle AMR are: 1. More restrictive use of antimicrobial agents; 2. The availability of antibiotics; 3. Addressing AMR globally; 4. Funding of research and technological innovation into AMR [13].

3.3.1. Status Quo of AMR in the EU/EEA

In the recently published annual epidemiological report on antimicrobial resistance in the EU/EEA for 2022 by the EARS-Net (European Antimicrobial Resistance Surveillance Network), the AMR situation was analysed based on bacteria retrieved from blood or cerebrospinal fluid samples in EU/EAA member states. The data collected and reported via national surveillance systems of EU/EEA member states is used to address AMR under coordination of the ECDC. The focus of the EARS-Net AMR surveillance activity is on invasive isolates of eight key bacterial species (*E. coli*, *Klebsiella pneumoniae* (*K. pneumoniae*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Acinetobacter* species, *Streptococcus pneumoniae* (*S. pneumoniae*), *S. aureus*, *Enterococcus faecalis* (*E. faecalis*) and *Enterococcus faecium* (*E. faecium*)). The following detection frequencies were obtained in 2022 for the EU/EEA: *E. coli* 39.2%, *S. aureus* 22.1%, *K. pneumoniae* 12.3%, *E. faecalis* 8.2%, *P. aeruginosa* 6.1%, *E. faecium* 5.9%, *S. pneumoniae* 3.7% and *Acinetobacter spp.* 2.5% [36]. A summary of the analysed data from 2022 is depicted in Table 1. The table is adapted from the above mentioned report and shows incidences of various resistant bacteria ([36]). Percentages are calculated as population-weighted mean in order to compensate for the issue that the total number of reported isolates by country might not reflect population size. Comparing the trend data (2018-2022) obtained for the different species over time, it is apparent that the overall rate of AMR tends to decrease, although remaining at high levels. However, for carbapenem-resistant *K. pneumoniae*, piperacillin-tazobactam resistant *P. aeruginosa*, penicillin non-wild-type and macrolide-resistant *S. pneumoniae*, and vancomycin- resistant *E. faecium* an overall increase of population-weighted mean AMR is observed. Of note, there is a wide variability in AMR percentages across EU/EAA countries for 2022. This might be due to the fact that infection prevention and control (IPC) strategies were successfully implemented by some countries, which could be an opportunity for other countries to follow their lead [36].

Data obtained for MRSA, third-generation cephalosporin-resistant *E. coli* and carbapenem-resistant *K. pneumoniae* were further analysed in the report since these resistant bacteria are specifically considered in the 'Council Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach' as with recommended targets for antimicrobial consumption (AMC) and AMR. The Council recommends to reduce the

total incidence of bloodstream infections with MRSA by 15%, third-generation cephalosporin-resistant *E. coli* by 10% and carbapenem-resistant *K. pneumoniae* by 5% until 2030 compared to the baseline year of 2019 [2]. Table 2 presents the analysed data in the EARS-Net report as estimated total incidences of bloodstream infections with special focus on the bacteria addressed by the Council Recommendation. As this defines 2019 as baseline year, the respective numbers are highlighted in bold in Table 2. Trend data suggests that incidences for MRSA and *E. coli* are decreasing. However, for carbapenem-resistant *K. pneumoniae* a strong increase is observed. This rather concerning increase in combination with the great variance of population-weighed percentages (0.0% in Finland to 72.0% in Greece) for carbapenem-resistant *K. pneumoniae* shows that further actions need to be taken to address the issue of AMR in the future [36].

Table 1 - Isolates with AMR phenotype in the EU/EEA [%], by bacterial species and antimicrobial group/agent, population-weighted EU/EEA mean and trend (2018–2022).

Adapted from [36]

Bacterial species	Antimicrobial group/agent resistance	2018 [%]	2019 [%]	2020 [%]	2021 [%]	2022 [%]	2022 EU/EEA range [%]	Trend 2018–2022
Escherichia coli	Aminopenicillin (amoxicillin/ampicillin) resistance	57.0	56.6	54.6	53.1	53.4	32.5–68.6	↓
	Third-generation cephalosporin (cefotaxime/ceftriaxone/ceftazidime) resistance	15.7	15.6	14.9	13.8	14.3	5.8–40.2	↓
	Carbapenem (imipenem/meropenem) resistance	0.1	0.3	0.2	0.2	0.2	0.0–1.5	-
	Fluoroquinolone (ciprofloxacin/levofloxacin/ofloxacin) resistance	26.4	24.7	23.8	21.9	22.0	9.9–46.4	↓
	Aminoglycoside (gentamicin/netilmicin/tobramycin) resistance	11.2	10.8	10.9	9.6	9.7	4.4–24.3	↓
	Combined resistance to third-generation cephalosporins, fluoroquinolones, and aminoglycosides	6.4	6.1	5.7	5.1	5.1	1.5–14.2	↓
Klebsiella pneumoniae	Third-generation cephalosporin (cefotaxime/ceftriaxone/ceftazidime) resistance	34.4	34.1	33.9	34.3	32.7	3.1–78.5	↓
	Carbapenem (imipenem/meropenem) resistance	8.5	9.0	10.0	11.6	10.9	0.0–72.0	↑
	Fluoroquinolone (ciprofloxacin/levofloxacin/ofloxacin) resistance	34.3	34.0	33.9	33.6	32.0	5.7–78.7	↓
	Aminoglycoside (gentamicin/netilmicin/tobramycin) resistance	24.7	24.5	23.7	23.7	22.5	0.0–67.9	↓
	Combined resistance to third-generation cephalosporins, fluoroquinolones, and aminoglycosides	21.6	21.5	21.0	21.2	20.0	0.0–66.2	↓
Pseudomonas aeruginosa	Piperacillin-tazobactam resistance	18.5	18.6	18.8	18.7	19.3	3.8–50.5	↑
	Ceftazidime resistance	15.5	15.7	15.5	15.7	16.2	2.1–56.6	-
	Carbapenem (imipenem/meropenem) resistance	18.8	18.1	17.9	18.1	18.6	2.4–53.9	-
	Fluoroquinolone (ciprofloxacin/levofloxacin) resistance	21.2	20.5	19.6	18.7	18.6	2.8–49.2	↓
	Aminoglycoside (gentamicin/netilmicin/tobramycin) resistance	12.9	12.6	9.4	8.9	8.9	0.0–42.2	NA
	Combined resistance to ≥3 antimicrobial groups (among piperacillin-tazobactam, ceftazidime, carbapenems, fluoroquinolones and aminoglycosides)	14.1	13.5	13.6	12.6	13.4	0.0–47.7	NA
***Acinetobacter* species**	Carbapenem (imipenem/meropenem) resistance	36.4	36.9	37.9	39.9	36.3	1.0–98.6	-
	Fluoroquinolone (ciprofloxacin/levofloxacin) resistance	41.1	40.9	41.7	43.0	38.8	0.0–98.6	-
	Aminoglycoside (gentamicin/netilmicin/tobramycin) resistance	35.2	36.9	37.0	39.6	34.1	0.0–96.2	-
	Combined resistance to carbapenems, fluoroquinolones and aminoglycosides	32.4	33.6	34.0	36.8	31.8	0.0–96.2	-
Staphylococcus aureus	MRSA	17.8	17.2	16.7	15.8	15.2	1.1–50.8	↓
Streptococcus pneumoniae	Penicillin non-wild-type	14.0	13.2	15.5	16.2	16.3	2.8–46.7	↑
	Macrolide (azithromycin/clarithromycin/erythromycin) resistance	16.6	15.9	16.8	18.3	17.9	3.4–36.1	↑
	Combined penicillin non-wild-type and resistance to macrolides	8.6	8.0	8.9	9.8	9.7	0.8–33.3	↑
Enterococcus faecalis	High-level gentamicin resistance	27.1	25.3	29.0	28.9	25.3	6.7–100.0	-
Enterococcus faecium	Vancomycin resistance	16.2	17.7	16.8	17.2	17.6	0.0–67.7	↑

Table 2 - Estimated total incidence of bloodstream infections (number per 100 000 population); trend (2018–2022); change 2019–2022 [%], by bacterial species and antimicrobial group/agent, EU/EEA.

Adapted from [36]

Bacterial species	Antimicrobial group/agent resistance	Estimated incidence of isolates from bloodstream infections with resistance phenotype (number per 100 000 population)						
		2018	2019 (baseline year)	2020	2021	2022	Trend 2018–2022	Change 2019–2022 (%)
Staphylococcus aureus	MRSA	5.80	**5.63**	5.41	4.76	4.94	↓	**-12.2**
Escherichia coli	Third-generation cephalosporin (cefotaxime/ceftriaxone/ ceftazidime) resistance	10.10	**10.42**	8.69	7.54	8.67	↓	**-16.8**
Klebsiella pneumoniae	Carbapenem (imipenem/meropenem) resistance	1.87	**2.18**	3.18	3.70	3.26	↑	**+49.7**

3.3.2. WHO Priority Pathogens

The findings described for the EU/EAA correlate with a report published in 2017 by the WHO which gives recommendations on prioritisation of research and development on antibiotics against critical drug-resistant bacterial infections [37]. *M. tuberculosis*, the causative agent of tuberculosis, is on top of this list (incl. multi- and extensively drug-resistant strains). Additionally, this report ranks resistant bacteria of concern into three different priority categories (i.e. critical, high, medium) which is summarised in Table 3. Bacteria ranked with critical priority are Gram-negative MDR bacteria that cause severe infections (bloodstream infections and pneumonia) [37]. These infections are especially of concern since they are associated with healthcare-associated infections and show increased mortality and morbidity [38]. In consensus with the 'Council Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach' *E. coli* and *K. pneumoniae* are considered of critical priority. However, MRSA is only of high priority according to the WHO list.

Table 3 - WHO Priority Pathogens Categorisation.

Adapted from [37]

Critical priority	○ *Acinetobacter baumannii,* carbapenem-resistant; ○ *Pseudomonas aeruginosa,* carbapenem-resistant; ○ *Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant; e.g. *Klebsiella spp.*, *E. coli*, *Serratia spp.*, and *Proteus spp.*
High priority	○ *Enterococcus faecium,* vancomycin-resistant; ○ *Helicobacter pylori,* clarithromycin-resistant; ○ *Salmonella spp.,* fluoroquinolone-resistant; ○ *S. aureus,* vancomycin-resistant, methicillin-resistant; ○ *Campylobacter spp.,* fluoroquinolone-resistant; ○ *Neisseria gonorrhoeae,* 3rd generation cephalosporin-resistant, fluoroquinolone-resistant.
Medium priority	○ *Streptococcus pneumoniae,* penicillin-non-susceptible; ○ *Haemophilus influenzae,* ampicillin-resistant; ○ *Shigella spp.,* fluoroquinolone-resistant.

