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Antibiotics: A multi-perspective challenge

Urgent challenges to the provision of effective antibiotics “today” and “tomorrow”.

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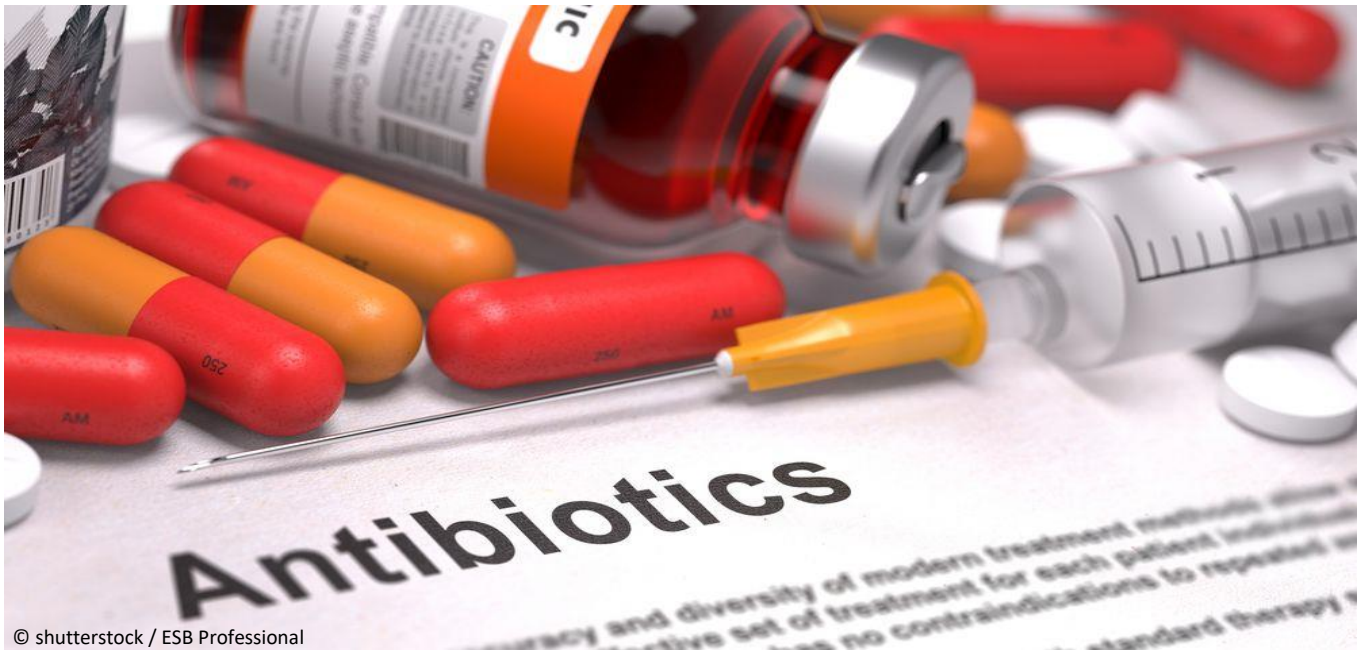

The introduction of antibiotics has made many modern medical procedures possible, including cancer treatment, organ transplants and open-heart surgery. However, misuse has resulted in the rapid rise of “antimicrobial resistance” (AMR) and some infections are now untreatable. Furthermore, the clinical pipeline for new antibiotics has dried up. We are facing a “silent tsunami”. The upcoming Commission proposal for a reform of EU pharmaceutical law – expected in March – presents an ideal opportunity to address the issues at hand in a comprehensive public discussion. Cooperation between the EU and its Member States is urgently needed to formulate a comprehensive approach. Such an approach should include:

- Efforts to reduce external dependence on countries like China by diversifying antibiotics supply chains. The creation of strategic partnerships with third countries may represent a promising long-term option for reducing existing supply risks.
- Regulatory action to promote the private stockpiling of essential antibiotics. Economic incentives should be designed to ensure that the societal benefits of reducing supply risks through stockpiling are internalized.
- A reduction in consumption through multiple actions by EU citizens, healthcare professionals, Member States and the EU aimed at responsible use of antibiotics, through e.g., training, guideline development and awareness campaigns.
- Efforts to create an incentive system focussing not on individual projects but on the long-term continuous innovation and development of new antibiotics and alternatives.
- In sum, there is no single solution, and any bundle of measures will come at some form of (economic) cost.

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1. Introduction

All medicines are important, but antibiotics are especially relevant for society at large. Antimicrobials, such as antibiotics, are substances used to kill microorganisms or to stop them from growing and multiplying. As such, they are commonly used in human and veterinary medicine to treat a wide variety of infectious diseases.[1]

The key challenge is the provision of effective antibiotics (1) "today" and (2) "tomorrow". In other words, the provision of effective antibiotics must be ensured, both now and in the future. This is clearly a multidimensional challenge and anything but trivial. Yet, a clear and present danger exists[2] as we are facing a "silent tsunami"[3] and therefore all stakeholders and political levels must come together to formulate a comprehensive EU approach.

The urgent challenges of "today" and "tomorrow"

Looking at the present, the fundamental challenges are (1) to ensure sufficient supply of currently available types of antibiotics and (2) to support the reasonable and responsible use of currently available types of antibiotics, so that they remain effective as long as possible.

The overuse or misuse of (currently available) antibiotics has been linked to the emergence and spread of antimicrobial resistance (AMR).[4] Existing antibiotics are becoming increasingly ineffective as drug-resistance spreads.[5] Generally, there is a downward trend in human use of antibiotics in the EU.[6] Yet, it is also clear that the situation remains critical,[7] as shown by an increase in the number of infections and deaths as a result of antibiotic resistant bacteria since 2016.[8]

Furthermore, the challenges of a worldwide supply chain and the resulting dependencies will need to be addressed. The issue of dependence on antibiotics (or their ingredients) from third countries has

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1 EFSA (n/a), Antimicrobial resistance. All sources last accessed: 31.01.2023.

2 See e.g. on the current situation in Germany: https://www.tagesschau.de/inland/gesellschaft/medikamentenmangel-101.html and more generally Ferreyra, C. et al. (2022), Diagnostic tests to mitigate the antimicrobial resistance pandemic—Still the problem child. The Commission has identified AMR (see section 2) and the lack of antimicrobials as one of the major challenges of EU health policy; see cep**PolicyBrief** 2021 on the Pharmaceutical Strategy for Europe.

3 "Silent", referencing the fact that the issue has, pre-COVID-19, commanded high-level meetings of the United Nations General Assembly and was top of the health agenda at G7 and G20 meetings, but which has then been side-lined on the political agenda. "Tsunami", referencing to the immense impact of the issue on each person and the society at large. See on these aspects: Mendelson, M. / Sharland, M. / Mpundu, M. (2022), Antibiotic resistance: calling time on the 'silent pandemic', JAC-Antimicrobial Resistance, Volume 4, Issue 2, April 2022, https://doi.org/10.1093/jacamr/dlac016 as well as the interview of University of Oxford's Professor Timothy Walsh from 22 April 2022, Antimicrobial resistance is a slow tsunami, HealthEuropa.

4 See section 2. EFSA (n/a), Antimicrobial resistance. See generally also WHO (2020), Antibiotic resistance and WHO (2021), Antimicrobial resistance. The topic can be separated between human consumption and use of antibiotics in veterinary medicine. Antibiotic consumption is a key driver of antibiotic resistance. Globally, they are often inappropriately prescribed for viral infections, like colds and flu; see WHO (n/a), Vaccines for Antimicrobial Resistance (AMR).

5 WHO (2021), Antimicrobial resistance.

6 European Commission (2022), Data on antimicrobial resistance (AMR): use of antibiotics in the EU decreases but more needs to be done and ECDC (2022), Antimicrobial consumption in the EU/EEA (ESAC-Net), Annual Epidemiological Report for 2021, p. 1.

7 See e.g.: Mendelson, M. / Sharland, M. / Mpundu, M. (2022), Antibiotic resistance: calling time on the 'silent pandemic', JAC-Antimicrobial Resistance, Volume 4, Issue 2, April 2022, https://doi.org/10.1093/jacamr/dlac016.

