New approaches to combat Antimicrobial Resistance (AMR)?

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Abstract

Antimicrobial resistance (AMR) is a complex global health challenge arising from improper antibiotic usage in both human and animal domains, including the misguided application of antibiotics as growth promoters in animals. A deficiency in public understanding of antibiotics among diverse stakeholders further compounds this issue. The European Commission, primarily via its agency HERA (European Health Emergency Preparedness and Response), is now better prepared to confront a potential outbreak of totally resistant bacteria that may kill many more millions of people globally than COVID-19. However, the Commission's current strategy mostly emphasizes the acceleration of new antibiotic development to replace obsolete treatments rendered ineffective against resistant infections. In July, the Commission also announced its intention to mandate the pharmaceutical industry, responsible for the overproduction of antibiotics that led to the AMR threat, to increase production of current antibiotics in anticipation of a potential rise in respiratory infections during the upcoming winter season. This article provides a critical overview of EU actions on AMR and delves into recent research, emphasizing a key insight: the development of new drugs is insufficient in combating AMR if these innovations inadvertently contribute to pathogen resistance. Concurrently, the study delves into fundamental components necessary for averting a potential global AMR crisis. These components encompass education, awareness, the imperative of equitable antibiotic access, and finally, the exploration of less resistance-creating alternatives, such as bacteriophages and vaccinations.

Central to the discourse are the pivotal roles assigned to responsible global authorities and stakeholders. They are urged to take the lead in incentivizing the pharmaceutical sector towards the production of AMR-resistant antibiotics, with a paramount goal of arresting the emergence of AMR in pathogens. Moreover, the article underscores the significance of promoting the development of "reserve" antibiotics, primarily reserved for severe emergency cases to effectively decelerate AMR progression. In this context, the HERA approach emerges as an invaluable tool, optimizing resource utilization within private and public inventories, while concurrently limiting the availability of medications for less critical conditions.

Confronting the existing market inadequacies in antibiotic development, particularly within animal husbandry, necessitates the implementation of targeted regulatory measures including legal bans, antibiotic usage taxes and a halt to antibiotics sales through veterinarians – sometimes supported by substantial price reductions for quantum sales to farmers. The Commission is on record to 'regret' such practices but asserts its inability to act against them. In other words, to comprehensively address AMR, an all-encompassing global strategy reminiscent of the United Nations' Tuberculosis (TB) action is advocated, and the Chinese law banning the use of human-targeted antibiotics in animals may serve as a remarkable example. Integral to this strategy is the establishment of dynamic public-private partnerships, essential for orchestrating a unified response to the multifaceted challenge of AMR, while avoiding the pouring in of tax monies without the required public control over the actual use of antibiotics by pharmaceutical industries.

Keywords: AMR, AMR-resistant drugs, Bacteriophages, HERA, Public-Private Partnerships

Introduction

AMR-related illnesses affect millions of individuals and lead to at least 1.2 million deaths annually [1–4]. The yearly mortality toll from infections caused by AMR is predicted to exceed 10 million by 2050 [1–4]. That is the entire population size of a country like Belgium, where the European Union is headquartered. The most well-known causes of antimicrobial resistance (AMR) include improper and excessive use of antibiotics in both humans and animals, the inappropriate use of antibiotics as growth promoters in animals, and a general lack of knowledge among the public and even pharmacists and pharmacologists regarding proper antibiotics husbandry [5–8].

Although the pharmaceutical industry's development of new antibiotics has nearly ceased for many years due to market failure, low prices and the fact that each new pill will take 10-15 years to produce and about $1 billion in funding, renewed efforts are now being made to jumpstart or even accelerate the creation of new antibiotics to replace obsolete ones which have become ineffective in the pathogens [9,10]. This is in line with the new strategy developed by the European Commission's HERA unit [1]. HERA must try to foresee future pandemics, and the most serious of these is the outbreak of totally resistant pathogens.

The most recent research, however, contradicts the EU action plans and shows that even if new drugs are developed in a way that prevents them from serving as sources of resistance in infections, AMR will still exist [15–18]. This article delves into the imperative of designing new antibiotics that do not contribute to AMR, as well as strategies to prevent a global AMR outbreak. It also addresses the enhancement of accessibility to these new medicines and explores the utilization of alternative technologies.