3.3.3. WHO AWaRe Classification of Antibiotics

In 2017, the WHO published the AWaRe (Access, Watch, Reserve) classification which classifies antibiotics into three categories, i.e. Access, Watch and Reserve. This list is updated every two years [39, 40]. The antibiotics are categorised based on clinical relevance and possible influence on increased AMR emergence. Antibiotics belonging to the Access classification are narrow-range antibiotics with few side-effects, e.g. amoxicillin and ampicillin [40]. Watch antibiotics exert a broader range and are recommended for more severe infections, including infections with pathogens that are likely to be resistant to Access antibiotics. Examples for Watch antibiotics are azithromycin and ciprofloxacin. Reserve antibiotics are strictly limited as last-choice antibiotics and should only be used to treat confirmed MDR bacterial infections [39–41]. Many of the listed antibiotics are effective against infections caused by pathogens classified as critical or high priority pathogens according to the WHO Priority Pathogens List described above [37]. Examples are cefiderocol and colistin which can be used for the treatment of carbapenem-resistant *Enterobacteriaceae* [40]. The AWaRe classification is intended as a tool assisting the monitoring of antibiotic consumption and prescription, thereby ultimately functioning as a read-out and measure for the

effectiveness of antibiotic stewardship programmes which aim to promote prudent antibiotic use [42]. Moreover, WHO declared that 60% of globally consumed antibiotics should belong to the Access class. The WHO published 'The WHO AWaRe (Access, Watch, Reserve) antibiotic book' in 2022 which gives further clinical guidance and recommendations on antibiotic treatment options and prescriptions to further promote prudent use of antibiotics [41].

3.3.4. Challenges in Antibiotic Therapy

3.3.4.1. Reasons for Emergence of AMR

As explained in the previous chapters, bacterial mechanisms of acquisition of resistance are versatile. A major driver of AMR is the presence of large amount of antibiotics in the environment due to antibiotic overuse and misuse, exerting selection pressure on bacteria [43]. This includes the use of antibiotics against infections which are not susceptible to the antibiotic (e.g. virus infections) or using too low doses or too short durations in the treatment of bacterial infections. The lack of compulsory prescription of antimicrobial agents in some countries outside the EU further increases the potential for overuse and misuse of antibiotics. This is accompanied by with the use of falsified medicines which can, for example, contain too low doses of the declared active substances [29].

Environmental contamination with antibiotics due to use as growth stimulant and for prevention of infections in agriculture is a huge factor leading to increased AMC and AMR [43]. Although the use as animal growth enhancer is prohibited in Europe, consumption of antibiotics in food-producing animals is still a major issue [43]. It is estimated that antimicrobial use in food-producing animals accounts for 73% of global antimicrobial sales [44]. According to a joint report by EDCD, EFSA (European Food Safety Authority), EMA, and OECD (Organisation for Economic Cooperation and Development) on antimicrobial resistance in the EU/EEA, AMC in food-producing animals decreased by 43% between 2011 and 2020 [45]. This is an important trend, since a clear correlation was established between resistance in bacteria from humans, resistance in bacteria from food-producing animals and AMC in animals as determined in the 'Third joint inter-agency report on integrated analysis of consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals in the EU/EEA' (JIACRA III) by ECDC, EFSA and EMA [46]. This was further confirmed in the recently published JIACRA IV report on 2019-

2021 (February 2024). Key findings of this report include decreased AMR in countries that reduced AMC in humans and animals and a correlation between increased susceptibility of *E. coli* to antibiotics in humans and animals and decreased overall AMC [47, 48]. Human antibiotic consumption is analysed in the 'Annual Epidemiological Report for 2022' on 'Antimicrobial consumption in the EU/EEA' published by the ECDC and based on data reported to the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) [42]. This report evaluates the mean total consumption (i.e. community plus hospital sectors) of antibacterials for systemic use, corresponding to the ATC group J01. Considering the data from 2019 (baseline year according to the 'Council Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach' [2]), the decrease in mean total consumption of antibacterials for systemic use is only 2.5%. The overall consumption between 2013 and 2022 in the EU/EEA decreased by 10% [42]. Figure 6 (adapted from the mentioned report) shows the community consumption of antibiotics for systemic use in the EU/EEA for 2022 as population-weighted mean determined as DDD (defined daily doses) which estimates the proportion of the population treated daily with antimicrobials. A DDD per 1,000 inhabitants per day of overall consumed antibiotics for systemic use of 19.4 was determined for the EU/EEA in 2022. As shown in Figure 6, the determined DDD for antibiotics consumed within the community sector showed wide variation between countries: from 9.1 DDD in the Netherlands to 33.5 DDD in Cyprus. This great variance is further emphasised when comparing the relative change (2019-2022) of total antibiotic consumption: e.g. -14.9% for Finland, and +24.1% for Bulgaria. Also of concern is the fact that an increased use of broad-spectrum antibiotics was determined between 2013 and 2022 [42].

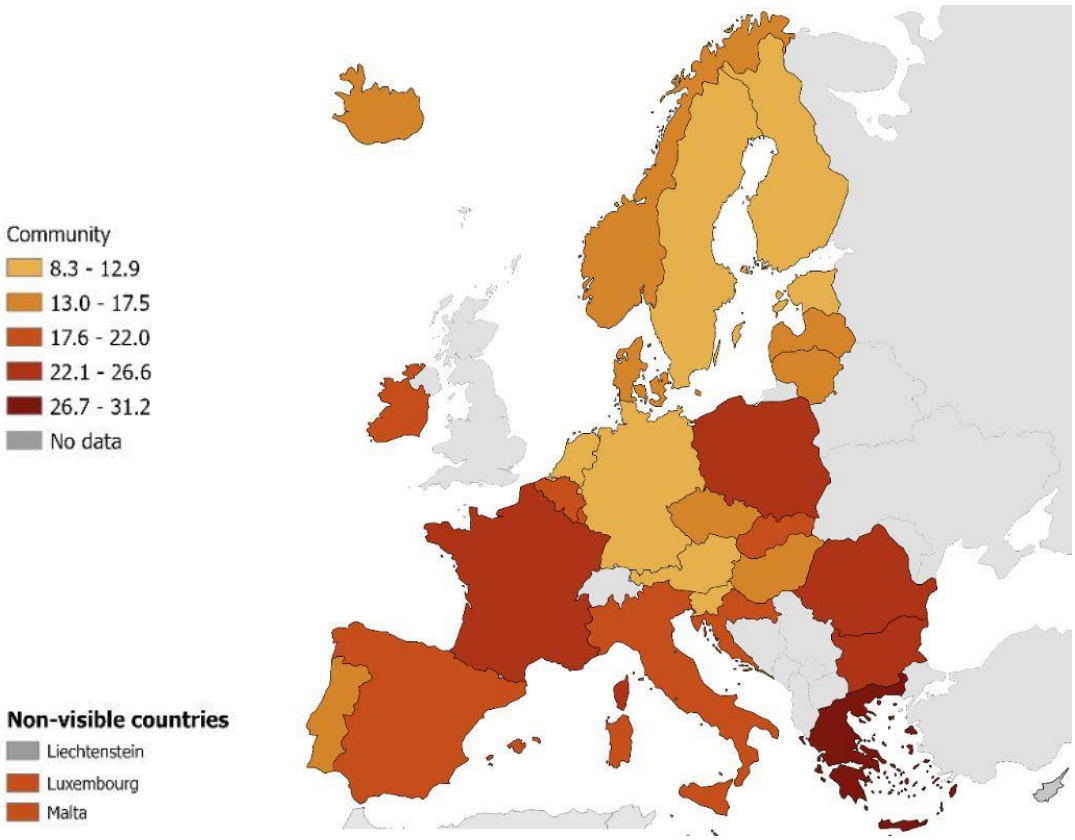


Figure 6 - Community consumption of antibacterials for systemic use (ATC group J01), EU/EEA countries, 2022 (expressed as DDD per 1 000 inhabitants per day).

Source [42]

3.3.4.2. Availability of Antibiotics

Overuse and misuse of antibiotics and the resulting emergence of AMR, are accompanied by a constant need for new therapeutic alternatives for bacterial infections. However, traditional effective antibiotics are subject to limited availability as well. Currently, the EMA shortages catalogue lists a shortage for amoxicillin and amoxicillin/clavulanic acid in various presentations [20]. On a national level for Germany, shortages are listed via the PharmNet.Bund Portal for all medicinal products authorised in Germany (excluding vaccines) which is hosted by BfArM. As of 28th February 2024, there are 97 notifications on ongoing shortages listed for systemic antibiotics (ATC Code J01xx) [21]. Due to a significantly increased demand for antibiotics since autumn 2022 and resulting critical supply shortages especially for paediatric formulations, the Federal Ministry of Health (*Bundesministerium für Gesundheit*, BMG) announced a critical supply shortage situation for syrups containing antibiotics for children on 25th April 2023 for Germany ("*Versorgungsmangel*" according to § 79(5) Medicinal Products Act ("*Arzneimittelgesetz*", AMG)). Since this critical

situation is observed for almost all EU member states and also internationally, compensation via importation is limited [49]. Of note, shortages of classic (generic) antibiotics are not only due to increased demand, but are influenced by several factors. Issues are, for example, unsecure supply chains relying on only few manufacturers and market withdrawals due to commercial reasons. As a result of unavailable narrow-spectrum antibiotics, the use of broad-spectrum antibiotics is increased. Considering newly approved antibacterials, there is a delay between authorisation and market launch. Moreover, distribution within EU member states varies [50]. This is confirmed by vfa (*Verband Forschender Arzneimittelhersteller e.V.*). According to the information provided, several newly authorised antibacterial products are, however, not yet commercialised (as of 2022/2023) [51].

3.3.4.3. Need for New Antimicrobial Substances

The fact that AMR is rising and it is estimated that by 2050 10 million deaths per year are linked to AMR, makes the need for new antimicrobials apparent [52]. Considering that not only the effectiveness of traditional antibiotics is decreasing due to emerging AMR, but also availability of classical treatment options is limited due to supply shortages, the need for novel therapeutics is further highlighted. Antibiotic treatment is crucial for the positive outcome of several standard medical treatments, such as surgeries, cancer chemotherapy, and transplantations [53]. Since there is a constant race between new antibacterial agents and acquired bacterial resistances from an evolutionary point of view, new strategies are required to target bacterial pathogens in the future.

Limited completely new classes of antibiotics were discovered in the last ten years. Most newly developed antibacterial substances are similar to the already available antibiotics and only differ by certain chemical adaptations [54]. However, with evolving technical improvements such as the use of artificial intelligence and new genetic opportunities (e.g. CRISPR-CAS), research on new antibacterial strategies is rising. Using artificial intelligence for the detection of new antimicrobial substances and possible targets is straightforward and will enhance and assist in AMR research [55].