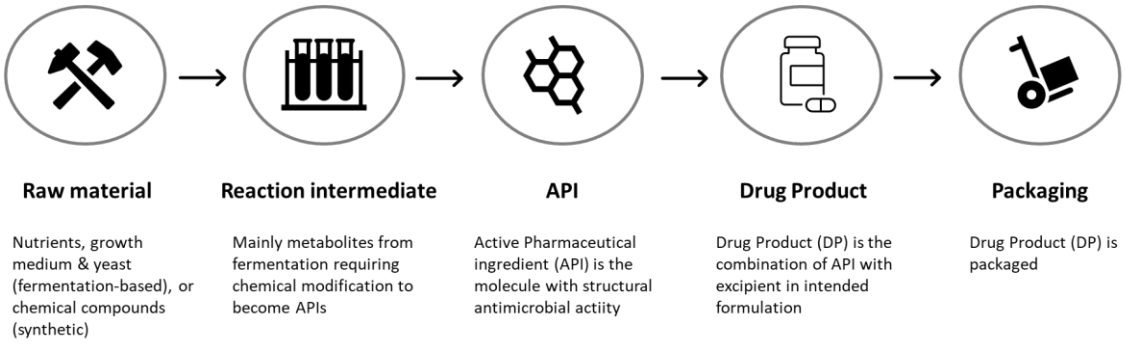
8 ECDC (2022), Assessing the health burden of infections with antibiotic-resistant bacteria in the EU/EEA, 2016-2020, pp.1, 4 and 5 and European Commission (2022), Data on antimicrobial resistance (AMR): use of antibiotics in the EU decreases but more needs to be done.

been addressed both in general terms[9] and specifically[10]. Thierry Breton, Commissioner for Internal Market, stated that some countries were using this as "a new kind of diplomacy".[11] However, although we have become aware of dependencies in other fields,[12] here the level of public awareness arguably does not reflect the level of severity.[13]

Looking to the future, the fundamental challenge is the fact that the clinical pipeline for new antimicrobials has dried up.[14] In 2019, the World Health Organization (WHO) identified 32 antibiotics in clinical development that address the WHO list of priority pathogens. It concludes that more new antimicrobials are urgently needed.[15]

To address the multidimensionality of the issue, we apply a supply chain perspective. Figure 1 sketches a stylized supply chain of antibiotics starting with raw material extraction and ending with the packaging of the final drug product. The single steps differ in the intensity of input use concerning labour, energy, auxiliary products and knowledge, affecting the suitability of countries as production locations, and thus providing motivation for international specialization. Therefore, from the perspective of the end consumer, each step comes along with its specific supply risks. Moreover, preceding the supply chain, the process of developing and marketizing new types of antibiotics is associated with significant long-term risks for supply as well. Each step in the whole process requires tailor-made policy answers.

Figure 1: Stylized supply chain for antibiotics



Source: own illustration based on AMR.Solutions.[16]

Consequently, potential causes for shortage situations are manifold. They could result from increases in production costs (e.g., higher energy prices) in single production steps, inducing production stops for intermediates that impair the whole supply chain. They could also be caused by sudden spikes in

[9] See e.g.: welt.de (2022), Plötzlich fehlen sogar Krebsmedikamente.

[10] See e.g.: Pharmazeutische Zeitung (2022), Antibiotikaproduktion in Europa: Pro Generika warnt vor gefährlicher Marktkonzentration - addressing the issue of the last penicillin production site in Europe.

[11] See Copley, C., EU must wean itself off Asia for key drug ingredients, Reuters, 7.10.2020.

[12] See Wolf, A. (2022), How green hydrogen will make Europe more independent; Küsters, A. (2022), Europas verwundbares Rückgrat.

[13] As Ulrike Holzgrabe, former Professor of Pharmacy at the University of Würzburg, put it in 2020 (own translation): „The Chinese don't need a nuclear bomb. They simply don't supply antibiotics [...], and then Europe will take care of itself." see Pharmazeutische Zeitung (2020), Produktion zurück nach Europa holen.

[14] WHO (2021), Antimicrobial resistance.

[15] WHO (2021), Antimicrobial resistance. Additionally, consumption remains a key factor for tomorrow too because if changes are not made to the way antibiotics are consumed, any new type of antibiotic will suffer the same fate as those currently available and become ineffective more rapidly.

[16] AMR.Solutions: Antibiotic Supply Chains: Challenges & Opportunities.

consumption, e.g., because of a spread of contagious diseases. Moreover, they could be due to regulatory changes in major producing countries, on a product-specific (stricter environmental standards) or on a general level (China's Zero-Covid Policy of the recent past). Shortages are not just a prediction for the future, but are in parts already present today. Recently, due to an increase in respiratory infections, shortages have been reported of antibiotics amoxicillin and amoxicillin with clavulanic acid, especially for children.[17] These are used for the treatment of Strep A infections. [18] In France, Ireland and the UK children have died from these infections.[19]

Trade, Consumption and Innovation

To begin with, it should be stated that there is no single solution to the challenges. Additionally, various dimensions will also need to be considered,[20] such as the risks connected to the worldwide supply chain and the corresponding dependencies; the overuse or misuse, in other words the "wrong" consumption of antibiotics (persons and animals); pharmaceutical residues in the environment and proprietary issues with regard to a sound system of intellectual property protection. The topic must be tackled from multiple perspectives. This cep**Input** will start by looking at the extent of the EU's external dependence (section 3) and at human use of antibiotics in Europe (section 4). It goes on to discuss specific solutions based on the current product portfolio and consumption pattern (section 5) and to assess the barriers and challenges to innovation (section 6). This may serve as a basis for initiating a broader and deeper discussion and contribute to finding a more comprehensive[21] solution.

2. Roots of the Problem

Many modern medical procedures, including cancer treatment, organ transplants and open-heart surgery, are only possible as a result of the introduction of antibiotics. However, misuse has resulted in the rapid rise of antimicrobial resistance (AMR) and some infections are now untreatable.[22] In other words, AMR refers to the ability of microorganisms to withstand antimicrobial treatments. Resistance to antibiotics renders these treatments ineffective.[23]

From 2016 to 2020, it is estimated that the number of deaths resulting from antibiotic resistant bacteria increased in the EU/EEA by around 16% from 30,730 in 2016 to 35,813 in 2020. The number

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17 EMA (2023), Joint statement by Executive Steering Group on Shortages and Safety of Medicinal Products (MSSG) on shortages of antibiotic medicines.

18 On treatment of Strep A with antibiotics see NHS (2023), Strep A.

19 ECDC (2022), Increase in Invasive Group A streptococcal infections among children in Europe, including fatalities. On the situation in the UK see: Financial Times (2022), UK pharmacies say they are being forced to dispense Strep A antibiotics at a loss and The Lancet (2022) Strep A treatment: working for now, p.1.

20 See appendix for a graphical representation.

21 It may be that, as has been argued, AMR should be included in the "Pandemic Treaty" currently negotiated at the World Health Organization (WHO) level; see UK AMR envoy Sally Davies: "I'm at the moment arguing that we really need to have antimicrobial resistance in any pandemic treaty that comes out of the negotiations that have just started at the WHO."; World Economic Forum, Antimicrobial resistance - how to stop a quiet pandemic, 14 April 2022.

22 Hutchings, M.; Truman, A.; Wilkinson, B. (2019), Antibiotics: past, present and future, p. 1.

23 EFSA (n/a), Antimicrobial resistance. The development of resistance is part of the normal adaptation mechanisms of organisms; see Deutsche Apotheker Zeitung (2000), Antibiotika. On an individual level, this risk can be demonstrated with regard to life-saving treatments such as organ transplantation and cancer chemotherapy which need antibiotics to prevent and treat bacterial infections following treatment. Furthermore, without effective antibiotics, also minor surgery could become a high-risk procedure. See Department of Health and Social Care, UK Health Security Agency, Department for Environment, Food & Rural Affairs and Veterinary Medicines Directorate (2022), Antimicrobial Resistance (AMR). See also EFSA (n/a), Antimicrobial resistance; WHO (2020), Antibiotic resistance and WHO (2021), Antimicrobial resistance.

of infections increased from 685,433 to 801,517 in the same time period.[24] It is arguably one of the greatest threats[25] to clinical and global health – with potentially immense health, economic and social consequences. It affects people worldwide[26], as well as those yet to come into existence, as all suffer the shared, interdependent vulnerability to this threat.[27]

The cost of AMR to national economies and their health systems is significant. It affects the productivity of patients and their caregivers through prolonged hospital stays and the need for more expensive and intensive care.[28] The costs related to expenditure and productivity losses in the EU are about € 1.5 billion per year.[29]

In short: AMR leads to higher medical costs, prolonged hospital stays, and increased mortality[30] and is often referred to as a "silent pandemic".[31] A pandemic that, pre-COVID-19, commanded a high-level meeting of the United Nations General Assembly and was top of the health agenda at G7[32] and G20 meetings, but which has now been side-lined on the political agenda.[33]

3. EU External Dependencies

From an EU perspective, the overall trade balance in the segment of antibiotics has remained negative for the last couple of years. Thus, antibiotics differ from other groups of APIs such as vitamins or glycosides (see Figure 2). Until very recently, the balance in the segment of hormones was worse. However, that balance switched to a plus in 2020, while no similar positive trend was visible for antibiotics. Thus, from a trade perspective too, Antibiotics would seem to be sufficiently different to deserve a separate investigation.

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[24] ECDC (2022), Assessing the health burden of infections with antibiotic-resistant bacteria in the EU/EEA, 2016-2020, p. 1, p. 4-5 and p. 12, figure 5.

[25] See also UK AMR envoy Sally Davies: "We've really got to move forward and take this seriously at every level. But it'll be much easier than climate change. And if we don't sort it people will be dead before climate change kills them."; World Economic Forum, Antimicrobial resistance - how to stop a quiet pandemic, 14 April 2022.

[26] To highlight this see Michael, C.A. / Dominey-Howes, D. / Labbate, M. (2014), The Antimicrobial Resistance Crisis: Causes, Consequences, and Management, p. 3: „… global humanity is now effectively a single biological population. Individuals may travel to most places on the planet within 1 or 2 days and may realistically access any other human population and indeed virtually any environment on the planet within a week. This means, firstly, that along with the ability to rapidly transport humans, their attendant microbes and pathogens may also cross the planet rapidly and without significant impediment. Such rapid travel can transport infected individuals across the planet many times before even the first symptoms of infections become apparent, so allowing pathogens to be distributed globally."