1. Global Strategies Against AMR

The World Health Organization (WHO) has identified numerous outbreaks across the globe, with one of the most notorious instances occurring during a G-20 gathering within a Hangzhou hospital in China back in 2016 [11]. In a discreet yet impactful move, Professor Mark Eyskens, Chairman of the PA International Foundation, and a former Belgian Prime Minister, personally advised all G-20 leaders to avoid seeking treatment at Hangzhou hospitals in case of necessity.

In September 2016, Professor Eyskens conveyed his insights to the UN General Assembly's Seminar on AMR, underscoring AMR's profound threat to public health, economic stability, and global harmony. He emphasized the imperative of a comprehensive examination of AMR, guided by evidence-based methodologies to prevent and mitigate resistance, all from the perspective of G20 value augmentation. He further urged esteemed organizations such as WHO, FAO, OIE, and OECD to address the overuse of antibiotics in agriculture and husbandry, which stands as the primary catalyst for AMR. Indeed, through conferences, high-level presentations, and constructive, effective cooperation with Chinese authorities and institutions, such as the Institute for Animal Science (IAS) of the Chinese Academy of Agricultural Sciences, PA International modestly contributed to China's National Action Plan and the establishment of effective and enforceable regulations.

In June 2017, the European Commission adopted the EU One Health Action Plan to address AMR, as requested by EU Member States in the Council Conclusions on June 17, 2016 [12]. The strategy comprises more than 70 initiatives addressing environmental, animal welfare, and human health factors, and its progress is continually monitored. As part of the action plan's

[1] In September 2022, the Health Emergency Preparedness and Response (HERA) published a report on AMR stockpiling feasibility study. This study was conducted in two stages. The first phase included mapping and assessing the most critical products, identifying weaknesses, and identifying other relevant stockpiling systems both within and outside the EU. The second phase included an analysis of the vulnerabilities of drugs identified in the first phase and proposed solutions. This aids in accelerating the development of new antibiotics to replace dated ones that have proven ineffective against infections.

execution, the Commission developed EU Guidelines on the Wise Use of Antibiotics in Human Health. The guidelines are intended to reduce inappropriate antimicrobial use and to encourage people to use antimicrobials appropriately. They are aimed at anyone who is involved in or responsible for the use of antibiotics. This encompasses hospitals (which are still not legally obligated to report AMR cases), nurses and their training (which still lack sufficient funding and support), veterinarians (who actually refuse to give up their prerogative to sell antibiotics), pharmacies (which, despite regulations, continue to sell antibiotics over the counter, especially in southern Europe), and health education (although a poll of 9 March 2021 among pharmacology students and experts at Leiden University in The Netherlands reveals that AMR awareness among this key important group is suboptimal [2]).

Following the approval of the 2017 AMR Action Plan, several key actions have helped to improve the EU's response to AMR [12]. Then, the COVID-19 pandemic, which caused damage across EU health systems and exposed gaps in our collective defenses against health threats, prompted new legislative measures. The European Union developed the European Health Union, which offers hope for the AMR eradication effort. Furthermore, they include the EU4Health program, specifically its EUR 50 million in direct grants to continue supporting Member States' efforts to combat AMR (joint action to support Member States' efforts to address infection prevention and control, prudent use of antibiotics, surveillance, awareness-raising, and strengthening of national action plans) for the years 2023-2026, as well as the establishment of the Commission's Health Emergency Preparedness and Response Authority (HERA) [12,13]. Currently, the European Union has approved a proposal to strengthen EU AMR activities through a One Health strategy. This proposal expands and concludes the 2017 EU One Health Action Plan against AMR in all three dimensions of the One Health spectrum to maximize synergies and ensure a robust and successful response to AMR. Examples of objectives include the creation of novel antibiotics and the promotion of global cooperation. Additionally, the use of bacteriophages is suggested to be included in the revised pharmaceutical legislation as one of the strategies to address AMR, according to European Commissioner Stella Kyriakides' final speech at the European Parliament Debate on AMR [14].