The following chapters will discuss the current status of antibacterial medicinal products (new MAs and ((pre-)clinical development) and promising research areas for future antibiotic substances. Furthermore, since pharmaceutical R&D and the process of obtaining and

maintaining a marketing authorisation are a highly complex and costly processes, regulatory measures intended to foster R&D, access and supply are described and evaluated.

4. Results and Discussion

4.1. New Approaches in Research and in Legislative Challenges

4.1.1. New MAs since 2017

Using the Cortellis RIR tool, all centrally authorised MAs of the last ~7 years (EC opinion from 2017 until February 2024) were extracted. Using the filters described in 2.2.1 all MAs were identified, which were either indicated for the systemic treatment of bacterial infections or for the prevention of bacterial infection (i.e. vaccines). The whole extract from Cortellis is shown in Annex I, a summary is presented in Table 4. In total 19 MAs were identified that have been authorised via the central procedure since 2017:

- thirteen complete MAs,
- one hybrid MA;
- three generic MAs;
- two fixed combination MA:
    - one MA with one known active substance in combination with one new active substance;
    - one MA with one known active substance in combination with two new active substance;
- thirteen MAs with new active substances,
- seven biologics,
- five MAs indicated for immunisation;
- twelve MAs have a paediatric indication;
- three MAs have an orphan designation;
- no MA was eligible for PRIME;
- one MA was conditionally approved;
- one MA was approved under exceptional circumstances;
- one MA has just obtained a positive CHMP opinion, with pending EC decision.

Most newly authorised antibacterials are classified as Reserve or Watch according to the WHO Classification list which is coloured in Table 4 accordingly (Access: n=1; Watch: n=3; Reserve: n=7).

The identified MAs can be classified into the following groups: (1) antibacterial agents (ATC J01xx); (2) antibiotics against mycobacteria (ATC J04xx); (3) agents targeting a bacterial toxin (ATC J06xx); and (4) vaccines against bacteria (ATC J07xx).

Of the identified MAs, only vaborbactam represents a new antibiotic class since it classifies as beta-lactamase inhibitor belonging to the new class of cyclic boronates [56]. Lefamulin is the first systemically administered pleuromutilin approved for humans, but topical formulations have been used in humans before. Moreover, it has been used in veterinary medicine [54, 57].

Table 4 - New MAs (CP) for Antibiotics since 2017 and WHO AWaRe Classification of antibacterial for systemic use.

Legend: green = Access; yellow = Watch; orange = Reserve.

ATC Code	Antibiotic Name	Active Substance	MA Date
J01 ANTIBACTERIALS FOR SYSTEMIC USE			
J01DE51	Exblifep	cefepime dihydrochloride monohydrate, enmetazobactam	CHMP Opinion: 25/01/2024
J01DH03	Ertapenem Sun	ertapenem	15/07/2022
J01GB06	Arikayce liposomal	amikacin sulfate	27/10/2020
J01XX12	Xenleta	lefamulin acetate	27/07/2020
J01DI04	Fetcroja	cefiderocol sulfate tosilate	23/04/2020
J01AA12	Tigecycline Accord	tigecycline	17/04/2020
J01DH56	Recarbrio	imipenem monohydrate, cilastatin sodium, relebactam monohydrate	13/02/2020
J01MA23	Quofenix	delafloxacin meglumine	16/12/2019
J01GB01	Vantobra	tobramycin	18/02/2019
J01DH52	Vaborem	meropenem trihydrate, vaborbactam	20/11/2018
J01AA13	Xerava	eravacycline	20/09/2018
J01XX09	Daptomycin Hospira	daptomycin	22/03/2017
J04 ANTIMYCOBACTERIALS			
J04AK08	Dovprela	pretomanid	31/07/2020

ATC Code	Antibiotic Name	Active Substance	MA Date
J06 IMMUNE SERA AND IMMUNOGLOBULINS			
J06BB22	Nyxthracis	nyxthracis	18/11/2020
J06BB21	Zinplava	bezlotoxumab	18/01/2017
J07A BACTERIAL VACCINES			
J07AL02	Prevenar 20	pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed)	14/02/2022
J07AL02	Vaxneuvance	pneumococcal polysaccharide conjugate vaccine (adsorbed)	13/12/2021
J07AH08	MenQuadfi	meningococcal group A, C, W-135 and Y conjugate vaccine	18/11/2020
J07AE02	Vaxchora	vibrio cholerae, strain cvd 103-hgr, live	01/04/2020
J07AH09	Trumenba	meningococcal group B vaccine (recombinant, adsorbed)	24/05/2017

MAAs for antibiotics *per se* do not fall under the mandatory scope of the central procedure (Article 3(1) of Regulation (EC) No 726/2004 [58]), unless they obtain an orphan designation. They can fall under the optional scope (Art. 3(2) of Regulation (EC) No 726/2004) in the context of a new active substance (Art. 3(2a)), or if the "*…medicinal product constitutes a significant therapeutic, scientific or technical innovation…*" (Art. 3(2b)) [58]. Moreover, generics of centrally authorised MAs are also covered by the optional scope of the CP. The national MA database of Germany (AMIce) was screened for new MAs from January 2017 until February 2024. No MAs authorised via MRP/DCP/purely national procedure with ATC Code J01/J04/J06/J07 containing new active substances were identified. This possibly indicates that for novel antibiotics most likely CP is chosen.

According to the information from EMA website on 'Applications for new human medicines under evaluation by the CHMP' (Feb 2024), one MAA with the therapeutic area antibacterials for systemic use and one meningococcal vaccine are currently under evaluation (as of February 2024) (Annex II) [17]. One medicinal product (Exblifep) obtained a positive CHMP opinion only very recently on 25th January 2024. The EC decision is still pending (as of 28/02/2024) [59].

4.1.2. (Pre-) Clinical Development

Ongoing and completed clinical trials which are/were conducted in the EU/EEA can be searched in the two European Databases (1) EU Clinical Trials Register (for trials under the

Clinical Trials Directive (CTD) 2001/20/EC [60]) and in (2) CTIS (Clinical Trials Information System) for trials under the Clinical Trials Regulation (CTR) ((EU) No 536/2014 [61]) [18, 19]. The EU Clinical Trials Register does not contain information on phase I trials, unless they are part of an agreed PIP (paediatric investigation plan). Moreover, the Register contains information on all clinical trials under the CTD from 1st May 2004 onwards, and also on trials conducted outside the EU/EEA if they are part of a PIP. Unfortunately, the limited filter features provided in the EU Clinical Trials Register Search engine, rendered a search for clinical trials with novel antibiotics unfeasible. Therefore, data on products in the clinical pipeline obtained from other sources (vfa [51], WHO Report on '2021 Antibacterial agents in clinical and preclinical development' [54] and others [62, 63]) was verified using the search for the exact name of the investigational medicinal product (IMP).

CTIS only contains information on new clinical trials under the CTR from 31st January 2022 and information on transitioned clinical trials under the CTD.

In CTIS 27 clinical trials with the therapeutic area 'Diseases [C] – bacterial infections and mycoses [C01]' were identified (as of 01/03/2024). Only three of those studies investigate the effect of new active substances or combinations with known active substances:

- (1) A Phase I study on a combination of ceftibuten (CTB) and PF-07338233 (avibactam prodrug) on bioavailability (authorised, not yet started, EUCT number 2023-507117-10-00 [64]);
- (2) a Phase II study to describe the safety and immunogenicity of a multivalent pneumococcal conjugate vaccine in healthy toddlers (authorised, started, EUCT number:2023-505154-18-00 [65]);
- and (3) a Phase II study to evaluate efficacy, safety, tolerability of CAL02 (a novel antitoxin liposomal agent) in patients (authorised, started, EUCT number:2022-502049-91-00 [66]).

A recently (2022) published report by the WHO on '2021 Antibacterial agents in clinical and preclinical development: an overview and analysis' summarises the global activities on R&D on new antibiotics over the past years (2017- 1st November 2021) [54]. In total, 80 antibiotics in the global clinical pipeline were identified. Of these, 46 substances are considered

as traditional antibiotics, and 34 substances belong to the class of non-traditional antibiotics, such as microbiome-modulating agents or bacteriophages. Most up-to-date and interactive data on the clinical pipeline can be retrieved from an WHO Global Observatory on Health R&D online tool [67]. Of the 46 traditional antibacterials, 28 candidates target WHO priority list pathogens, 13 target *M. tuberculosis,* and 5 target *Clostridium difficile (C. difficile)*. Similar to the newly authorised antibacterials, also the antibacterials which are in clinical development mostly belong to already established antibiotic classes. One of these substances has filed for a MAA at EMA in the meantime and obtained a positive EMA opinion only very recently on 25th January 2024 (Exblifep) [59]. Of the 34 non-traditional antibacterials, 21 candidates target WHO priority list pathogens, 1 targets *M. tuberculosis,* and 12 target *C. difficile* [67].

The aforementioned WHO report also summarises the pre-clinical developments on a global level [54]. Of a total of 217 agents which are currently under development (Figure 7), the majority comprises direct acting small molecules (41.5%). However, research on antimicrobial peptides (AMPs) and bacteriophage approaches covers the second (15.2%) and third (12.9%) largest groups, respectively [68]. These novel antibacterials are presented in more detail in the following sections.

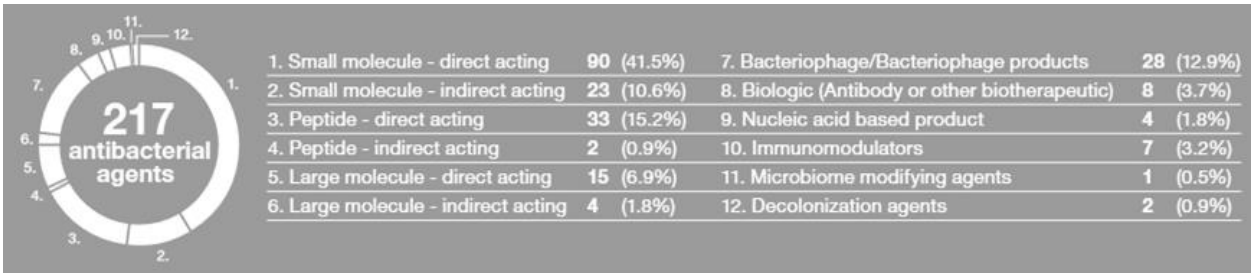


Figure 7 - Categorisation of Antibiotics in Pre-clinical Development.

Source [68]

The development of antibacterial agents is accompanied by several challenges. The first hurdle is the identification of a promising lead compound, which is followed by the just as challenging second step, i.e. compound optimisation to increase antibacterial activity, safety and tolerability. Optimisation of antibacterial activity has to be achieved without negatively affecting the bacterial cell penetration of the investigated substance or susceptibility to bacterial efflux pumps. Moreover, the relatively high blood levels of antibacterials which are required to inhibit bacterial growth and to prevent the occurrence of resistance

during treatment, are accompanied by issues with safety and tolerability [69, 70]. Mimicking the *in vivo* cellular environment during infection in *in vitro* models is challenging as the cellular environment can greatly influence bioactivity of an antibacterial compound [70]. Ultimately, promising antibacterial candidates should show high *in vivo* efficacy against a broad spectrum of pathogens with only minimal harmful effects to human targets [71]. The development of novel antibacterials face even further challenges due to their diverse mode of action. Alternative *in vitro* models are typically required and the suitability of current *in vivo* models is still to be determined. In addition, usually standard validated preclinical pharmacokinetic (PK) and pharmacodynamic (PD) models cannot be applied for novel antibacterials [72].