[27] See Littmann, J. / Viens, A.M. / Silva, D.S , The Super-Wicked Problem of Antimicrobial Resistance, in: Jamrozik, E. / Selgelid M. (eds.), Ethics and Drug Resistance: Collective Responsibility for Global Public Health, 2020, p. 421 with further evidence (see esp. footnote 1).

[28] WHO (2021), Antimicrobial resistance.

[29] ECDC (2022), Antimicrobial consumption in the EU/EEA (ESAC-Net), Annual Epidemiological Report for 2021, p.23 and European Medicines Agency (2022), Antimicrobial resistance.

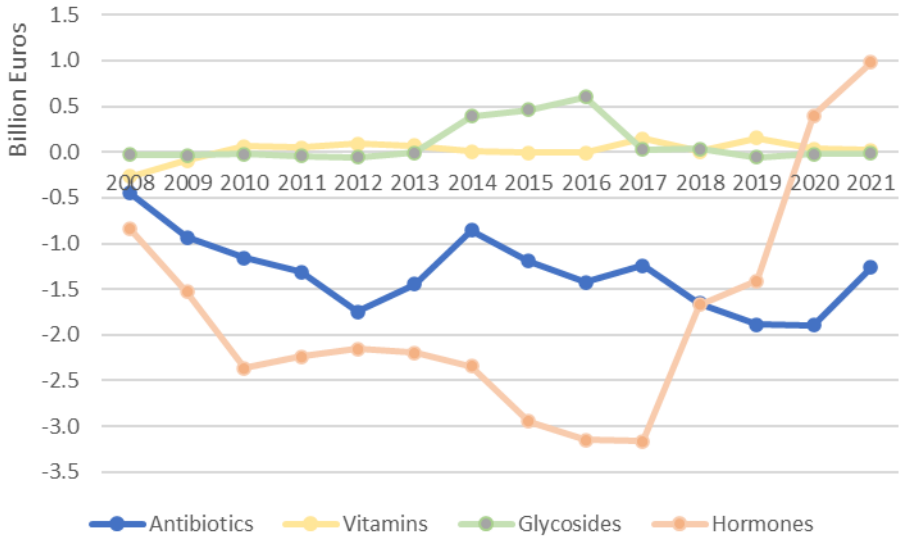
[30] See WHO (2020), Antibiotic resistance.

[31] Instead of many: https://www.imperial.ac.uk/stories/antimicrobial-resistance/.

[32] The topic was picked up again by the G7 in 2021: https://www.mof.go.jp/english/policy/international_policy/convention/g7/g7_20211213.pdf.

[33] See altogether: Mendelson, M. / Sharland, M. / Mpundu, M. (2022), Antibiotic resistance: calling time on the 'silent pandemic', JAC-Antimicrobial Resistance, Volume 4, Issue 2, April 2022, https://doi.org/10.1093/jacamr/dlac016.

Figure 2: EU trade balance (net exports) with respect to different categories of APIs



Source: UN Comtrade (2022); own representation

3.1 Country pattern of EU imports

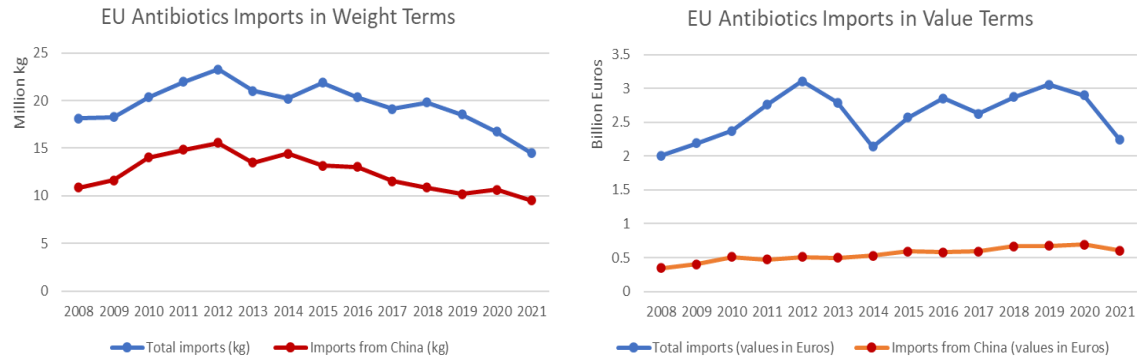
The biggest antibiotics exporter in the world in terms of weight and value is China. According to UN Comtrade Statistics, its share in global export value amounted to 45% in 2021.[34] It is not surprising, therefore, that in terms of product weight the EU imports most of its antibiotics from China. Its share of EU imports by weight amounted to 66% (or 9.52 kt), far bigger than that of the USA (5 %), Singapore (3 %) and Switzerland (2 %). However, in value terms most EU antibiotics imports come from Switzerland with 42% (1.1 billion USD), followed by China (27 %), the USA (16%) and South-Korea (3%). This discrepancy reveals significant differences in import prices. In 2021, the average import price[35] per kg of antibiotics imported from China (75 USD / kg) was about 80% lower than the average price of EU antibiotics imported from the rest of the world (393 USD / kg). In turn, China's dominance in weight terms is to some extent explained by its significant cost advantage. Hence, the trade value figures on their own conceal the true degree of Europe's dependence on China in antibiotics trade. From a supply chain perspective, this dependence mostly concerns the production of generic antibiotics, as well as raw materials and other inputs from the early stages of antibiotics production.

When looking at the evolution of this dependence over time (see Figure 3), it becomes clear that it is not the result of recent structural shifts or a temporary distortion but has been a constant development over the last thirteen years. The fact that imports from China have shown a slight decline in weight terms in recent years appears only to reflect the general trend to lower antibiotics imports, and no specific strategy of disentanglement from China. In value terms, the continuity of imports from China in fact stabilized the fluctuations in the overall import value for antibiotics.

[34] UN Comtrade (2022), Comtrade Database. https://comtrade.un.org/data, United Nations.

[35] Average prices are calculated as a ratio of cif-value and net weight of imported goods. Hence, the price includes all costs accruing until the imported good reaches the EU frontier (i.e. transport costs, insurance etc.).

Figure 3: Evolution of EU Antibiotics imports from China



Source: UN Comtrade (2022); own graphs

3.2 Import-Related Risk Factors

As a result of this dependence, Europe is potentially exposed to various import-related risks. In the following section, we will highlight the size of specific risks using quantitative risk indicators. For reasons of transparency, we apply indicators used by the EU Commission itself in preparing its regular assessment of critical raw materials.[36]

3.2.1 Supplier Concentration

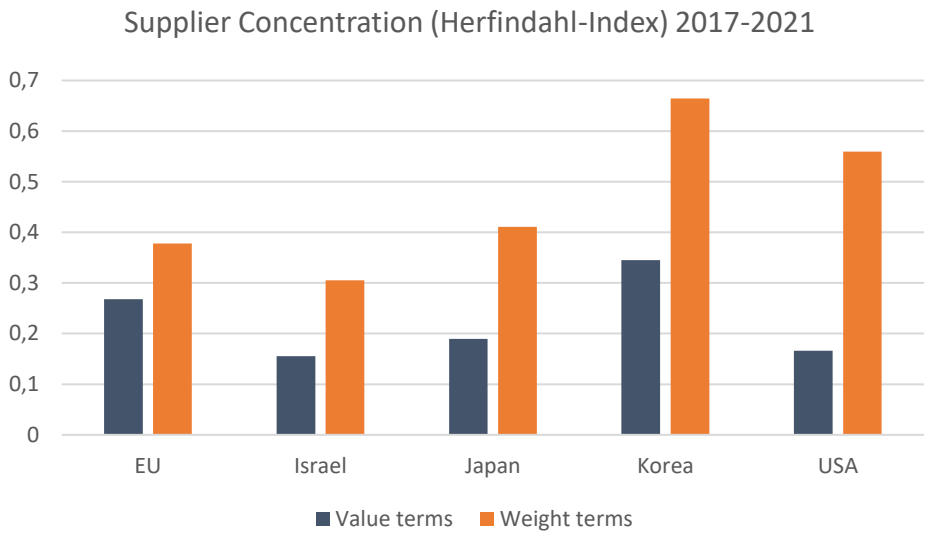
The figures on bilateral antibiotics trade from UN Comtrade form the starting point for this analysis. They offer a complete picture of EU trading partners in the field of antibiotics. The first step in analysing this picture is to calculate a figure for the degree of concentration. Being dependent on one or only a few suppliers represents per se a certain risk for an importing country/region, as any negative economic shock that impairs production in the supplying country could lead to significant shortages. In regional economics, a standard measure to express the degree of spatial concentration is the Herfindahl-Hirschman-Index (HHI).[37] It is defined as the sum of the squared market shares of each supplier and thus represents a measure ranging from (almost) zero to one.

In this context, a value of one would indicate that total antibiotics imports stem from just one supplying country. Figure 4 represents average annual values of the HHI for the last five years (2017-2021), to cancel out any year-specific effects. The EU situation is put into perspective by comparing it with the HHI-values for the antibiotics import structure in four non-EU countries: Israel, Japan, South Korea and the USA.