[2] On March 9, 2021, Mr Rio Praaning Prawira Adiningrat, the Managing Partner of PA Europe, engaged in a comprehensive discussion with pharmacology students and experts at Leiden University in The Netherlands. The focal point of this discourse was the critical concern of antimicrobial resistance and its far-reaching implications on a global scale. The discussion underscored the shared responsibility of various stakeholders, including industrial management, national and international health institutions, scientific and pharmacological experts, as well as political leaders, in addressing this pressing issue. During the poll, a series of potential solutions were put forth. These included advocating for investments in Small and Medium Enterprises (SMEs), the establishment of a market entry rewards system, and the proposition of classifying antibiotics as a global public good, supported by a universal budget and contingency stockpiles. Mr Praaning Prawira Adiningrat emphasized the necessity of fortifying the pharmaceutical distribution network to ensure its security, along with the paramount importance of unwavering adherence to existing European Union regulations pertaining to both environmental protection and human rights.

One might question why the Commission took so long to permit the use of bacteriophages for saving human lives, especially considering the strong support from its own science advisers.

2. Challenging Conventional Approaches: Novel Drug Development and Accessibility Bridge

Contrary to the European Commission's approach, recent research on the successful control of AMR proves that creating new antibiotics according to the current approach will only increase pathogen resistance beyond its current level, and exponentially so –thus increasing the risk of an AMR outbreak [15–18]. Instead, data analysis shows that new approaches for effective AMR control must be developed, and this has to do with the way the drugs are designed [15,18,24–34]. This design generates exponential resistance in pathogens, raising concerns that producing even a small quantity of new antibiotics could escalate resistance due to the current design's favouring of resistance proliferation [15–18]. In other words, providing taxpayers' funds to pharmaceutical companies to produce new antibiotics will boost pathogen resistance exponentially, beyond its current level, further aggravating the situation for everyone across-the-board by making the problem even more serious than it is today. This is in addition to the question of whether, after causing the threat of an AMR outbreak through overproduction of AMR-facilitating antibiotics, it is appropriate for the European Commission and European Member States to 'reward' the pharma industry with such funds, apparently without requiring various forms of oversight and control through, for instance, a public/private partnership. Like such public/private partnership, there are UN-funded entities like GARDP and US-funded initiatives like CARB-X and ARAC [19–21]. These organizations are fully committed to accelerating the advancement of AMR treatments, preventatives, and diagnostics.

Ultimately, the imperative of ensuring the effectiveness of novel drugs extends beyond their mere creation. It encompasses the critical need for equitable access once these drugs are brought to the market [22,23]. Resources shouldn't focus solely on design, but also on the entire process, from creation to distribution. The endeavour of developing replacement antibiotics cannot be confined solely to rich countries; it must be accompanied by robust measures that guarantee registration, affordability, and a reliable supply chain in regions grappling with the most severe resistance challenges. According to Dr Jayasree Iyer, CEO of the Access to Medicine Foundation, the design of the process along with the compounds must be reformed and rewarded differently.

3. Urgent Imperative: Designing Non-AMR Generating Drugs to Counter Pathogens

Since AMR data over roughly a 100-year period indicate that the antibiotics we have been manufacturing up to this point lead to the emergence of an exponential quantity of resistance in pathogens, there is now an evident need to design drugs that will be capable of 'resisting' the emergence of AMR in pathogens (so-called 'AMR-resistant' drugs) [15,18,24–34]. When it comes to drug design and the emergence of resistance in pathogens, many scientists maintain that medicinal plants have not generated any resistance in pathogens over millions of years, and, by conducting a comparative analysis between medicinal plants and the current design of drugs, the analysis lays out in a coherent manner what needs to be done to produce/manufacture AMR-resistant drugs [33,35–38]. In a nutshell, data analysis shows that the number of molecules entering drug combinations must be increased, in addition to synergism which is currently considered in drug design, both potentiation and antagonism must also be considered for integration into drug design to produce AMR-resistant drugs [15,18,24–34]. To that end, it can be expected that Artificial Intelligence will help accelerate the process by helping design and combine molecules in combination drugs which will not generate resistance in pathogens [24–27,39]. Indeed, the discovery of new molecules takes time and various approaches which offer a high throughput, such as Bacterial Cytological Profiling, have been conceived to speed up the discovery of new molecules and it is expected that harnessing the power of Artificial Intelligence with such tools can help identify and combine new molecules in order to produce AMR-resistant drugs [24–27]. Furthermore, research has shown that novel drugs can be successfully designed to cure AMR infections and that their structures can be simply modified to match current and future patient needs [18,28].