4.1.3. Novel Approaches for Antibacterial Treatment

Several new approaches in the fighting of bacterial infections in times of increasing AMR are currently investigated (Figure 8). In the following chapters bacteriophages, AMPs (antimicrobial peptides), antibodies and antibody–antibiotic conjugates (AACs), antisense-based antimicrobials and microbiome-modulating therapeutics are presented in more detail. In comparison to traditional antibiotics, the structural diversity of the novel approaches tends to be more complex [73]. Nevertheless, the increasing number of potential targets might help to overcome the issue of AMR in the future.

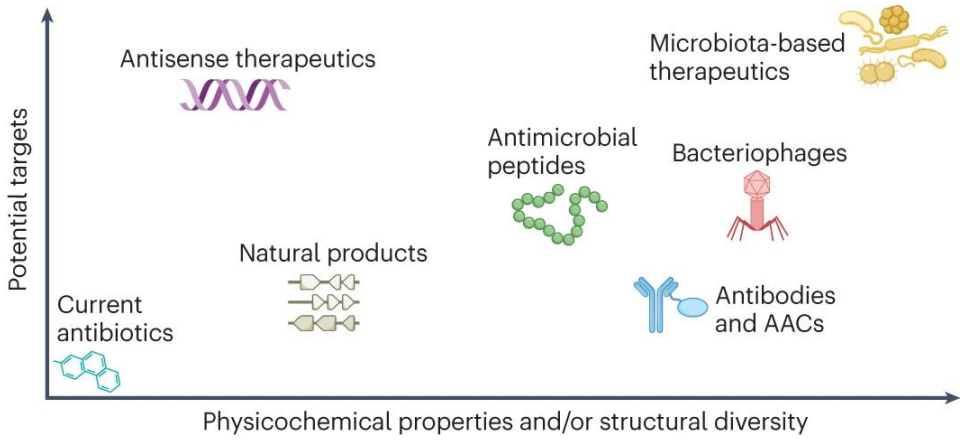


Figure 8 - Alternative antibiotic agents with different complexity.

Adapted from [73]

4.1.3.1. Bacteriophages and Phage-derived Enzymes

Bacteriophages are viruses that infect bacteria. They attach to the bacterial surface and inject their genetic material into the bacterial cell. The bacterial machinery is hijacked, thereby producing phage components which are assembled and released from the bacterial cell upon phage-triggered lysis. The newly synthesised phage progeny can then infect further bacterial cells. Phages can specifically target certain bacteria, e.g. *S. aureus*, *P. aeruginosa*, *Shigella*, and *Salmonella*. They can be used for the directed treatment of bacterial infections by triggering lysis of only the pathogenic bacteria. Moreover, the phage genetic material could be adapted using genetic engineering techniques. However, there are several drawbacks for potential phage therapy. Since phages are highly specific to bacteria, the susceptibility of the to be targeted bacterial pathogen would need to be determined prior to phage administration. Since testing is time consuming, bacterial cocktails would need to be applied; however, this might decrease efficacy. Moreover, since phages are highly immunogenic, application at individual patient level might be limited to a one-time only approach, since the immune system of the patient would recognise and trigger clearance of phages which are administered for the second time. Factors which are also required to be considered are bacterial resistances to phages or the possible production of endotoxins which could lead to sepsis [74]. Moreover, since tempered phages employ HGT between bacterial cells (contributing to bacterial resistance), only lytic phages should be used for therapy [75]. Phage therapy has been used in Eastern Europe and the former Soviet Union on individual patient level with promising results, but clinical trials have missed to prove efficacy so far [73]. No bacteriophage therapeutic has obtained a MA in the EU yet. This is in part due to issues associated with regards to GMP (Good Manufacturing Practice) and GCP (Good Clinical Practice). In 2015-2017, a first GMP- and GCP-compliant phase I/II clinical trial was conducted in France and Belgium evaluating the efficacy and safety of topical applications of a cocktail of anti-*P. aeruginosa* bacteriophages on infected third-degree wounds compared with standard of care ('PhagoBurn', EudraCT number 2014-000714-65 [76]). The study failed to prove efficacy of the bacteriophage cocktail, mostly likely due to too low levels of mixture applied to the wounds due to stability problems after manufacturing of the bacteriophage cocktail [77].

Although large scale proof of efficacy in clinical use is still to be determined, bacteriophages might nevertheless provide suitable potential for the fighting of bacterial pathogens. This

could be achieved by not using the phage *per se* as antibacterial agent, but utilising the mechanisms by which way they kill bacteria as therapeutic alternatives, i.e. phage-derived enzymes. One example are endolysins which disrupt the bacterial cell wall [73]. The endolysin exebacase has been successfully used in a phase II trial against MRSA when applied on top of standard-of-care antibiotic treatment (EudraCT Number: 2016-003059-31 [78]) [79]. However, a phase III trial did not show efficacy and was stopped for futility following interim efficacy analysis by the DSMB (Data and Safety Monitoring Board) (ClinicalTrials.gov ID NCT04160468) [73, 80].

The relevance of regulatory hurdles for large scale use of bacteriophage therapies were discussed in a workshop organised by EMA ('Workshop on the therapeutic use of bacteriophages') in 2015 [75, 81]. According to Directive 2001/83/EC bacteriophages belong to the class of biological products [82]. However, they do not qualify as ATMPs (Advanced therapy medicinal products) according to Regulation (EC) No 1394/2007 [83]. A change in bacteriophage strain or composition of a phage cocktail would qualify as extension application (Annex I of Commission Regulation (EC) No 1234/2008, Variation Regulation [84]). Similar approaches as for human influenza and corona virus seasonal adaptions were suggested for bacteriophage strain or phage cocktail adaptions (i.e. classification as type II variation rather than as extension application) in order to be more flexible when reacting to newly developing bacterial resistances [75].

The relevance of possible bacteriophage-based treatment options is underlined by the fact that the EMA only recently adopted the new 'Guideline on quality, safety and efficacy of veterinary medicinal products specifically designed for phage therapy' (EMA/CVMP/NTWP/32862/2022) [85].

4.1.3.2. Antimicrobial peptides (AMPs)

AMPs are produced by a wide variety of organisms, including humans, animals and plants. They are considered the first line of defence of the innate immune system and show antimicrobial activity towards bacteria, fungi and viruses [86]. Over 3000 AMPs have been discovered so far [87]. Most AMPs are rather small, i.e. less than 100 amino acids. They act via disintegration of the bacterial cell membrane due to their amphipathic and cationic nature, resulting in bacterial death. Because of this rather unspecific mode of action, they exert

their effect on a broad-spectrum of membranes. Associated with this is an increased toxicity to eukaryotic cells. Moreover, immunogenicity and drug resistance also need to be considered. To overcome possible side effects, it might be promising to (semi)-synthetically synthesise AMPs in order to render these molecules less toxic to eukaryotic cells. By utilising the membrane disintegrative effect of AMPs on bacterial cells, combination therapies of AMPs with classic antibiotics have shown to be effective [86].

Several AMPs are already clinically used for the treatment of bacterial infections, i.e. daptomycin, gramicidin, tyrothricin, colistin, vancomycin, oritavancin and dalbavancin [29, 87]. Both latter AMPs obtained MAs in the EU only quite recently in 2015 (Table 4). Colistin, daptomycin, oritavancin and dalbavancin are all classified as Reserve antibiotics according to the WHO AWaRe Classification. Vancomycin is classified as Watch antibiotic [40]. Gramicidin and tyrothricin are not included in the WHO AWaRe classification list since they are not used for systemic infections, but only applied locally, due to high toxicity [29].

4.1.3.3. Antibodies and Antibody–Antibiotic Conjugates (AACs)

Antibodies designed for antibacterial treatment can neutralise bacteria-secreted toxins or they can directly target the bacterial cell membrane [53]. Two toxin-neutralising antibodies have been recently approved by the EMA, i.e. Nyxthracis (obiltoxaximab, MA November 2020) and Zinplava (bezlotoxumab, MA January 2017) (Table 4). Obiltoxaximab binds the protective antigen of the anthrax toxin of *Bacillus anthracis*, thereby preventing the intracellular entry of the toxin [88]. Bezlotoxumab binds and neutralises *C. difficile* toxin B. Moreover, due to passive immunisation against the toxin, CDI (C. *difficile* infection) recurrence is prevented [89].

Another approach is to link antibiotics to antibodies (AACs). The antibody epitope recognises and binds extracellular bacteria. The AAC-bacteria complex is then taken up by Fc-receptor mediated phagocytosis or via bacterial entry mechanisms into the host cell. Upon cleavage of the antibody-antibiotic link within the phagolysosome, the antibiotic is released and can directly target the bacterium within the host cell. Thereby, side effects on gut microbiota are limited [73]. This has only been investigated in phase I clinical trials so far [90, 91]. AACs have also been designed to target biofilm formation, but this has not been tested in clinical trials yet [90, 92].

4.1.3.4. Antisense-based Antimicrobials

Antisense single-stranded nucleic acid oligomers can bind to complimentary mRNA (messenger ribonucleic acid) sequences [73, 74]. These short antisense oligomers (ASO) can be designed to specifically target and silence essential bacterial genes which leads to inhibition of bacterial growth. Increased stability is achieved by linking the desired nucleobases to a pseudo-peptide backbone, thereby creating peptide nucleic acids (PNAs). Entry into the bacterial cell is obtained by utilising species-specific cell-penetrating peptides [93]. Knowledge on possible genetically relevant targets of bacteria has increased due to new methods such as next-generation and high-throughput RNA sequencing (RNA-seq) [94]. *In vitro* and *in vivo* data show that targeting of bacterial resistance genes with antisense oligonucleotides can in fact re-sensitise bacteria towards certain antibiotics [73]. However, little is known regarding resistance mechanisms and host responses in case the ASO reaches the nucleus of an eukaryotic cell [94]. Currently, no antisense therapies are investigated in clinical trials [73].

4.1.3.5. Microbiome-modulating Agents

The mammalian microbiome of the gut comprises more than 1000 microbial species. Classic antibiotic treatment often is accompanied by changes to the composition of the patient's gut microbiota, since antibiotics do not specifically only target pathogenic bacteria. This often renders the patient more prone to infections with drug-resistant bacteria [74]. Microbiota-modifying therapies are used to restore the microbiota of patients suffering from *C. difficile* infections [95]. This can either be achieved by administration of pre- or probiotics, or via faecal transplant treatment (FTT) [74]. Several clinical trials investigating the effects of FFT are ongoing. However, the high complexity of these products and incomplete knowledge of the microbiota are challenging factors for the clinical development [95].