[36] European Commission (2020), Critical raw materials resilience: charting a path towards greater security and sustainability. Communication from the European Commission to the European Parliament, the Council, the European Economic and Social Committee, and the Committee of the Regions. (2020) 474 final.

[37] Rhoades, S. A. (1993), The herfindahl-hirschman index. Fed. Res. Bull., 79, 188.

Figure 4: Supply concentration measures of imported antibiotics for five countries/regions over the period 2017-2021



Source: UN Comtrade; own calculations

In value terms, supplier concentration for EU imports was substantially higher than for the countries of comparison, except for South Korea. In weight terms, imports for both South Korea and the US are shown to be much more concentrated than those for the EU. Again, the special role of China lies behind this discrepancy. South Korea and the USA recently in fact sourced a higher physical share of imported antibiotics from China than EU countries did. In the case of South Korea, this share amounted to 83 % in 2021. Due to the comparatively low prices of Chinese antibiotics, concentration in value terms was lower for all countries. Hence, while there are examples, like Israel, where import structure is more diversified, Europe is certainly not alone in its dependence on China in this product field.

3.2.2 Political Stability and Regulatory Quality

Other important risk factors typically assessed are related to the political-regulatory situation in the producing countries. Firstly, a low degree of political stability among major suppliers could raise the procurement risk for an importing country / region. Political overthrow or terrorist activity could impair production capabilities of the suppliers. Secondly, low efficiency or lack of adequacy in the field of product-related regulation entails risks related to product quality or compliance with environmental standards. When it comes to antibiotics, no product-specific country indicators are currently available for this area. Therefore, like the EU in its critical raw material assessment, the general country indicators on quality of governance produced by the World Bank are used.[38]

Specifically, indicators of “Political Stability” and “Regulatory Quality” are selected, as they capture most closely the aforementioned risk factors. They are based on subjective assessments by a range of international experts and are scaled based on an ordinal range from -2.5 to +2.5. By calculating a weighted average of the indicator values obtained for trading partners (with import shares as weights), we get a general indication of the policy-related risk exposure of the EU’s imports of antibiotics. Figure 5 represents results for the EU and again for four non-EU countries, distinguishing as above between

[38] World Bank (2022), Worldwide Governance Indicators. https://info.worldbank.org/governance/wgi/

imports by weight and by value. The overall political stability of the EU's antibiotics suppliers is judged as higher than for all countries of comparison, both in value and in weight terms. This is in large part due to the relative importance of Switzerland as a neighbouring trading partner of the EU. For regulatory quality, the picture is qualitatively similar. When measuring trade in value terms, regulatory quality is only higher for Israel's trading partners, mainly due to the role of the Netherlands as an exporter of antibiotics to Israel.

Figure 5: Governance quality of the antibiotics suppliers of five countries over the period 2017-2021

Source: UN Comtrade (2022); World Bank (2022); own calculations

Finally, it should be stressed that supply risks are certainly not limited to country risks but also relate to the market behaviour of specific companies in third countries and their reliability. To analyse this, a detailed look at the supply chains of specific antibiotics is required, involving (non-public) company-level data which is outside the scope of this report. In this regard, the reader is referred to the recent

vulnerability assessment conducted by the European Health Emergency Preparedness and Response Authority (HERA).[39]

4. Human Consumption of Antibiotics in the EU

The three main sources used hereinafter to measure human consumption are (1) data from the European Centre for Disease Prevention and Control (ECDC) contained in the "antimicrobial consumption database (ESAC)"[40], (2) data from the Eurobarometer[41] and (3) data from the WHO surveillance report on antibiotic consumption 2016-2018[42], which has data on consumption in 65 countries worldwide.

The ESAC database is used to describe the European situation by using data on consumption[43] in the community sector (primary care), thereby excluding hospital consumption.[44] For the comparison with non-EU countries, total consumption data is used from this database.

The unit of measurement "Defined Daily Doses per 1.000 inhabitants per day" (hereafter "DDD") is used to express antibiotic consumption. One DDD is the assumed average maintenance dose per day per drug used for its main indication by adults.[45]

Consumption in the EU: General Aspects

ECDC data generally shows a reduction of consumption of antibiotics in the community sector from an average of 18.7 DDD in 2017 to 15.0 DDD in 2021.[46] See also table 1. This is a trend that can be observed from 2015 onwards.[47]

The Eurobarometer 2022 also shows a downward trend. Fewer respondents took antibiotics in 2022 compared to 2018 and 2009. According to the Eurobarometer 2022, almost a quarter (23%) of European respondents took antibiotics in the past year. Based on these answers, there has been a significant decrease in the consumption of antibiotics in the EU, with 40% of EU respondents reporting in 2009 that they had used antibiotics in the past year, compared to almost a third (32%) of EU

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39 European Commission, European Health and Digital Executive Agency (2022), HERA AMR feasibility study on stockpiling D-1-D-5 Final Report, Publications Office of the European Union.

40 The data in this database is reported to the European Surveillance of Antimicrobial Resistance Network (ESAC-Net) and retrieved from the European Surveillance System (TESSy). See: ECDC (2022), Antimicrobial consumption in the EU/EEA (ESAC-Net), Annual Epidemiological Report for 2021, p. 3.

41 See European Union (2022), "What is the Eurobarometer" for more information on Eurobarometer. The data from the Eurobarometer, is based on interviews with EU citizens, specifically on the question of whether they had taken antibiotics in an oral form over the past 12 months; see Special Eurobarometer 522 (2022), downloadable from Antimicrobial Resistance, Summary, pp.5 and 7.

42 WHO (2019) WHO Report on surveillance of Antibiotic Consumption 2016-2018 Early Implementation.

43 Data on antibiotics in the subgroup Anatomical Therapeutic Chemical (ATC) JO1 shows that consumption is much higher in this group compared to other ATC subgroups. See: ECDC (2022), Antimicrobial consumption in the EU/EEA (ESAC-Net), Annual Epidemiological Report for 2021, pp. 1 -2 and 21-22.

44 The reason is that Germany did not report data on the hospital sector. See: ECDC (2022), Antimicrobial consumption in the EU/EEA (ESAC-Net), Annual Epidemiological Report for 2021, p. 4. Additionally, most antibiotics in the EU are consumed in the community sector. Hospital consumption is very small compared to consumption in the community sector. For example, in 2021 the average DDD per 1,000 inhabitants in the hospital sector in the EU/EEA was 1.41 DDD per 1.000 inhabitants compared to 15.0 for the community sector. See: ECDC (2022), Antimicrobial consumption in the EU/EEA (ESAC-Net), Annual Epidemiological Report for 2021, pp. 12 and 17.

45 ECDC (2022), Antimicrobial consumption in the EU/EEA (ESAC-Net), Annual Epidemiological Report for 2021, p. 3.

46 ECDC (2022), Antimicrobial consumption in the EU/EEA (ESAC-Net), Annual Epidemiological Report for 2021, p.12 table 3.

47 ECDC (2022), Antimicrobial consumption in the EU/EEA (ESAC-Net), Annual Epidemiological Report for 2021, p.12 table 3.

respondents in 2018. Altogether, there was a total reduction of 17 percentage points from 2009 to 2022.[48] Since 2009 there has been an increase in respondents in the EU saying that they took antibiotics without a prescription. A minority of respondents (8%) in 2022 said that they took antibiotics without a prescription.[49] This number is slightly higher than in 2018[50] and 2009[51].[52]

Major Differences among the Member States

Consumption of antibiotics in the EU differs significantly between Member States.[53] According to data from the ECDC, consumption of antibiotics in the community sector is generally high in South-Eastern Europe, particularly in Greece, Romania and Bulgaria and low in North-Western and Northern Europe, particularly in Austria, The Netherlands and Germany. For example, the consumption of antibiotics in Romania in 2021 was 24.3 DDD compared to 7.2 DDD in Austria.[54] EU countries with high population figures,[55] e.g., France and Italy, also show a high level of consumption in absolute terms, with France in first place followed by Italy[56].[57]

Data collected from the Eurobarometer published in 2022 shows a slightly different picture compared to the ECDC data from 2021. The smallest EU Member States, Malta and Luxemburg, record the highest levels of consumption with 42% and 36% of respondents saying that they took antibiotics in the past year, whilst Germany and Sweden record the lowest levels with 15%[58].[59] The 2018 Eurobarometer, on

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48 European Union (2022), Special Eurobarometer 522 Antimicrobial Resistance.

49 This means antibiotics were obtained without prescription from a pharmacy (4% of respondents) or elsewhere (2% of respondents) or usage of a left over from a previous course (2% of respondents). See: European Commission (2022) downloadable from Special Eurobarometer 522 Antimicrobial Resistance, Summary, p. 8.

50 The number of respondents who said they took antibiotics without prescription in 2018 was 7%. See: European Commission (2018), Special Eurobarometer 478 Antimicrobial Resistance, p.13.

51 In 2009, 5% of all respondents in the EU took antibiotics without a prescription. See: European Commission (2010), Special Eurobarometer 338 Antimicrobial Resistance, p.17.