These research results contradict the objectives of the EU's AMR action plan and EMA guidance, which seek to develop novel antibiotics to combat AMR but are designed according to the current design scheme. However, proceeding that way may generate an additional exponential quantity of resistance, which may make the AMR situation even worse. While applauding the Commission for establishing HERA and taking the emerging threat of a global AMR outbreak seriously, it is hoped and expected that the Commission's leadership and notably President Dr Ursula von der Leyen (herself a medical scientist) and Public Health Commissioner Dr Stella Kyriakides will engage in a deeper analysis of the notion that more antibiotics designed according to the current design scheme exponentially aggravate the drug resistance situation and will seek and implement consequential alteration to the current EC Action Plan against AMR.

4. Key Elements to Prevent a Global AMR Outbreak

4.1. Appropriate use of existing antibiotics

According to a 2015 report by the National Institute for Health and Care Excellence (NICE), millions of antibiotic prescriptions are incorrectly given each year [40]. Some doctors might end up prescribing antibiotics for infections that are already resistant to the said antibiotics or even for viral infections that are not at all treatable by antibiotics. In some cases, second- or third-line antibiotics reserved for last-resort illnesses may be given by doctors when the first-line antibiotic would have correctly treated the infection. During COVID, antibiotic prescriptions have grown along with the number of telemedicine appointments [41–43]. In the absence of physical examinations or test results to evaluate if antibiotics are essential, prescriptions are made for a wider range of symptoms.

Apart from human use, antimicrobials are utilized more frequently on animals than on people worldwide. For instance, in the US, animal husbandry accounts for more than 70% of antibiotics that are considered essential for human use [44]. The risk of AMR increases when antibiotics are used in animals because low-level antibiotic intake in the food chain reduces antibiotic effectiveness in people [45]. In Norway, the use of antibiotics in food production is rigorously regulated through pharmacy sales and prescriptions issued only by veterinarians and aqua medicine scientists [46–48]. Following the recent announcement by the Norwegian government about its ongoing commitment to reducing antibiotic consumption and consumption patterns for food-producing animals, Norway has received praise for setting the standard among EU/EEA countries for maintaining low use of antibiotics for their food-producing animals [46–48]. Together, these studies show that the public and professionals need to be educated on how to use antibiotics appropriately while regulations continue lagging in content, efficacy, and enforcement. An unfortunate demonstration of this occurred when both European Parliament (despite an adopted position by its own ENVI Committee) and European Commission prioritised industrial profitability over the clear AMR threat. In mid-September 2021, ENVI's effort to stop using still-effective human-destined antibiotics in animals was defeated after an aggressive industry-supported veterinarian lobby [49–51]. Veterinarians, unlike medical doctors, are allowed to sell antibiotics not only to family pets, but also to commercial farm animals (about 66%) [50]. According to statistics, the continued sale of antibiotics to farmers through veterinarians is the cause of antibiotic overproduction and overuse. Multiple- or completely resistant bacteria can cause incurable infections in humans by consuming animals that are fed antibiotics to prevent disease and promote growth (chicken, pork, cattle, fish), contributing to an eventual AMR outbreak. Such epidemics are now common in China, where major antibiotic misuse and associated outbreaks have resulted in governmental bans on the use of numerous antibiotics in husbandry.

4.2. Equitable access to antibiotics

The access to the antibiotics and antifungals, both patented and off-patent, involves the responsibility of various actors, including pharmaceutical companies, governments, international organizations, NGOs, and healthcare providers [22,23]. Ensuring appropriate access is crucial for public health and global equity, particularly in cases where novel drugs are introduced without provoking AMR. Key points include the importance of responsible drug use, addressing AMR, pricing considerations, regulatory roles, licensing agreements, and collaboration among stakeholders [22,23]. The overarching goal is to enhance the accessibility, affordability, and effectiveness of vital medications, including AMR drugs. This is especially critical in low- and middle-income countries where access to fundamental treatments is deficient.