4.1.4. Regulatory Measures - A Pharmaceutical Strategy for Europe

The Pharmaceutical Strategy for Europe was adopted in November 2020. This strategy is based on four pillars: (1) fulfilling unmet medical needs and ensuring accessibility and affordability of medicines; (2) supporting a competitive and innovative European pharmaceutical industry; (3) ensuring diversified and secure supply chains; environmentally sustainable pharmaceuticals; crisis preparedness and response mechanisms; (4) ensuring a

strong EU voice globally. Flagship initiatives specifically addressing AMR highlight the promotion of innovative R&D approaches, implementation of new types of incentives, promotion of prudent use of antibiotics and raising public awareness on AMR [96]. These topics are further addressed in the review of the pharmaceutical legislation. The EC adopted a proposal for the reform of the EU pharmaceutical legislation in April 2023. This update shall revise and replace the existing general pharmaceutical legislation, i.e. Regulation 726/2004, Directive 2001/83/EC, the legislation on medicines for children (Regulation 1901/2006) and for rare diseases (Regulation 141/2000/EC) [97]. The aim of this revision is to establish a more patient-centred approach, e.g. by improving access and supply with safe, effective and affordable medicinal products. In addition, industry interests are considered as research and innovation shall be fostered and administrative burdens during regulatory processes shall decrease. AMR shall be addressed in a One Health approach, also generally considering the environmental impacts of pharmaceuticals [35, 98].

Along with this, the Council adopted the 'Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach' in June 2023 [2]. Several recommendations are provided that shall be targeted in the future in the fighting of AMR. The objectives are to (1) strengthen national action plans against AMR; (2) reinforce surveillance and monitoring of AMR and antimicrobial consumption; (3) strengthen infection prevention and control; (4) strengthen antimicrobial stewardship and prudent use of antimicrobials; (5) recommend targets for antimicrobial consumption and antimicrobial resistance; (6) improve awareness, education and training; (7) foster R&D and incentives for innovation and access to antimicrobials and other AMR medical countermeasures; (8) increase cooperation; and (9) enhance global action [2, 99].

This recommendation aims to complement the 'A European One Health Action Plan against Antimicrobial Resistance (AMR)' published by the EC in 2017 [99, 100]. Within the 2023 'Study on a future-proofing analysis of the 2017 EU AMR Action Plan' further need for improvements of several topics was identified [101]. These issues are addressed by the 'Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach' [2]. The strategies described in the above-mentioned recommendations/plans are further evaluated in the following chapters.

4.1.4.1. The ‘One Health’ Approach

The One Health Approach is defined by the One Health High Level Expert Panel (OHHLEP) as “*…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 interdependent*…” [102]. This is thought as a global baseline consensus, as there is a broad level of interpretation of the widely used term One Health [103].

The Quadripartite Organisations, i.e. the Food and Agriculture Organization of the United Nations (FAO), the United Nations Environment Programme (UNEP), the World Organisation for Animal Health (WOAH) and the WHO developed the ‘One Health Joint Plan of Action (2022–2026)’ (OH JPA) to further strengthen the global One Health approach [104]. AMR qualifies as a central topic which should be addressed in a One Health approach since it is greatly dependent on human, animal, and environmental interaction. Moreover, AMR is considered a cross-border threat that requires interaction on an international level [2].

4.1.4.2. Action Plans against AMR

In 2015, the World Health Assembly (WHA) adopted the Global Action Plan on AMR (WHO GAP) developed by WHO with the contribution of FAO and WOAH. This plan represents an international consensus recognising AMR as a global health threat which needs to be addressed in order to ensure that it will still be possible to treat microbial infections in the future. This plan helps to develop national action plans by setting out key objectives which are to be considered on a national level [105]. The already established ‘Action plan against the rising threats from Antimicrobial Resistance’ in force in the EU as of 2011 ([106]) served as a basis for the development of the action plan implementing the requirements described in the WHO GAP, i.e. the ‘European One Health Action Plan against Antimicrobial Resistance (AMR)’ in 2017 [105]. On a national level, Germany already established the ‘*Deutsche Antibiotika-Resistenzstrategie’* (DART) in 2008. In order to implement improvements according to the WHO GAP and the EU Action Plan, DART 2020 followed [107]. Recently, DART 2023 was published [108]. The five key objectives which are common to all AMR action plans are:

- Improving AMR awareness and understanding;
- Strengthening AMR surveillance;
- Reducing incidence of infections;
- Optimising use of antimicrobial medicines in human and animal health; and
- Making an economic case for sustainable AMR-related investments [38, 45].

As obtained from an OECD analysis and the 2022 overview report by the EC's Directorate-General for Health and Food Safety (DG-SANTE), there are country-specific foci of national action plans. Of note, the implementation of the measures described in the national action plans varies among countries [45, 109]. All officially approved national AMR action plans can be obtained from the online WHO Library [110]. In order to monitor the status of national action plan implementation the annual 'Tripartite antimicrobial resistance country self-assessment survey' (TrACSS) was established. Results from these surveys can be obtained from a global database hosted by the WHO [111]. To assess the implementation of national action plans in the EU/EEA the 'Study on the barriers to effective development and implementation of national policies on antimicrobial resistance' was conducted and recently published by the EC in 2023. The main issue identified in this study is insufficient funding for implementing the measures foreseen in the national action plans to combat AMR [112].

4.1.4.3. Surveillance and Monitoring of AMR and AMC

In order to be able to make estimations of increasing or decreasing AMR or AMC, proper surveillance mechanisms are required [100]. Along with the implementation of the WHO GAP the need for standardised international assessment of AMR data was recognised. In order to provide reliable data from all countries, the Global Antimicrobial Resistance and Use Surveillance System (GLASS) was established to foster AMR surveillance using a standardised approach. This was later expanded to also include data an AMC [113]. As of October 2023, 132 countries are participating in GLASS [114].

Most recently in January 2024, the 'Antimicrobial Sales and Use (ASU) Platform' hosted by the EMA was implemented. Data on antibiotic sales and use in animals will now be submitted annually by the EU/EEA countries via this platform. This will further help to address AMR in a One Health approach [115].

Generally, conclusions on the effectiveness of specific measures used to tackle AMR and AMC can only be evaluated if extensive surveillance is continued and the data quality provided by the national reporting systems is high and reliable. However, the implementation of measures, as foreseen in national action plans, has partly failed because of insufficient funding [112]. In order to generate robust data, surveillance and monitoring should be further expanded. Moreover, the level of detail should be increased when evaluating AMR and AMC [2]. So far, community- and hospital-associated human AMC is monitored in the ESAC-Net report, however, not all national surveillance systems provide information on consumption using this level of detail [42]. Currently, the EARS-Net surveillance report provides AMR information on invasive isolates from human blood or cerebrospinal fluid samples [36]. This could be expanded to other isolates from clinical microbiology laboratories. Moreover, AMC and AMR in plant health, wastewater and the environment should also be taken into account [2]. Overall, it should be aimed at establishing a more integrated surveillance system which helps to gather complete and reliable data on all aspects of AMR and AMC in a true One Health Approach.

4.1.4.4. Infection Prevention and Control

Proper sanitary measures are essential for the prevention of infections [38]. The development of infection prevention and control (IPC) guidelines in human health will address this topic especially with regards to vulnerable healthcare settings and long-term care facilities [2]. Since IPC is also relevant for animal health, measures should be taken which improve the health and welfare of food-producing animals. This also includes proper manure and wastewater management to reduce environmental exposure to substances with antimicrobial properties [2, 100].

Further promising strategies against AMR are prophylactic vaccinations against bacterial infections and implementing national immunisation programmes [2]. Vaccines against tetanus (*Clostridium tetani*), pertussis (*Bordetella pertussis*), diphtheria (*Corynebacterium diphtheriae*) and tuberculosis (*M. tuberculosis*) have been successfully used for years [116, 117]. Vaccines are promising tools which can help to reduce AMR. Most recent MAs for bacterial vaccines covered *S. pneumoniae* and *Vibrio cholerae*. R&D targeting *S. aureus* and other pathogens will provide further opportunities, resulting in optimisation of the use of vaccines against AMR [117]. Of note, vaccination not only exerts a benefit to the individual

person by providing protection against infection by a certain bacterium, it also provides positive effects on population level, since abundance of the respective pathogen and possible resistance genes is decreased [118].

4.1.4.5. Prudent Use of Antimicrobials (Antimicrobial Stewardship, Awareness, Education and Training)

Since overuse and misuse of antibiotics are major drivers for AMR, the promotion of prudent use of antimicrobials is an important pillar in the fighting of AMR. Developing EU guidelines for the treatment of infections in humans in accordance with the WHO AWaRe antibiotic book [41] will help to endorse appropriate antibiotic use. This can be achieved by providing detailed information on diagnostic tests, use of the suitable antibiotic, and treatment regimens [2]. Currently, diagnostics of infections are costly and time-consuming. Therefore, the development of straightforward diagnostic alternatives that are rapid and less costly might be feasible. Ultimately, the determination of the exact bacterial species causing an infection helps choosing the right antibiotic with the narrowest spectrum as possible. In addition, unnecessary antibacterial treatment of virus infections would thus be avoided [52, 100].

Together with the implementation of the EU action plan against AMR, the EC adopted the 'EU Guidelines on the prudent use of antimicrobials in human health' specifically addressing the promotion of more prudent use of antibiotics in humans [119]. Antimicrobial stewardship programmes promote considered antimicrobial prescription. They should be accompanied by education, training and raising awareness on AMR among healthcare professionals and the public [119]. This includes the safe disposal of unused, expired and leftover antimicrobials [2]. The decrease in MRSA levels since 2018 (presented in the EARS-Net annual epidemiological report) might show that successful measures were in fact engaged. However, as a very versatile distribution among countries was observed, ranging from 1.1% in Norway to 50.8% in Cyprus, the need for specific country-tailored actions becomes apparent. National data on AMR and AMC should be evaluated in relation to the nationally applied measures targeting AMR and AMC in order to determine their efficiency. Sharing this information on an international level would provide great benefit for other countries as it provides an important indicator how to successfully address AMR and AMC. The higher

public awareness regarding MRSA needs to be widened towards the threat of AMR in general. To highlight the relevance of AMR, the ECDC founded the EAAD (European Antibiotic Awareness Day) which takes place during the WHO initiative WAAW (World AMR Awareness Week) [11]. The update of the pharmaceutical legislation will implement measures for prudent use of antimicrobials directly into the marketing authorisation process. This includes the prescription status, adequate pack sizes and monitoring and reporting of AMR [35].