52 European Commission (2022) downloadable from Special Eurobarometer 522 Antimicrobial Resistance, Summary p. 6, European Commission (2018), Special Eurobarometer 478 Antimicrobial Resistance, p.13 and European Commission (2010), Special Eurobarometer 338 Antimicrobial Resistance, p.17.

53 Consumption between Member States also differs by looking at consumption using the WHO "Access, Watch and Reserve" classification. In 2017 WHO introduced the 'Access, Watch and Reserve" classification as a tool to improve the use of antibiotics. Access antibiotics are mostly first and second choice antibiotics that offer the best therapeutic value while minimising the potential for AMR. WHO proposes that at least 60% of all antibiotics consumption should be in this category. "Watch" antibiotics should be used with caution because of their high potential to cause antimicrobial resistance or their side-effects. Reserve group antibiotics should only be used for specific indications as a 'last resort'. The average EU/EEA consumption of antibiotics in the access category in both the hospital and community sector in 2021 was just above 60%, with 8 EU Member States having a consumption in this category of less than 60%. Generally, Northern and Western EU Member States, use a higher proportion of antibiotics in the "Access" category than Southern and Eastern European Member States. For example, usage of antibiotics in the "Access" category is lowest in Bulgaria with around 40% of all antibiotics, compared with around 80% in Denmark. See: ECDC (2021), Antimicrobial consumption in the EU/EEA (ESAC-Net), Annual Epidemiological Report for 2021, pp. 8 and 24; WHO (2019), Report on surveillance of Antibiotic Consumption 2016-2018, p. V and p. 21; WHO (2021), 2021 AWaRE classification and WHO (2022), AWaRe WHO Antibiotic Categorization.

54 ECDC (2022), Antimicrobial consumption in the EU/EEA (ESAC-Net), Annual Epidemiological Report for 2021, pp.9 and 11-12.

55 For population numbers for EU countries see: European Union (2022), Facts and figures on life in the European Union.

56 These numbers are for 2015 in metric tonnes. France roughly consumed 764 and Italy 662 See WHO (2019) WHO Report on surveillance of Antibiotic Consumption 2016-2018 Early Implementation pp.27-28, Table 4.2.

57 WHO (2019) WHO Report on surveillance of Antibiotic Consumption 2016-2018 Early Implementation pp.27-28, Table 4.2.

58 The figures from the EU Barometer are based on interviews. In total there were 26,511 interviews in the EU of which 1,521 were in Germany, 1,018 in Italy, 1,008 in France, 1,064 in Sweden, 528 in Malta, 505 in Luxemburg, 1,012 in Austria, 1,065 in Romania, 1,017 in the Czech Republic and 1,015 in The Netherlands. See: European Commission (2022), downloadable from Special Eurobarometer 522 Antimicrobial Resistance, Summary, p. 31.

59 European commission (2022), downloadable from Special Eurobarometer 522 Antimicrobial Resistance, Summary, p. 7.

the other hand, shows the highest level of consumption in Southern Europe with almost half of the Italian respondents saying that they took antibiotics compared to only one fifth in Sweden.[60] There are also big differences between Member States in terms of consumption without a prescription, with 20% of respondents in Romania saying they got their antibiotics without a prescription compared to 2 % of respondents in the Czech Republic.[61]

As can be seen from table 1, from 2017 to 2021, Germany and The Netherlands had a much lower consumption rate than Italy and France, who had comparable consumption rates which were above the EU/EEA average. France was among the highest (fourth highest in 2021) in the EU in terms of consumption, whereas The Netherlands is second lowest after Austria. Consumption levels in these four countries decreased in this period, with the most significant proportional decrease in Germany[62].[63]

Tab. 1: Average community consumption of antibacterials for systematic use (in DDD, 2017-2021)

Year	France	Germany	Italy	The Netherlands	EU/EEA*
2017	23.0	12.6	19.0	8.9	18.7
2018	23.6	11.7	19.5	8.9	18.6
2019	23.3	11.4	19.8	8.7	18.3
2020	18.7	8.9	16.5	7.8	15.0
2021	19.9	8.1	16.0	7.6	15.0

Source: ECDC, Antimicrobial consumption in the EU/EEA (ESAC-Net) (2022). *: The UK is included for 2017-2019.

Eurobarometer data presents a similar picture on consumption levels relating to the EU average of these four Member States: based on the answers of respondents, France and Italy have higher levels of consumption, whereas Germany and The Netherlands have lower consumption levels than the EU. It is also clear that there has been a decrease in consumption in all four Member States. The largest decrease in percentage points occurred in Italy, with 30% fewer respondents saying that they used antibiotics. In proportional terms the largest decrease has been in Germany.[64] See also table 2.

[60] European Commission (2018), Special Eurobarometer 478 Antimicrobial Resistance, p. 9.
[61] European commission (2022) downloadable from Special Eurobarometer 522 Antimicrobial Resistance, Summary, p. 8.
[62] The decrease in Germany was 35.7%, in France 13.5%, in Italy 15.8% and The Netherlands 14.6%. See ECDC (2022), Antimicrobial consumption in the EU/EEA (ESAC-Net), Annual Epidemiological Report for 2021, p. 12 and own calculation.
[63] ECDC (2022), Antimicrobial consumption in the EU/EEA (ESAC-Net), Annual Epidemiological Report for 2021, p.12.
[64] European Commission (2022) downloadable from Special Eurobarometer 522 Antimicrobial Resistance, Summary, p. 7; Special Eurobarometer 478 Antimicrobial Resistance (from 2018), p. 9 and Special Eurobarometer 338 Antimicrobial Resistance (from 2010), p. 14.

Tab. 2: Percentage of respondents who used antibiotics in the past year (2009, 2018, 2022)

Year	France	Germany	Italy	The Netherlands	EU27
2009	42	28	57	30	40
2018	37	23	47	21	32
2022	28	15	27	18	23

Source: Special Eurobarometer 522 (2022), Special Eurobarometer 478 (2018) and Special Eurobarometer 338 (2010) on antimicrobial resistance

EU consumption in comparison with Japan and South Korea

Looking at consumption in Japan and South-Korea provides a perspective on EU consumption in comparison with other democratic and developed countries in the world. The EU's average consumption levels in the community and hospital sector combined are between these two countries. In 2015 Japan had a consumption of 14.2 DDD, South Korea 27.7 DDD and the EU 21.7 DDD.[65] Japan´s consumption declined even further to 10.2 DDD in 2021, compared to 16.4 DDD in the EU/EEA in the same year.[66] Also, South Korea has seen a decline in consumption[67] but is still high compared to the EU/EEA average and Japan, and it has one of the highest levels[68] of consumption among Organisation for Economic Co-operation and Development (OECD) countries.[69]

5. Implications and Recommendations

Looking at the present, the fundamental challenges are to ensure sufficient supply of currently available types of antibiotics and to support the reasonable and responsible use of currently available types of antibiotics, so that they remain effective as long as possible. Even though there is no single solution, supply channels, stockpiling and consumption deserve particular attention.

5.1 Supply Channels

In principle, the problem of external dependency could be addressed in two ways via changes to supply channels. The first way is to attempt to (re-)Europeanize value chains. Such an approach first requires sufficient production capacities at the European level. The part of the antibiotics value chains currently localized in third countries is essentially the upstream part, i.e., the extraction of raw materials and precursors, and the production of generic antibiotics. This part is relatively labour-intensive and relatively less knowledge-intensive. The current geographical distribution of production chains is thus at least partly also an expression of a natural division of labour: countries such as China have their

65 ECDC (2022), Antimicrobial consumption in the EU/EEA (ESAC-Net), Annual Epidemiological Report for 2021, p. 7 and WHO (2019), WHO Report on surveillance of Antibiotic Consumption 2016-2018 Early Implementation, p.28.

66 AMR Clinical Reference Center (2022), National antimicrobial sales data and ECDC (2022), Antimicrobial consumption in the EU/EEA (ESAC-Net), Annual Epidemiological Report for 2021, p. 7.

67 For example, in 2014 South-Korea had a consumption of 31.7 DDD. See: European Commission (2014), AMR: a major European and Global challenge. For a downward trend in consumption see also J. Chae, B. Kim & D. Kim (2022), Changes in antibiotic consumption patterns after the implementation of the National Action Plan according to Access, Watch, Reserve (AWaRe) classification system, p. 347, figure 1.

68 In 2014, South Korea had the third highest level of consumption of OECD countries, behind Greece and Turkey. See: OECD (2016) Antimicrobial resistance: policy insights, p.3.

69 OECD (2016), Antimicrobial resistance: Policy insights, p.3.

comparative advantages in the labour-intensive part of the production process. This will not change in the foreseeable future, especially against the background of the rampant shortage of skilled workers in some EU countries. Reversing this process would require high investment in additional production capacities on the European side; money that would then be lacking elsewhere, such as in the area of innovation, and would thus jeopardize Europe's competitiveness. On the other hand, a roll-back of the international division of labour would also be associated with global productivity losses in the manufacture of medicines. Against the background of possible future crises, this poses new risks, especially for developing countries that are dependent on cheap medicines.