Sharing trade secrets is a critical component of pandemic agreements, as it plays a pivotal role in ensuring the availability of pharmaceutical products during future emergencies. In this context, a newly published article delves into the intricate realm of intellectual property rights, with a specific focus on patents and trade secrets [52]. The article underscores that manufacturing complex pharmaceutical products on a large scale during a pandemic necessitates the sharing of crucial knowledge and expertise. One of the central observations made in the article is that some intellectual property owners may be either unwilling or unable to grant licenses or share their closely guarded trade secrets. This reluctance or inability to share vital information can, in turn, pose significant obstacles to the timely and efficient production of the necessary countermeasures required to combat a pandemic.

To tackle this pressing issue, the article proposes a groundbreaking solution that calls for countries to take proactive measures in compelling intellectual property owners to share their trade secrets when deemed necessary during a pandemic emergency. This forward-thinking approach seeks to strike a balance between safeguarding intellectual property rights and prioritizing public health. Importantly, such a policy shift is envisioned to yield far-reaching benefits, not only for high-income countries but also for low- and middle-income nations, by fostering global collaboration and equitable access to life-saving pharmaceutical products in times of crisis.

4.3. Education and awareness

Education and awareness can be improved through the dissemination of scientific and technological advancements for society. This should start at schools and must certainly continue – as the poll among pharmacological students strongly suggests – at universities and professional education, including for nurses. Both approaches rely on professionals' ongoing relationships with governmental or private groups that are involved in providing healthcare [53–56]. As indicated above, several investigations have reported that veterinarians have a significant influence on farmers' antimicrobial use [57,58]. Institutions can also coordinate collective activity to address a collective problem [59]. In human medicine, for example, consumer education efforts coordinated by the French government resulted in a drop in antibiotic consumption [60].

In the animal health sector, research describing the effects of implemented regulations is missing and should be promoted, in conjunction with national antimicrobial consumption monitoring systems that illustrate worldwide trends in antimicrobial consumption. Thus, an in-depth awareness of the decision-making process is necessary, according to a recent study, as it can explain the success or failure of policy measures [61–63]. The results of these can subsequently be used to establish more targeted and enforceable regulations. In a globalised world such regulations should open the door to globally effective laws and regulations through the WHO and possibly through an UN-established global fund as was successfully practiced in the case of combating TB [3].

4.4. Over-the-counter antibiotics

Buying antibiotics over-the-counter, i.e. without a prescription, provides the perfect environment for AMR to flourish [64]. For instance, anti-tuberculosis medications have been widely accessible and frequently used for non-bacterial illnesses [64]. There are two safety issues with non-prescription use: adverse drug reactions and concealing underlying infectious processes [64]. Absence of policies or, more frequently, non-enforcement of existing rules (as is the case in southern European nations) leads to poor regulation and implementation of

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[3] The WHO's "Stop TB" program was led by Dr. Werner Christie, a board member of the PA International Foundation and a former minister of health in Norway, from the beginning until it included more than 40 international organizations (www.stoptb.org). More than two thousand partners have joined since then.
The new WHO End TB Strategy, adopted by all WHO Member States in May 2014 at the World Health Assembly, acts as a roadmap for countries to follow to end the global TB epidemic (https://www.stoptb.org/news/time-action-antimicrobial-resistance-tb). The framework's primary goals are as follows: 1) To encourage, strengthen, and increase tuberculosis research and innovation at the national level, with an emphasis on low- and middle-income countries, by developing country-specific TB research strategies and strong research capability. 2) To promote, strengthen, and catalyze global tuberculosis research through education, awareness, advocacy, sharing innovations, discussion of global priorities in TB research and development of regional and international networks for research and capacity building.

antimicrobials [65–69]. Further regulatory oversight over these over-the-counter antibiotics can and needs to be developed immediately.

4.5. Standards of hygiene

Significant evidence supports the idea that environmental health issues including sanitation, and hygiene (washing), waste management, food safety, and improved water quality, are vital in the battle against AMR [70–72]. AMR prevention measures include:

i) adequate washing through having access to and using safe water; appropriately containing, treating, and discarding human waste and other wastewater discharges, including that from medical facilities; and maintaining good personal hygiene, such as washing one's hands with soap when necessary to prevent the spread of resistant microorganisms,

ii) proper disposal of solid waste, which includes unneeded and outdated antimicrobials to avoid their needless exposure to environmental microorganisms, and

iii) providing appropriate food safety and hygiene measures, such as cultivating vegetables in unpolluted soil and selling and consuming animal products with suitable antimicrobial withdrawal periods [72].