4.1.4.6. Targets for AMR and AMC

Specific targets are recommended by the Council which will help to evaluate if the measures taken against AMR are in fact working. On one hand, precise targets for AMC and AMR are anticipated. On the other hand, general aspects such as IPC, antimicrobial stewardship and reduction of antimicrobial sales in animal farming, agriculture and aquaculture are highlighted [2]. The recommended targets include:

- To reduce the total consumption of antibiotics in humans (as DDD per 1000 inhabitants per day) in the community and in combined hospital sectors in the EU by 20% compared with 2019;
- At least 65% of antibiotics used in humans should belong to the WHO Access group by 2030;
- MRSA: To reduce total incidence of bloodstream infections (number per 100,000 population) in the EU by 15% compared with 2019;
- Third generation cephalosporins-resistant *E. coli*: To reduce total incidence of bloodstream infections (number per 100,000 population) in the EU by 10% compared with 2019;
- Carbapenem-resistant *K. pneumoniae*: To reduce total incidence of bloodstream infections (number per 100,000 population) in the EU by 5% compared with 2019 [2].

Since the actual AMC and AMR levels differ greatly amongst EU member states, country-specific targets are provided in the annex of the Council Recommendation [2].

4.1.4.7. Promotion of R&D; Incentives for Innovation; Access and Supply; AMR Medical Countermeasures

The development of pharmaceuticals is a very costly process. Since the use of antibiotics is strictly limited, the return of investment based on sales volumes and price is small for pharmaceutical companies, especially in comparison with other therapeutic areas, such as cancer [14, 120, 121]. These issues resulted in withdrawal of big pharmaceutical companies from antibiotic R&D [14]. According to WHO statistics, currently, antibiotic R&D is mostly dominated by micro-, small- and medium-sized enterprises (SMEs) [54]. During the workshop on 'New incentives to improve the accessibility and availability of antimicrobial medicinal products', held on 26th October 2022 before the European Parliament's Health Working Group it was emphasised to abandon the link of financial return of investment for companies from sale volumes for antibiotics [50]. Several factors influenced and resulted in an overall decrease in antibacterial R&D, i.e. (1) the availability of cheap generic antibacterials; (2) relatively short duration of treatment of acute bacterial infections; (3) costly R&D; (4) stewardship measures which promote prudent use of antibiotics and classification as last line treatment option for new antibiotics; and (5) lack of funding for phase II and phase III clinical trials [57]. In order to still be able to treat bacterial infections in the future, completely new thinking with regards to pharmaceutical R&D, financial revenue and access and supply is required. Moreover, the diversity of the mechanisms applied by bacteria to evade eradication by antibiotic treatment should be considered during R&D of antibiotics. Hence, innovative and clinically differentiated antibacterials are required in the future to still be able to cope with emerging AMR in the long run [57].

Although several new antibacterials were authorised in the last decades, only few belong to a new antibiotic class, the majority are derivates of known classes. Most recently authorised antibacterials have been classified as Reserve or Watch according to the WHO AWaRe Classification and only one antibacterial belongs to the WHO Access class (Table 4). This highlights that newly approved antibiotics are likely to be classified as last-resort antibiotics which are only used when no other treatment options are available [54]. This increasing number of last-line treatment options is important in view of strengthening the healthcare system. However, the prospect that actual sales volumes will be very low as a result to this classification offers limited financial attractiveness to pharmaceutical companies.

Although 80 antibacterial agents in the clinical pipeline and 217 agents in the pre-clinical pipeline were identified in the 2022 report by the WHO, the (pre-) clinical pipelines are not considered to be sufficient to address future antibiotic needs. This applies especially to the lack of antibiotic agents targeting carbapenem-resistant *A. baumannii* and *P. aeruginosa* [54]. One issue is that the newly authorised products mainly do not belong to new antibiotic classes with innovative mode of actions and are therefore considered to be highly susceptible to evolving AMR [57]. It has been estimated that 5-20 truly novel and innovative antibiotics are required in clinical development to address the future need for new antibiotics. Considering the high number of discontinued candidates during early R&D, this would require at least 200 discovery programmes [38, 63].

In an attempt to compensate for increasing AMR, several novel approaches are currently investigated. Some of these are presented in chapter 4.1.3 of this thesis, i.e. bacteriophages, AMPs, antibodies and AACs, PNAs and microbiome-modulating agents. Of note, there are more non-traditional antibiotics which target for example bacterial virulence, adhesion, or biofilm formation [54]. Non-traditional antibacterials authorised in the last decade are for example the bacterial toxin-neutralising antibody products Nyxthracis (obiltoxaximab, MA November 2020) and Zinplava (bezlotoxumab, MA January 2017). The use of non-traditional antibacterials as adjuvants to traditional antibiotics is also investigated [72]. Since non-traditional antibacterials are rather complex biological products, the design and conduct of clinical studies is especially challenging. Pathogen-specific non-traditional antibacterials require extensive diagnostics prior to administration of the IMP. Moreover, the compliance with GMP, dose-finding and patient-tailored approaches further impede entry into clinical phase [72].

The majority of products of the pre-clinical pipeline are developed in Europe (52%). Interestingly, 38% of these developers categorise as micro-size (<10 employees), 36% as small-size (11-50 employees), 16% as medium-size (51-500 employees) and only 10% as large-size enterprises (>500 employees) according to WHO [67]. This indicates that newly developed funding mechanisms in Europe for SMEs in the future could be of great success, since apparently the necessary expertise to develop novel antibacterials is available in Europe. Moreover, measures specifically targeting the needs of SMEs would be of great benefit

since these are the stakeholders mostly involved in early R&D of antibacterials. Nevertheless, support during clinical stages of drug development should not be underestimated since study design can be challenging for non-traditional antibacterials [57].

The fact that the current clinical and preclinical antibiotic pipeline is not considered sufficient to compensate for emerging AMR in the future, highlights the need for effective R&D incentives [54]. These include incentives for the development and the access to antimicrobials and other AMR medical countermeasures such as vaccines and diagnostic tools. On one hand, push incentives that help to bring antimicrobials to the market via funding of research and innovation are required. On the other hand, pull incentives need to be established to ensure access to effective antimicrobials and reward successful development. Financing could be accomplished by novel incentive models such as milestone prices which are coupled to the successful completion of specific steps during development [122]. Novel incentive models for funding of antimicrobial R&D are part of the Commission Communication on the 'Reform of the pharmaceutical legislation and measures addressing antimicrobial resistance' and the Council Recommendation 'on stepping up EU actions to combat antimicrobial resistance in a One Health approach' [2, 35]. The classic incentives, such as data protection, accelerated assessment, orphan designation, and PRIME scheme, are considered inappropriate for promotion of antimicrobial research, which can be concluded from the insufficiently filled (pre-) clinical pipelines. Two different types of pull incentives for antimicrobials are suggested in the Commission Communication on the 'Reform of the pharmaceutical legislation and measures addressing antimicrobial resistance', i.e. transferable data exclusivity vouchers and mechanisms which guarantee revenue. Developers of novel antimicrobials which are qualified to obtain the innovative voucher can benefit from an additional year of regulatory data protection for any of their products or they can sell the voucher. Granting of the voucher will be limited to specific antimicrobials, e.g. against pathogens of the WHO priority list. It is proposed that the voucher scheme will be tested for 15 years, and is limited to a total of 10 vouchers [35].SMEs might only profit by selling their voucher to other companies. Since this will most likely be possible only after obtaining a MA for the product, it needs to be considered that at this point, all costly R&D stages are already completed. This would mean that the capital from selling the voucher could only be used for the development of yet another product in the pipeline of the SME, given that

there actually is another promising candidate in the pipeline. However, for larger pharmaceutical companies the transfer of data exclusivity to other products of the portfolio of the MAH (marketing authorisation holder) is very favourable. Data exclusivity could be expanded for products which generate the most benefit for the MAH, considering that the entry of generics to that product is delayed. However, this is associated with increased costs for the healthcare system, since the entry of generics to the market helps to lower the price of a pharmaceutical. This is also highly criticised by the ReAct Group, a global AMR network [123]. The exact means how such a voucher would be transferred to another product must be elucidated in detail before implementation of such incentive mechanisms. Factors such as the exact timepoint of transfer are questionable. This is associated with higher risks for pharmaceutical companies specialised on the authorisation of generics, since market entry of the to-be-authorised generic will be delayed, in worst case on relatively short notice. This is especially difficult since the timing of a generic MAA is highly dependent on expiry of data protection periods of originators.

Similar uncertainties also apply to the second pull incentive strategy suggested in the Commission Communication on the reform of the pharmaceutical legislation, i.e. mechanisms which guarantee revenue. These incentives are intended to increase the expected revenue for developers [35]. The European Commission 'Study on bringing AMR Medical Countermeasures to the Market' evaluated four different pull incentives that may help increase the expected revenue for antimicrobial developers: revenue guarantee, small market entry reward combined with revenue guarantee, milestone-based reward, lump-sum market entry reward [124]. Depending on the development stage, different funding models are considered feasible. At the pre-clinical stage, combinations of push and pull incentives were found to be most effective. Moreover, the more advanced the development of a product, the less funding is required to reach the profitable range [124]. The aforementioned pull incentives raise various questions which are to be considered at a national and international level. In theory, guaranteed revenue sounds promising. However, the exact realisation will be challenging. Factors which have to be considered include: (1) How is the actual monetary value of a novel antimicrobial calculated? (2) Who calculates this value? (3) How are additional fundings considered? (4) Are national HTA (health technology assessment) processes considered in the calculation? (5) How are possible mistakes in the calculation addressed if a product shows to be more/less profitable than expected? Moreover, in reality the sales of

a newly launched pharmaceutical often compensate for the losses of a pharmaceutical company which are due to discontinued or failed other substances in their R&D pipeline. The aforementioned study suggests to implement a central EU entity such as a common HTA which could assess the developers R&D costs, the patient and societal value and decide on the individual incentive award [124]. As national HTA is complex, the definition of an EU-wide patient and societal value is challenging. Moreover, further difficulties are the definition of eligibility criteria and limiting the number of potential EU-funded incentives in order to not stress the funding system too much. The patient and societal value should be larger than the paid incentive [124]. Overall, diverse incentive mechanisms are required in the future to address the specific needs of developers during antimicrobial development. Product-tailored approaches and the combination of push and pull incentives which support R&D at various stages will most likely have the most beneficial effect, resulting in increased availability of new and old antibiotics [124]. In addition, post-authorisation processes regarding market access and supply need to be targeted. Therefore, funding mechanisms should focus on procurement, i.e. result in more antimicrobials which are available on the market and ultimately reach the patient.