A second path as an alternative to Europeanization is to diversify the existing portfolio of EU trading partners in this area. Our comparative analysis of trade patterns has shown that countries such as Japan have been quite successful in the past in reducing existing supply chain risks by diversifying their trading partners. In the area of critical mineral commodities, the EU is already seeking a reorientation through the instrument of strategic partnerships with third countries.[70] This is not just about intensifying trade relations through tariff reductions. The partnerships also include forms of long-term cooperation through knowledge sharing, joint research, infrastructure development and regulatory harmonization. All these measures are aimed at creating new stable supply chains. Such an approach could also serve as a model for antibiotics production. For the competitiveness of new supply chains, the reduction of trade costs alone will not be sufficient. After all, the current advantage of Chinese producers is not based solely on lower labour costs, but also on economies of scale and low regulatory standards. In order to create more competition here, strategic cooperation with third countries requires above all joint efforts in capacity building (production + infrastructure) and regulatory cooperation (common quality standards). This is also a difficult and lengthy path. The heterogeneity of antibiotics and the complexity of production chains implies that there may be different ideal partners for different parts of supply chains and different product types. A sufficient degree of diversification of partners is therefore needed, also to avoid the creation of new dependencies. Strategic partnerships are therefore a measure for the long term. For the shorter term, complementary measures are needed to reduce risk in the existing supply structure.

5.2 Stockpiling

One short-term way to hedge against supply fluctuations is to promote the build-up of domestic stockpiles of antibiotics. In principle, promoting stockpiling can take various forms. The most direct form of intervention is to build up central antibiotic stockpiles in the EU through public procurement. On the regulators' side, this requires a sufficient level of information on what types of antibiotics are needed and in what quantities to provide adequate coverage for emergency situations. In view of the variety of antibiotics required, this presupposes extensive risk analyses and permanent monitoring of the market situation. It also requires carefully worked out distribution plans for the allocation of antibiotics to the relevant actors in the healthcare system in the event of an emergency. Physical stockpiling itself also involves costs and is associated with risks going forward; there is a risk that stockpiled types of antibiotics may become obsolete in the long term due to innovation, resulting in a loss of value.

[70] European Commission (2020), Critical raw materials resilience: charting a path towards greater security and sustainability. Communication from the European Commission to the European Parliament, the Council, the European Economic and Social Committee, and the Committee of the Regions. (2020) 474 final.

For limiting public risks, therefore, a decentralized approach may be more fruitful, i.e., to promote and coordinate stockpiling at the level of the relevant distributors in the healthcare system. In its simplest form, this may include specifications for better information exchange on intra-European stockpiles between relevant stockholders. This will facilitate better coordination of the liquidation of inventories in emergency situations. In the long term, it could also help to optimize the distribution of stocks in Europe and thus limit the costs of warehousing. Beyond information exchange, it may also make sense for the government to provide financial support for decentralized warehousing. It is true that relevant players also have an incentive of their own to use stockpiling to hedge against future supply risks. However, in addition to the private advantages of hedging, every externally procured quantity stored within Europe will also give better access to other European actors in case of emergency. This additional positive effect is not fully considered by companies during stockpile planning, so that without public-sector support stockpiling will tend to occur at an economically sub-optimal level.[71] HERA has in a recent report conducted a detailed review of existing stockpiling strategies for antibiotics.[72]

5.3 Consumption

There was a downward trend in consumption in the EU between 2015 and 2021, with significant differences between Member States in consumption levels and the rates of decrease. Data shows that consumption without prescription did not go down between 2018 and 2022 and the level differs significantly between Member States. There is a need, especially with an ageing population in the EU[73], to reduce consumption further[74], to stop the significant health threat from antimicrobial resistance and to ensure that current antibiotics remain available and effective for those who need them.

In comparison with Japan, the EU had much higher consumption levels from 2015 to 2021 and the reduction in levels of consumption has been less than in Japan. Japan is a good example outside the EU in terms of reducing consumption levels when these are already relatively low. Despite an ageing population[75], Japan has been able to reduce the consumption of antibiotics significantly.[76] Japan

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71 Wolf, A. (2022), Stockpiling of Critical Metals as a Risk Management Strategy for Importing Countries , Journal of Resilient Economies (ISSN: 2653-1917), 2(2).

72 European Commission, European Health and Digital Executive Agency (2022), HERA AMR feasibility study on stockpiling: D1-D5 Final report, Publications Office of the European Union.

73 For information on ageing in the EU see: Eurostat (2019), Ageing Europe: Looking at the lives of older people in the EU, pp. 14-16. EU countries have shown that consumption of antibiotics is generally higher among older adults than other age groups. See for example in Spain: S.P. de la Cruz & J. Cebrino (2020), Prevalence and Determinants of Antibiotic Consumption in the Elderly during 2006-2017, p.1. See also for example in Finland E. Pyöräla, K. Sepponen, A. Lauhio & L. Saastamoinen (2022), Outpatient Antibiotic Use and Costs in Adults: A Nationwide Register-Based Study in Finland 2008-2019, pp.3 and p. 4 figure 3.

74 Consumption should particularly be reduced in those Member States with high consumption rates such as Bulgaria and Romania. See: ECDC (2022), Antimicrobial consumption in the EU/EEA (ESAC-Net), Annual Epidemiological Report for 2021, p.12.

75 See data on usage of antibiotics in Japan by age group from 2013 to 2019: Antibiotic use by age group. In Japan usage of antibiotics is higher in children under the age of 15 and the elderly over the age of 65 than other age groups. See: Y. Muraki, Y. Kusama, M. Tanabe et. al. (2020), Impact of antimicrobial stewardship fee on prescribing for Japanese pediatric patients with upper respiratory infections, p. 2. Some EU countries have shown that consumption of antibiotics is higher among older adults than other age groups. See for example in Spain and Finland: S.P. de la Cruz & J. Cebrino (2020), Prevalence and Determinants of Antibiotic Consumption in the Elderly during 2006-2017, p.1 and E. Pyöräla, K. Sepponen, A. Lauhio & L. Saastamoinen (2022), Outpatient Antibiotic Use and Costs in Adults: A Nationwide Register-Based Study in Finland 2008-2019, p. 3 and p. 4 figure 3.

76 AMR Clinical Reference Center (2022), National antimicrobial sales data.

reduced its consumption by almost a third compared to 2013, which was a goal in the Countermeasure Action Plan established in 2016.[77]

Generally, consumption levels are influenced by many different factors and many actors are involved including in Europe: citizens, medical professionals, the pharmaceutical and medical devices industry, national governments and the EU itself. Factors that can influence levels of consumption include among other things raising awareness of AMR among individual citizens and medical professionals, training for medical professionals on the prudent use of antibiotics, the availability and development of diagnostic tests and alternative medicines and treatments, prices of effective alternatives compared to antibiotics and the general health of the population. This shows that all these actors need to address the issue and work together to put multiple practical solutions in place, whether it be at the level of the individual citizen, health professionals, national government or at EU level. Multiple actions need to be taken by various actors to address the high level of (unnecessary) consumption. This sections provides an overview of the measures currently undertaken at EU level, examples of specific measures by Member States which can be considered as good practice as well as actions which can be taken personally as an individual.

The EU is also already trying to tackle the issue with its limited competences in the field of health, mainly by supporting the right use of antimicrobials in human and veterinary medicine[78] and with regard to pharmaceuticals in the environment[79]. For example, new EU regulations came into force in 2022 prohibiting the use of certain antimicrobials in veterinary medicine so that these remain effective in human medicine.[80] The new EU Health Emergency Authority (HERA)[81] has defined the issue as part of its work programme to face future health threats.[82] HERA and the WHO recently initiated a new partnership under the EU4Health Programme to fund global initiatives for the development of medical countermeasures to address AMR as means for ensuring pandemic preparedness.[83] Also, the European Medicines Agency (EMA) plays a role in the global response to the threat of antibiotics, by promoting responsible use of antibiotics[84] and by supporting[85] the development of new medicines and treatments.[86] Since 2008, the ECDC has coordinated the European antibiotics awareness day, as a way to support campaigns in Member States, which presumably contributed to the increase in the number

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77 AMR Clinical Reference Center (2022), National antimicrobial sales data. Consumption in 2013 was 14.91 DDD and decreased to 10.21 DDD in 2021 which is a decrease of 31.5%.

78 See e.g. cep**PolicyBrief** 1/2018 on the European One Health Action Plan against Antimicrobial Resistance.

79 See e.g. cep**PolicyBrief** 2/2020 on the European Union Strategic Approach to Pharmaceuticals in the Environment.

80 European Commission (2022), Data on antimicrobial resistance in the EU decreases but more needs to be done.

81 See on this Stockebrandt, P. / De Petris, A. (2022), Strengthen Democratic Oversight of HERA.

82 HERA (2022), HERA Work Plan 2022, p. 14 – see points 4.2 and 4.7.

83 WHO (2022), The European Union and WHO further enhance their partnership for stronger pandemic preparedness and response.

84 Referral procedures of old antibiotics show restriction of antibiotic use and in many cases adjustment of dosage of specific populations with the aim of ensuring appropriate use. See: A. Opalska, M. Kwa, H. Leufkens and H. Gardarsdottir (2020), Enabling appropriate use of antibiotics: review of European Union procedures of harmonising product information, 2007 to 2020, p. 1.

85 The development of new medicines and treatments is supported by scientific advice to developers, at any stage of the development of a medicine, on how to generate evidence on the medicine's benefit and risks. See EMA (2023), Scientific advice and protocol assistance. There is also specific support for micro, small and medium-sized enterprises (SME's) by offering guidance on the EMA centralised procedure and financial advantages in the form of partial or total fee reductions. See: EMA (2023), Support to SME's and EMA (2023) Financial advantages of SME status.