4.6. Monitoring of antimicrobial usage and AMR

One of the most important aspects of controlling AMR is surveillance [73]. Many countries started monitoring bacterial zoonotic and commensal resistance concurrently. These steps should be used in conjunction with monitoring antimicrobial usage. Data collection practices are being standardized in Europe since comparisons between nations may be a major motivator for reform [74]. However, hospitals are still not required to report AMR cases; from many EU Member States – let alone non-EU countries – essential data are either not or not properly collected. The required funds for such activity are often withheld or not provided.

4.7. Regulations

Denmark, Norway, the Netherlands, and France have imposed restrictions on the use of Critically Important Antibiotics or CIAs, resulting in a significant fall in consumption of these antibiotics [56,75–78]. However, little research has been done on price regulation of antibiotics. Sales prices are not often regulated. Setting high pricing for antimicrobials may undoubtedly help restrict overconsumption given the concept of price/benefit to the farmers and the close connection between antibacterial cost and consumption. Successful examples in Belgium and

Denmark with taxation of antibiotics have neither been properly reported nor discussed at the highest levels of EU decision making.

5. Exploring Alternative Technologies to Combat AMR

5.1. Bacteriophages

Bacteriophage therapy has the potential to become one of the most effective tools in the fight against AMR infections [79,80]. They selectively attack harmful bacteria, preserving beneficial ones. However, unlocking their potential requires swift and accurate pathogen identification through improved diagnostics. Bacteriophages multiply even faster than the bacteria and therefore any resistance against them can be compensated by another mutation in the bacteriophage. CRISPR is also used to modify bacteriophages so that they are more effective in attacking and eliminating dangerous bacteria [81]. Researchers are focusing on developing bacteriophage preparations, such as bacteriophage cocktails and liposome-encapsulated bacteriophages [79,80]. Outside the EU, bacteriophages are already developed and used. Inside the EU – and reportedly under pressure of the pharmaceutical industry – the development and use of bacteriophages is not regulated. During a PA International webinar on 4 June 2020, Dr Jean-Paul Pirnay presented what his Military Hospital 'Queen Astrid' can effectively do as it falls outside European Commission control. This may have contributed to the very welcome decision of Health Commissioner Dr Stella Kyriakides to allow bacteriophages to be included in the revised pharmaceutical legislation as one of the measures to combat AMR [14]. To the extent that the European Commission has requested or possesses science-based evaluations of the use of bacteriophages in human health and food safety issues, the Commission is encouraged to share these with the EU Member States and all relevant EU institutions, particularly the European Parliament, in view of its relevant questions in the recent past.

5.2. Nanotechnology and vaccines

The nanoscale transformation of therapeutic agents can change their chemical-physical properties. This can improve a drug's bioavailability, enhance its interaction with bacteria, increase its penetration into their wall, and increase its effectiveness against resistant strains. Clarithromycin nanocrystal formulations have demonstrated effectiveness against multidrug-resistant *Helicobacter pylori*: nanocrystals allow the medicine to be directed to the desired location with a better therapeutic profile than clarithromycin solution and powder [82]. Clinical trials for some nanostructured products using antibiotics and antimicrobial peptides are underway [83]. For instance, multiple liposomal ciprofloxacin inhalation formulations are in Phase I, II, and III of clinical development, while a liposomal amikacin formulation for the treatment of recurrent *P. aeruginosa* infections in individuals with cystic fibrosis is in Phase III. The benefits of employing liposomes as antibiotic carriers in nanomedicine include a decrease in toxicity as well as an improvement in pharmacokinetic parameters, particularly biodistribution. The liposomal vesicles' fusing with the bacterial cell's outer membrane improves the antibiotic's release and entry into the bacterial cell. Furthermore, nanoparticles allow a better internalization of antibiotics, both hydrophilic and hydrophobic, that are not enzymatically inactivated and selectively reach the site of infection, overcoming resistance mechanisms [84].