Of note, the revision of the EU pharmaceutical legislation aims to drive innovation for a competitive pharmaceutical industry in general. Hence, developers of antimicrobials will benefit from these measures in addition to the measures specifically directed at AMR R&D. These general measures include: (1) implementation of an effective incentives framework for innovation, access and addressing unmet medical needs; (2) rewarding innovation in areas of unmet medical need by boosting regulatory support for the development of promising medicines; and (3) improving the regulatory system for Europe to remain an attractive place to invest and innovate [35]. The current regulatory protection model of 8 years of regulatory data protection, 2 years of market protection, extension up to 11 years if a new therapeutic indication is added after the initial marketing authorisation, six-month extension of SPC (supplementary protection certificate) due to a conducted the paediatric development plan and 10 years of market exclusivity for orphans will be changed in the reform of the EU pharmaceutical legislation. The regulatory data protection will decrease to 6 years. However, new additional conditional protection periods shall be implemented, for example, 2 years additional regulatory protection for market launch in all Member States [35]. However, this new regulatory protection model has been criticised by the European

Federation of Pharmaceutical Industries and Associations (EFPIA) and other industry representatives who argue that this will slow down R&D of new medicines in Europe as potentially reduced protection periods will make the EU less attractive for pharmaceutical R&D [125–127].

In order to simplify authorisation processes and help to reduce the regulatory burden to companies especially for medicines addressing unmet medical needs in the future, general regulatory support mechanisms shall be implemented. These include early regulatory support by EMA, rolling-reviews, temporary emergency marketing authorisation for public health emergencies, simplifying regulatory procedures and optimising EMA structure, reducing assessment times by EMA and digitalisation [35]. Increased regulatory support could compliment funding models by establishing increased global cooperation, for example by promoting alignment of global regulatory requirements and sharing of knowledge and dissemination of best practices [124]. Several strategies for the promotion of R&D of antibiotics are already implemented by the EMA, i.e. early dialogue with developers, guidance on the use of pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products, guidance on the evaluation of medicinal products indicated for treatment of bacterial infections, and support on the exploration of new therapeutic options for difficult-to-treat infections due to MDR bacteria (e.g. an EMA-hosted workshop on the therapeutic potential of bacteriophages). Developers are encouraged to contact EMA's Innovation Task Force (ITF) during all development stages in order to facilitate an early dialogue during ITF briefing meetings to provide informal basic regulatory guidance [128]. This opportunity is especially advertised for SMEs, academics and researchers since they comprise the main developers for new antimicrobials in early development stages and might benefit the most from the discussion of scientific, legal and regulatory issues and requirements [129]. Moreover, EMA refers to the possibility for parallel scientific advice by EMA and FDA (Food and Drug Administration) for developers of antibiotics. In addition, efforts are made by the EMA, the FDA and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) to provide guidance on clinical trials with aligned data requirements [128].

Several EU initiatives have provided funding for the promotion of EU health, research and innovation regarding AMR, i.e. Horizon 2020, Horizon Europe and the EU4Health Programme [13]. The EU supported international Joint Programming Initiative on AMR

(JPIAMR) helps to coordinate national research funding and to align global AMR research [130]. Several government-supported programmes, including as CARB-X (Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator), GARDP (Global Antibiotic Research & Development Partnership) and ND4BB (New Drugs 4 Bad Bugs) have already been implemented [124]. The latter was established by the Innovative Medicines Initiative (IMI) upon initiative of the 2011 EU Action Plan on AMR. This partnership between industry, academia and biotech organisations was established to fight AMR in Europe. To do so, currently eight projects are financed with a total budget of €650 million. The funded projects aim to develop antibiotics and include research topics on basic science, drug discovery, clinical trials and economic models [131]. Increased public funding and a network of public-private-partnerships (PPPs) can help to overcome the underfinanced early development stages in the future [120].

In December, the German Federal Ministry of Health presented the key points of the planned Medical Research Act ("*Medizinforschungsgesetz*") which aims to improve conditions for pharmaceutical development and foster drug R&D in Germany. Special focus is applied to early R&D on antibiotics and funding of new production facilities in order to enhance and expand Germany's attractiveness as a location for the pharmaceutical industry and to ensure a reliable supply with critical medicinal products [132–134]. In an effort to further promote research, development and market launch of new antibiotics that are effective against MDR bacteria, additional financial and economic incentives are provided for new antibiotics designated as reserve antibiotics within the meaning of § 35a of the SGB V (German Social Code, Book V; *Sozialgesetzbuch Fünftes Buch*). These antibiotics are exempted from the additional benefit assessment requirement by the Federal Joint Committee (GBA, *Gemeinsamer Bundesausschuss*). RKI and BfArM developed criteria for classifying an antibiotic as a reserve antibiotic based on the WHO Priority Pathogen list considering further criteria addressing the national needs of Germany. This non-exhaustive list was introduced in 2021 and was updated in February 2024 to now contain 25 MDR bacterial pathogens or pathogen-resistance combinations that are considered relevant for Germany [135, 136].

In an attempt to increase antibacterial treatment options, other strategies such as the combination or repurposing of older medicinal products, changing the formulation, the route of administration or indication are also pursued. Improving of older products, for example

by developing of new paediatric or oral formulations, contributes to this [54]. Studies on antibiotic cycling and mixing did not show a benefit [137]. In contrast to this, sequential antibiotic therapy showed promising effects [138]. Generally, the authorisation of additional generic products helps to strengthen supply with traditional antibiotics and should not be underestimated. The relevance of the need for access to and supply of traditional antibiotics is highlighted by the large number of reports listed in the BfArM shortage database and the critical shortage situation of syrups containing antibiotics for children [49]. The 'Council recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach' highlights the importance of continuous access and supply with already authorised antimicrobials and other AMR medical countermeasures. Therefore, access and supply shall be secured and shortages shall be avoided, for example by implementing targeted antibiotic stockpiling actions and improved demand forecasts [2].

4.1.4.8. Global Cooperation and Action

Since AMR is most efficiently addressed using a One Health Approach, global cooperation and action are fundamental. The ECDC, the European Chemicals Agency (ECHA), the European Environment Agency (EEA), EFSA and EMA established a One Health cross-agency task force supporting the One Health approach in Europe [139].

The 'Council recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach' furthermore encourages to continue AMR data reporting to GLASS and actively using the EU AMR One Health Network, for example to share and exchange national action plans on AMR. Moreover, the topic of AMR shall be addressed in the context of negotiations of the WHO international agreement on pandemic prevention, preparedness and response accord and low-and-middle income countries shall be supported on AMR actions. In order to facilitate global coordination, cooperation with the United Nations, G7, G20 and with the quadripartite organisations shall be enhanced [2]. In order to make best possible use of research resources, setting research priorities is straightforward and is most efficient and promising when globally coordinated. Sharing of knowledge on antibacterial research topics via databases (e.g. AntibioticDB hosted by GARDP [140]) and compound libraries helps to efficiently bundle resources [122].

5. Conclusion and Outlook

Fighting AMR must be considered on several levels. First, the reasons for increasing emergence of AMR are required to be tackled. Second, antibiotic R&D needs to be strengthened and must become more (financially) attractive in the future. At last, affordable newly developed and also traditional antibiotics must reach the patient via secure supply chains. Ultimately, all these measures are required to be addressed in a One Health approach, on a national level, but also on international level since AMR is a cross-border issue and human and animal health and the environment are intertwined. The 'European One Health Action Plan against Antimicrobial Resistance (AMR)' implemented in 2017, the pharmaceutical strategy for Europe, including the revision of the pharmaceutical legislation and the 'Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach' aim to address these topics. Novel incentive models are suggested which aim to promote and reward antibacterial R&D by delinking the financial return of investment for companies from sale volumes for antibiotics. Overall, product-specific push and pull incentives tailored to the needs of the specific R&D stage and the developer are required. This will foster research and innovation and will ultimately help to overcome the lack of new antibacterials [124]. Promising novel antibacterial research strategies have been identified, such as bacteriophages, or bacteria-specific or bacterial toxin-specific antibodies. Some novel therapeutics have already reached MA, MAA or clinical testing phases. However, issues with GMP, GCP requirements or translation issues to later development stages are still holding back others at preclinical or earlier development stages [72, 73]. General regulatory support mechanisms with simplified authorisation processes should reduce the regulatory burden to companies especially for medicines addressing unmet medical needs. Antibiotic stewardship programmes which promote prudent use of antimicrobials in humans, animals and the environment and effective IPC measures are required since antibiotic overuse and misuse are major drivers for AMR [2]. This is accompanied by the Zero Pollution Action Plan and the Farm to Fork Strategy which target a 50% reduction in overall EU sales of antimicrobials for farmed animals and in aquaculture until 2023 and the Regulations on veterinary medicinal products and on medicated feed. These measures play an important role in addressing AMR in a One Health approach [141]. In addition, access to and supply with newly developed, as well as traditional antibiotics must

be ensured. Governmental support in investing in secure supply chains will benefit the healthcare system in the long run. Moreover, considering the global One Health approach, access and supply should not be limited to specific countries, since the availability of effective antimicrobials is crucial to the whole world. Therefore, global cooperation and coordination is required to provide support to low- and-middle income countries. Nevertheless, since AMR is diverse and shows large national differences, country-specific approaches are required which ultimately follow the same overall global goal, i.e. tackling AMR. Of note, these considerations also apply to antimicrobials that are active against parasitic and fungal infections.

6. Summary

The discovery of the first antibiotic penicillin in 1929 by Alexander Fleming was shortly followed by the identification of penicillin-resistant bacteria. During the golden era of antibiotics from 1940 to 1970, numerous antibacterial substances were identified and the occurrence of further resistances was observed. The decline in the identification of new antibiotic substances from 1970 onwards and increasing emergence of AMR pose a growing threat to human and animal health and the environment. Since the bacterial processes of acquiring resistance are part of natural evolution, there is a constant need for new effective therapeutics for the treatment of bacterial infections. The number of antimicrobial compounds currently under development is considered not sufficient to compensate for the increased amount of antibiotics that will be needed in the future to successfully treat (multi)drug-resistant bacterial infections. Several new strategies to combat bacteria have been developed. These include the use of bacteriophages, bacteria- or bacterial toxin-specific antibodies and others. In order to address the issue of increasing AMR, the 'European One Health Action Plan against Antimicrobial Resistance (AMR)' has been implemented in 2017. AMR is a key component of the revision of the pharmaceutical legislation and the 'Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach'. They aim to (1) strengthen national action plans against AMR; (2) reinforce surveillance and monitoring of AMR and antimicrobial consumption; (3) strengthen infection prevention and control; (4) strengthen antimicrobial stewardship and prudent use of antimicrobials; (5) recommend targets for antimicrobial consumption and antimicrobial resistance; (6) improve awareness, education and training; (7) foster R&D and incentives for innovation and access to antimicrobials and other AMR medical countermeasures; (8) increase cooperation; (9) enhance global action. Fighting AMR must be considered on several levels. First, the reasons for increasing emergence of AMR are required to be tackled. Second, antibiotic R&D needs to be strengthened and must become more (financially) attractive in the future. At last, affordable newly developed and also traditional antibiotics must reach the patient via secure supply chains. Ultimately, all these measures are required to be addressed in a One Health approach, on a national level, but also on international level since AMR is a cross-border issue and human and animal health and the environment are intertwined. The pharmaceutical strategy for Europe aims to address all these topics.