86 EMA (2022), Antimicrobial resistance.

of national campaigns since 2008.[87] Awareness campaigns have reduced consumption at national level in the past, for example in France.[88]

EU countries that already have a low level of consumption and have also shown a decrease in the community sector, could be a source of measures to reduce consumption further in the EU as a whole or to keep levels of consumption low when a reduction is no longer possible. Countries showing this pattern are Austria, The Netherlands[89] and Germany.[90] Factors that contribute to low consumption levels in these countries are multidimensional and involve different actors, in particular healthcare professionals, individual citizens and the government. Apart from a culture[91] in which consumption and prescription is generally low, The Netherlands took a number of actions which may help to reduce consumption and keep it low. These include:

- Awareness campaigns to increase knowledge about antibiotics and antimicrobial resistance among citizens.[92]
- The work of the Dutch working party on antibiotic policies (SWAB)[93] regarding the production of guidelines. The SWAB is a collaboration between professional societies, which is funded by the Dutch government.[94]
- A national and local AMR surveillance system including hospitals and the public sector.[95]
- Investment in Research and Development at national[96] and international level.[97]

These actions are not all unique to The Netherlands. However, embedded in a high-quality healthcare system, the existence of proactive professional associations supported by government and a culture of low prescription levels among medical professionals has led to one of the lowest levels of consumption in the EU.[98]

At an individual level, each person can contribute to a reduction in consumption by only using antibiotics when prescribed by a health professional. This can especially have an impact in Member

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87 ECDC (2022), European Antibiotic Awareness Day (EAAD) 2022; ECDC (2022), ECDC's role and B. Huttner, M. Saam and L. Moja et al. (2019), How to improve antibiotic awareness campaigns: findings of a WHO global survey, pp. 3-4, figure 3.

88 B. Huttner, M. Saam and L. Moja et al. (2019), How to improve antibiotic awareness campaigns: findings of a WHO global survey, p. 7. On France see A. Bernier, E. Delarocque-Astagneau, C. Ligier et al. (2013), Outpatient Antibiotic Use in France between 2000 and 2010: after the Nationwide Campaign, it is time to focus on the elderly pp.71 and 76.

89 The Netherlands is very diligent in its prescriptions for antibiotics compared to other Western countries. See: Ministerie van Volksgezondheid, Welzijn en Sport (2021), Voortgang aanpak antibioticaresistentie, p.2.

90 ECDC (2022), Antimicrobial consumption in the EU/EEA (ESAC-Net), Annual Epidemiological Report for 2021, p. 12.

91 N. Stadhouders A. Auzin, and S Auener et al. (2020), Antimicrobial resistance in The Netherlands, four good practices, p. 32.

92 N. Stadhouders, A. Auzin, and S Auener et al. (2020), Antimicrobial resistance in The Netherlands, four good practices, p. 30 and Ministerie van Volksgezondheid en Sport (2016), Antibiotica.

93 The SWAB is a collaboration between professional societies: the Dutch society for clinical pharmacists, Dutch society of medical microbiology and the Dutch society for infectiology. See: N. Stadhouders, A. Auzin and S Auener et al. (2020), Antimicrobial resistance in The Netherlands, four good practices, pp. 30 - 31, Table 3.

94 N. Stadhouders, A. Auzin and S Auener et al. (2020), Antimicrobial resistance in The Netherlands, four good practices, pp. 21 and 28-29 and Ministerie van Volksgezondheid, Welzijn en Sport (2021), Voortgang aanpak antibioticaresistentie, p.8.

95 N. Stadhouders, A. Auzin and S Auener et al. (2020), Antimicrobial resistance in The Netherlands, four good practices", pp. 29 and 31 Table 3. Ministerie van Volksgezondheid, Welzijn en Sport (2021), Voortgang aanpak antibioticaresistentie, p.10.

96 An example of a national funding programme is ZonMW see: ZonMw (2023), Programme Antibiotic Resistance.

97 N. Stadhouders A. Auzin, S Auener et al. (2020), Antimicrobial resistance in The Netherlands, four good practices, Ministerie van Volksgezondheid, Welzijn en Sport (2021), Voortgang aanpak antibioticaresistentie, p.11.

98 And the lowest level of resistance. See altogether: N. Stadhouders, A. Auzin, S Auener et al. (2020), Antimicrobial resistance in The Netherlands, four good practices, pp. 32 and 38.

States where it is common to consume antibiotics without prescription, e.g. in Romania[99].[100]Individual citizens have a responsibility to reduce unnecessary consumption which can be done through educating themselves on the issue.

6. Addressing the Fundamental Challenges of "tomorrow"

Consumption will remain a factor in the future as any new type of antibiotic will suffer the same fate as those currently available and become ineffective at some point.[101] The fundamental challenge for the future though remains the fact that the clinical pipeline of new antimicrobials has dried up. Hence, efforts must be made to utilise research and development for the production of new antibiotics and alternatives. At a global level, there are initiatives to align regulatory requirements for the approval of new antibiotics to stimulate and accelerate development – e.g. between medicine regulators in the EU (EMA), the USA (U.S. Food and Drug Administration (FDA)) and Japan (Pharmaceutical and Medical Devices Agency (PMDA)).[102] Additionally, regulatory authorities from some countries regularly meet and exchange information in order to identify best practice and learn from this.[103]

Yet, there is a need to create an incentive system which fosters the continued innovation and development of new antibiotics and alternatives. The current system does not do this. There is widespread reluctance to invest in corresponding research and development due to unfavourable economic conditions. Specifically, the combination of long development times, regulated prices and low levels of expected consumption implies that funds can be more profitably invested elsewhere.[104] The societal benefit of new types of antibiotics lies mainly in the option of having them available when the existing (cheaper) ones fail. However, production "for the shelf" does not provide sufficient private return, as availability as such is not rewarded by the reimbursement system.

The upcoming Commission proposal for a reform of EU pharmaceutical law – postponed again and again[105] and now scheduled for March 2023[106] – presents an ideal opportunity to address the issues at hand in a comprehensive public discussion. In this section we thus consider the current tools to

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99 20% of respondents from Romania said they obtained antibiotics without a prescription or as a left over from a previous course. See: European Commission (2022) downloadable from Special Eurobarometer 522 Antimicrobial Resistance, Summary p. 8.

100 European Commission (2022) downloadable from Special Eurobarometer 522 Antimicrobial Resistance, Summary p. 8, and WHO (2020), Antibiotic resistance.

101 WHO (2021), Antimicrobial resistance. To extend this period, vaccinations may prevent the need for antibiotics in the first place, as they can prevent certain infections. The decreased number of infections then reduces the chance of a pathogen mutating to a resistant form; see WHO (n/a), Vaccines for Antimicrobial Resistance (AMR). Besides this, rapid testing at the point of care may help, as antibiotic prescriptions are given to treat viral infections, which they have no effect on; see Standford Medicine News Center, New blood test to identify infections could reduce global antibiotic overuse, 20.12.2022. Even though, diagnostics may not always lead to less prescription of antibiotics in community care settings; see e.g. F. Antoñanzas, F., Juárez-Castelló, C., Rodríguez-Ibeas, R., Does diagnostic testing always decrease antibiotics prescriptions?, in: The European Journal of Health Economics (2022).

102 EMA (2023), Antimicrobial resistance.

103 ICMRA (2022), Best practices to fight antimicrobial resistance.

104 See cep**PolicyBrief** 2021 on the Pharmaceutical Strategy for Europe, p. 3. See generally also McKenna, The next pandemic is already here. Covid can teach us how to fight it., MIT Technology Review, 23.06.2021. Some Member States have acknowledged that the current system of incentives has failed to stimulate the development and marketization of (novel) antimicrobials to tackle the emerging global crisis of antimicrobial resistance.

105 See https://www.europarl.europa.eu/doceo/document/E-9-2022-003475_EN.html.

106 https://ec.europa.eu/commission/presscorner/api/files/document/print/en/speech_22_7628/SPEECH_22_7628_EN.pdf.

incentivise innovation at EU level before outlining the current discussion on new incentives and looking at the development of alternative treatments.

6.1 Available Tools to Incentivise the Innovation of new Antibiotics at EU Level

Currently available tools at EU level are principally based on time-limited financing programmes, such as Horizon Europe, to "push" innovation with earmarked funds which are paid out to researchers, companies, Member States, and others, mainly in the form of grants, if the specific conditions for the financing programme are met.[107]

Also, the new European Health Authority (HERA) has the task of strengthening precautionary health-related measures.[108] This includes fostering the development of new antibiotics.[109] However HERA is responsible for preparing the EU for several threats and this is just one of them.[110] In addition, HERA's work focusses mainly on emergency preparedness.

As another example, some Member States have signed up for an Important Project of Common European Interest (IPCEI) on Health. This IPCEI is intended to support innovation and improve the quality and accessibility of healthcare for European citizens.[111] The financed projects should, among other things, support innovation with regard to strategic challenges such as fighting AMR.[112] Yet, initially only 16 Member States have signed up.[113] It remains to be seen how the practical implementation will work and whether and how this commitment will be made permanent on the level of the participating Member States.[114]

These tools are therefore focused on selective, individual projects, rather than a system for long-term continuous innovation and development.