Vaccination remains the most effective means of protecting against infectious diseases [85]. However, many new prospective vaccine candidates have limited practical application [86,87], because of their low immunogenicity and incapacity to induce an efficient, long-lasting immunity. Therefore, appropriate adjuvants and new delivery methods are required to improve immunogenicity, strengthen innate and adaptive immunity, and offer a long-term memory response. Considering this, nanotechnology provides an excellent platform for creating new, modern vaccinations. There are numerous vaccinations using nanomaterials that have been tested in pre-clinical or clinical trials to prevent bacterial infections in humans [88,89]. Nanomaterials can also be created to deliver several antigens and adjuvants at the same time, which is particularly essential for controlling the quality and duration of immune responses. Thus, nanomaterials-based vaccine formulations are a beneficial, safe, and effective approach to developing vaccines to combat AMR. The responsible authorities worldwide should focus on developing new regulations to promote nanotechnologies against AMR while taking safety and ethical concerns into consideration.

5.3. RNA silencing and the CRISPR-Cas system

Scientists have lately identified new techniques for combating AMR, in addition to treatments such as combination therapy, drug delivery systems, physicochemical methods or bacteriophages [90–98]. Examples include RNA silencing and the CRISPR-Cas system. RNA silencing is utilized to create very sensitive antimicrobial screens, determine the level of stringency needed for particular targets, as well as the mode of action. [99]. CRISPR for editing the bacterial genome is utilized to reduce or eliminate AMR and to create effective treatment options for multidrug resistance [92,100–102]. These gene-editing tools can quantitatively, specifically, and selectively target bacterial genomes [92,100–103]. The CRISPR system offers a distinct advantage in its ability to differentiate between commensal and pathogenic bacteria. It further enables the targeted removal of genes associated with AMR from bacterial populations, as well as virulence factors. Moreover, the CRISPR system enhances bacteria's susceptibility to antibiotics by effectively eliminating plasmids containing AMR-related genes [93,102,103].

Conclusions

- New drug development will not stop AMR if those new drugs are manufactured in such a way that they continue to be generators of resistance in pathogens like current drugs do. ‘AMR-resistant’ drugs are needed to prevent the rise of resistance in pathogens in the first place. This is the most important as worldwide AMR data show that drugs designed according to the current approach provoke an exponential increase in pathogen resistance. Until AMR-resistant drugs are manufactured, alternative strategies to contain AMR should be optimised in the meantime. Responsible authorities and stakeholders worldwide should lead efforts to promote the pharmaceutical industry's production of AMR-resistant drugs. These efforts should be guided by the latest research in drug design theory, with the aim of preventing the development of AMR in pathogens [15,18,24–34].
- Responsible authorities and stakeholders should not only encourage the development of new ’reserve’ antibiotics, but their use must also be restricted to extreme emergency scenarios *only* to slow down resistance development. HERA went deeper in analysing from different perspectives and targets the possible approaches to the stockpiling of antibiotics [13]. HERA approaches help to lower wastage in existing private and public inventories and stockpiles and limit the number of therapies for severe and potentially fatal illnesses. Using HERA approaches will help target the diseases in the EU and globally as well as slow the spread of AM.
- In addition to HERA, it is imperative to formulate new strategies aimed at establishing global agreements for the distribution of effective medications, including AMR-resistant drugs. These initiatives would significantly influence access to these crucial treatments on a worldwide scale.
- The current ‘market failure’ in the development of ‘new’ antibiotics due to low prices caused by overproduction, overselling, and overuse (particularly in husbandry) must be addressed by specific legal bans and taxes on antibiotic use, as well as by a global strategy like the TB action at the UN level some years ago [104]. This global strategy must incorporate public-private partnerships.
- The Stop TB Partnership's Global Drug Facility (GDF) as well as the US Strategic National Stockpile (SNS) were recognized as international models of interest [104]. The GDF has over 2,000 partners and is the world's largest purchaser and provider of tuberculosis drugs in the public sector. The European Parliament, the European

Commission, and the European Council are encouraged to task the European Commission's HERA with using the GDF as a model for the production and storage of (new) antibiotics intended for outbreak cases that pose a threat of developing into a global pandemic.

- The alternative approaches, as described above, and the suggested rapid action are equally required for tackling AMR as the careful and limited production of new antibiotics under the strictest Governments' controls, and indeed through Public-Private Partnerships.
- Veterinarian use of human-targeted antibiotics must immediately be halted and enforced; sales of antibiotics by veterinarians must be stopped; large-volume antibiotics sales with quantum reductions must be banned; over-the-counter sales of antibiotics must be outlawed; AMR education at relevant universities and in specific health educational institutions must be mandatory.

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