This thesis analyses the current antibiotic (pre-) clinical R&D pipelines and evaluates the planned regulatory measures which shall combat AMR.

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Annexes

I. Excerpt from Cortellis RIR of new CAP MAs from 2017-Feb 2024

Active Ingredient(	Name	Application Numbe	Therapeutic Area	Indication(s)	Product Typ	Application /Submission Type	Registration Statu	Active Substance Status	Fixed Dose Combination Status (if applicable)	Orphan Designatic	Pediatric Use	Company	European Commission Opinion Date
ertapenem	ERTAPENEM SUN	EMEA/H/C/005815	Infections	ERTAPENEM SUN is indicated for: Treatment: ERTAPENEM SUN is indicated in paediatric patients (3 months to 17 years of age) and in adults for the treatment of the following infections when caused by bacteria known or very likely to be susceptible to ertapenem and when parenteral therapy is required: - Intra-abdominal infections - Community acquired pneumonia - Acute gynaecological infections - Diabetic foot infections of the skin and soft tissue Prevention: ERTAPENEM SUN is indicated in adults for the prophylaxis of surgical site infection following elective colorectal surgery. Consideration should be given to official guidance on the appropriate use of antibacterial agents.	Chemical	Generic	Approved	Known active substance	Not applicable	No	Yes	Sun Pharmaceutical Industries Europe BV	15-Jul-2022
pneumococcal polysaccharide conjugate vaccine, 20-valent, adsorbed	APEXXNAR	EMEA/H/C/005451	Infections	APEXXNAR is indicated for active immunisation for the prevention of invasive disease and pneumonia caused by Streptococcus pneumoniae in individuals 18 years of age and older. It should be used in accordance with official recommendations.	Biologic	Complete	Approved	New active substance	Not applicable	No	No	Pfizer Europe MA EEIG	14-Feb-2022
pneumococcal polysaccharide conjugate vaccine (15-valent, adsorbed)	VAXNEUVANCE	EMEA/H/C/005477	Infections	VAXNEUVANCE is indicated for active immunisation for the prevention of invasive disease and pneumonia caused by Streptococcus pneumoniae in individuals 18 years of age and older. The use of VAXNEUVANCE should be in accordance with official recommendations.	Biologic	Complete	Approved	New active substance	Not applicable	No	No	Merck Sharp & Dohme BV	13-Dez-2021

obiltoxaximab	OBILTOXAXIMAB SFL	EMEA/H/C/005169	Infections	OBILTOXAXIMAB SFL is indicated in combination with appropriate antibacterial drugs in all age groups for treatment of inhalational anthrax due to Bacillus anthracis. - OBILTOXAXIMAB SFL is indicated in all age groups for post-exposure prophylaxis of inhalational anthrax when alternative therapies are not appropriate or are not available.	Biologic	Complete	Approved	New active substance	Not applicable	Yes	Yes	SFL Pharmaceuticals Deutschland GmbH	18-Nov-2020
meningococcal groups A, C, W-135 and Y conjugate vaccine	MENQUADFI	EMEA/H/C/005084	Infections	MENQUADFI is indicated for active immunisation of individuals from the age of 12 months and older against invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, W, and Y. The use of this vaccine should be in accordance with available official recommendations	Biologic	Complete	Approved	Known active substance	Not applicable	No	Yes	Sanofi Pasteur	18-Nov-2020
amikacin	ARIKAYCE LIPOSOMAL	EMEA/H/C/005264	Infections	ARIKAYCE liposomal is indicated for the treatment of non-tuberculous mycobacterial (NTM) lung infections caused by Mycobacterium avium Complex (MAC) in adults with limited treatment options who do not have cystic fibrosis. Consideration should be given to official guidance on the appropriate use of antibacterial agents.	Chemical	Complete	Approved	Known active substance	Not applicable	Yes	No	Insmed Netherlands BV	27-Okt-2020
pretomanid	PRETOMANID FGK	EMEA/H/C/005167	Infections	PRETOMANID FGK is indicated in combination with bedaquiline and linezolid, in adults, for the treatment of pulmonary extensively drug resistant (XDR), or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB). Consideration should be given to official guidance on the appropriate use of antibacterial agents.	Chemical	Complete	Approved	New active substance	Not applicable	Yes	Yes	FGK Representative Service GmbH	31-Jul-2020
lefamulin	XENLETA	EMEA/H/C/005048	Infections	XENLETA is indicated for the treatment of community-acquired pneumonia (CAP) in adults when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of CAP or when these have failed. Consideration should be given to official guidance on the appropriate use of antibacterial agents.	Chemical	Complete	Approved	New active substance	Not applicable	No	Yes	Nabriva Therapeutics Ireland DAC	27-Jul-2020
cefiderocol	FETCROJA	EMEA/H/C/004829	Infections	FETCROJA is indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options. Consideration should be given to official guidance on the appropriate use of antibacterial agents.	Chemical	Complete	Approved	New active substance	Not applicable	No	Yes	Shionogi BV	23-Apr-2020

tigecycline	TIGECYCLINE ACCORD	EMEA/H/C/005114	Infections	TIGECYCLINE ACCORD is indicated in adults and in children from the age of eight years for the treatment of the following infections: Complicated skin and soft tissue infections (cSSTI), excluding diabetic foot infections; Complicated intra-abdominal infections (cIAI). TIGECYCLINE ACCORD should be used only in situations where other alternative antibiotics are not Suitable. Consideration should be given to official guidance on the appropriate use of antibacterial agents.	Chemical	Generic	Approved	Known active substance	Not applicable	No	Yes	Accord Healthcare SLU	17-Apr-2020
live oral cholera vaccine	VAXCHORA	EMEA/H/C/003876	Infections	VAXCHORA is indicated for active immunisation against disease caused by Vibrio cholerae serogroup O1 in adults and children aged 6 years and older. This vaccine should be used in accordance with official recommendations.	Biologic	Complete	Approved	New active substance	Not applicable	No	Yes	Emergent Netherlands BV	01-Apr-2020
cilastatin ; imipenem ; relebactam	RECARBRIO	EMEA/H/C/004808	Infections	RECARBRIO is indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options; Consideration should be given to official guidance on the appropriate use of antibacterial agents	Chemical	Fixed combination	Approved	New active substance	One new active substance ; Two known active substances	No	Yes	Merck Sharp & Dohme BV	13-Feb-2020
delafloxacin	QUOFENIX	EMEA/H/C/004860	Infections	QUOFENIX is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections.	Chemical	Complete	Approved	New active substance	Not applicable	No	Yes	A. Menarini Industrie Farmaceutiche Riunite SRL	16-Dez-2019
tobramycin	TOBRAMYCIN PARI	EMEA/H/C/005086	Infections	TOBRAMYCIN PARI is indicated for the management of chronic pulmonary infection due to Pseudomonas aeruginosa in patients aged 6 years and older with cystic fibrosis (CF). Consideration should be given to official guidance on the appropriate use of antibacterial agents.	Chemical	Hybrid	Approved	Known active substance	Not applicable	No	Yes	PARI Pharma GmbH	18-Feb-2019
meropenem ; vaborbactam	VABOMERE	EMEA/H/C/004669 Rev 4	Infections	VABOREM is indicated for the treatment of the following infections in adults: Complicated urinary tract infection (cUTI), including pyelonephritis; Complicated intra-abdominal infection (cIAI); Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP). Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above; VABOREM is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.; Consideration should be given to official guidance on the appropriate use of antibacterial agents.	Chemical	Fixed combination	Approved	New active substance	One known active substance ; One new active substance	No	No	Menarini International Operations Luxembourg SA	20-Nov-2018

eravacycline	XERAVA	EMEA/H/C/004237	Infections	XERAVA is indicated for the treatment of complicated intra-abdominal infections (cIAI) in adults. Consideration should be given to official guidance on the appropriate use of antibacterial agents.	Chemical	Complete	Approved	New active substance	Not applicable	No	Yes	Tetraphase Pharmaceuticals Ireland Ltd.	20-Sep-2018
meningococcal group B vaccine (recombinant, component, adsorbed)	TRUMENBA	EMEA/H/C/004051	Infections	TRUMENBA is indicated for active immunisation of individuals 10 years and older to prevent invasive meningococcal disease caused by Neisseria meningitidis serogroup B. The use of this vaccine should be in accordance with official recommendations.	Biologic	Complete	Approved	New active substance	Not applicable	No	No	Pfizer Ltd.	24-Mai-2017
daptomycin	DAPTOMYCIN HOSPIRA	EMEA/H/C/004310	Infections	DAPTOMYCIN HOSPIRA is indicated for the treatment of the following infections. • Adult and paediatric (1 to 17 years of age) patients with complicated skin and soft-tissue infections (cSSTI). • Adult patients with right-sided infective endocarditis (RIE) due to Staphylococcus aureus. It is recommended that the decision to use daptomycin should take into account the antibacterial susceptibility of the organism and should be based on expert advice. • Adult patients with Staphylococcus aureus bacteraemia (SAB) when associated with RIE or with cSSTI. Daptomycin is active against Gram-positive bacteria only. In mixed infections where Gram-negative and;or certain types of anaerobic bacteria are suspected, daptomycin should be co-administered with appropriate antibacterial agent(s). Consideration should be given to official guidance on the appropriate use of antibacterial agents.	Chemical	Generic	Approved	Known active substance	Not applicable	No	No	Hospira UK Ltd.	22-Mrz-2017
bezlotoxumab	ZINPLAVA	EMEA/H/C/004136/0000	Infections	ZINPLAVA is indicated for the prevention of recurrence of Clostridium difficile infection (CDI) in adults at high risk for recurrence of CDI.	Biologic	Complete	Approved	New active substance	Not applicable	No	No	Merck Sharp & Dohme Ltd.	18-Jan-2017

II. Applications for new human medicines under evaluation by the CHMP (February 2024)

The report was published on 12/02/2024 with EMA reference number EMA/58689/2024 [17].

Excerpt from EMA filtered for relevant therapeutic areas. Source [17]

International non-proprietary name (INN) / Common Name	Substance type (classification)	Therapeutic area (ATC level 2)	Accelerated Assessment (Art. 14(9) Reg 726/2004)	Revert to standard Time Table (MM/YY)	Orphan Product	Generic, hybrid or Biosimilar	Start of evaluation
Aztreonam / Avibactam	Chemicals	Antibacterials for systemic use	Y		N	N	14.09.2023
Meningococcal groups A, B, C, W and Y vaccine	Biologicals	Vaccines	N		N	N	15.06.2023

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

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Ort, Datum Unterschrift