6.2 New Incentives Under Discussion

Arguably, incentives for the continuous development of antimicrobials and alternatives must be fundamentally improved.[115] This could take various forms and discussions are ongoing regarding e.g. subscription models, market-entry rewards, ongoing revenue incentives, exclusivity extensions, accelerated approval and priority review vouchers.[116] Currently, the most prominently discussed

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107 For an overview see EU Commission, Research and innovation on antimicrobial resistance (AMR).

108 See Stockebrandt, P. / De Petris, A. (2022), Strengthen Democratic Oversight of HERA.

109 See HERA (2022), HERA Work Plan 2022, p. 14 – see points 4.2 and 4.7.

110 See HERA (2022), HERA Work Plan 2022.

111 French Presidency of the Council of the European Union, Launch of an IPCEI on Health Announced During the Ministerial Conference 'Towards an Independent, Competitive and Innovative European Healthcare Sector', 03.03.2022.

112 French Presidency of the Council of the European Union, Launch of an IPCEI on Health Announced During the Ministerial Conference 'Towards an Independent, Competitive and Innovative European Healthcare Sector', 03.03.2022

113 These are Austria, Belgium, Denmark, France, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Poland, Romania, Slovenia and Spain, see French Presidency of the Council of the European Union, Launch of an IPCEI on Health Announced During the Ministerial Conference 'Towards an Independent, Competitive and Innovative European Healthcare Sector', 03.03.2022. Germany then joined later, see Tagesspiegel Background Gesundheit & E-Health, Deutschland beteiligt sich nun doch an IPCEI Health, 14.11.2022.

114 Germany first declined to participate – see Olk, Warum Deutschland beim großangelegten EU-Projekt für Gesundheit nicht mitmacht, Handelsblatt 03.05.2022 – and then committed to it, yet with, e.g. compared to France, relatively low funds: 10 million for 2023 plus 175 million Euros for upcoming years in comparison to 1.5 billion Euros. See Tagesspiegel Background Gesundheit & E-Health, Deutschland beteiligt sich nun doch an IPCEI Health, 14.11.2022.

115 See already cep**PolicyBrief** 2021 on the Pharmaceutical Strategy for Europe, p. 3.

116 See e.g. BCG (2022), The Case for a Subscription Model to Tackle Antimicrobial Resistance, p. 12 et seq.

incentives are "subscription models" and "voucher models"[117]. Any model will need cooperation between the EU and the Member States, especially with regard to competences[118].

A "voucher model" aims to reward companies, that bring a new antibiotic onto the market, by issuing them with a voucher. This voucher is a right to extend some form of legal protection to a medicinal product. Therefore, it is a protective measure against competition. This protection can come e.g. in the form of patent-like protection[119] or it can cover data exclusivity, so that clinical trial data is protected against competitors.[120] What makes the idea special, is that the voucher does not need to be applied to the new antibiotic product but can be used for any (economically successful) medicinal product in the company's portfolio. Additionally, the voucher can also be sold to another company so that it becomes a tradable good with a negotiable price.

With a "subscription model", the state would undertake to pay (annual) fees – decoupled from sales volumes – to a company for a certain period of time in return for the guaranteed supply of an antibiotic.[121] The aim is to ease concerns about the return on investment as this would serve as a form of guaranteed revenue for that company. It is sometimes dubbed the „Netflix-style" model in the discussions.[122] The USA[123], the UK[124] and Sweden[125] usually serve as examples, as some kind of subscription model is either being tested there (pilot projects) or its introduction is being discussed. There are also proposals for a concrete EU model.[126] The versions under discussion vary in many details, however, and therefore need to be individually assessed.

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117 Generally see: Joint Action EU-JAMRAI (2021), Improving access to essential antibiotics (which argues in favour of a specific subscription model) as well as Anderson M. / Wouters, O. (2022), Transferable exclusivity extensions to stimulate antibiotic research and development: what is at stake?, p. 1, and the „Non-Paper Novel stimuli for the development and keeping on the market of antimicrobials" of the Netherlands, Austria, Belgium, Finland, France, Hungary, Ireland, Latvia, Lithuania, Luxembourg, Poland, Portugal, Slovakia and Slovenia, stating that the Commission is considering the use of transferable exclusivity extension vouchers.

118 See generally on this: Stockebrandt, P. (2021), Three Steps Towards a European Health Union.

119 BCG (2022), The Case for a Subscription Model to Tackle Antimicrobial Resistance, p. 13. Essentially, that is what a Supplementary Protection Certificate does as well, see generally on that issue cep**PolicyBrief** 35/2018.

120 Various versions are discussed as the Commission has yet to publish its concrete proposal. For a general overview see: Anderson M. / Wouters, O. (2022), Transferable exclusivity extensions to stimulate antibiotic research and development: what is at stake?, BCG (2022), The Case for a Subscription Model to Tackle Antimicrobial Resistance, p. 13; the „Reflection Paper" of the BEAM-Alliance from 31.01.2022 (which argues in favour of such a voucher system referred to as „Transferable Exclusivity Extension") as well as the „Non-Paper Novel stimuli for the development and keeping on the market of antimicrobials" of several Member States (which against such a voucher system).

121 See BCG (2022), The Case for a Subscription Model to Tackle Antimicrobial Resistance, p. 13 (arguing in favour of such a subscription model). Again, various versions of this model are discussed, see e.g. also the „Non-Paper Novel stimuli for the development and keeping on the market of antimicrobials", p. 2 (guarantee for minimum turnover per Member State, regardless of volumes actually prescribed), or as a general overview the „Reflection Paper" of the BEAM-Alliance from 31.01.2022, p. 10.

122 See McKenna, The next pandemic is already here. Covid can teach us how to fight it., MIT Technology Review, 23.06.2021 as well as Dall, For PASTEUR Act advocates, the finish line is in sight for antibiotic development aid, Special project: Antimicrobial Stewardship, Center for Infectious Disease Research and Policy of the University of Minnesota, 06.12.2022 – both focusing on the US Pasteur Act. On this legislative proposal, see also next footnote.

123 The so called „Pasteur Act". See on this McKenna, The next pandemic is already here. Covid can teach us how to fight it., MIT Technology Review, 23.06.2021 and McKenna, The $6 Billion Shot at Making New Antibiotics—Before the Old Ones Fail, wired.com, 14.11.2022.

124 See Dall, For PASTEUR Act advocates, the finish line is in sight for antibiotic development aid, Special project: Antimicrobial Stewardship, Center for Infectious Disease Research and Policy of the University of Minnesota, 06.12.2022 as well as NHS England, NHS lands breakthrough in global battle against superbugs, 15.06.2022.

125 See Public Health Agency of Sweden, Questions and answers – Agreements signed for a pilot study of a new reimbursement model.

126 In the form of a revenue guarantee, see Joint Action EU-JAMRAI (2021), Improving access to essential antibiotics.

All the incentives have their advantages and disadvantages and have been discussed in various versions and in various fora.[127] None can or should be ruled out in advance. Indeed, the options need to be explored further[128] as the devil is indeed in the detail here. The optimal or most reasonable option for Europe may also very well be a combination of different incentives which would allow for competition.

6.3 Alternative Treatments

There are also alternatives to conventional antibiotics that should be considered when planning a system to meet the needs of "tomorrow". An important example is the bacteriophage or phage therapy. Discovered in 1917, bacteriophages are viruses that have evolved naturally to attack bacteria. The treatment largely disappeared in the 1940s when the Western world shifted to antibiotics.[129] In short, a phage is a virus which can destroy a certain bacterium in persons and animals without harming other cells.[130] Each bacterium has its own phage, however, so the "correct" one has to be found, like the "key" to a door.[131] Phage therapy is regarded as having the potential to substitute or at least support existing antibiotics.[132] It appears to have had modest success with patients around the world[133] but more research must be done to find practically viable therapy options. Any European approach should therefore also focus on such alternatives to conventional antibiotics.

7. Conclusion

The introduction of antibiotics has made many modern medical procedures possible, including cancer treatment, organ transplants and open-heart surgery. However, misuse has resulted in the rapid rise of "antimicrobial resistance" (AMR) and some infections are now untreatable. Furthermore, the clinical pipeline of new antibiotics has dried up. In other words, the increase in resistance to currently available antibiotics at some point renders them ineffective and, at the same time, too few new antibiotics are being developed. Those affected as well as society at large are thus facing a dire situation. Cooperation between the EU and its Member States is urgently needed to formulate a comprehensive approach. It should include (1) attempts to diversify existing supply channels; (2) promotion of private stockpiling; (3) reduction of consumption and (4) promotion of continuous innovation, jointly at EU and Member State level.

Europe's dependence on China for its current supply of antibiotics involves significant long-term supply risks. Member States and the European Commission should work collaboratively on opening up new supply channels, especially with respect to precursors and generic antibiotics. Strategic partnerships with third countries exhibiting favourable conditions for a future competitive production of the necessary components may represent one promising exit strategy. To stand up to Chinese dominance,

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127 See e.g., footnote 32 and 33.

128 See also the "Non-Paper Novel stimuli for the development and keeping on the market of antimicrobials", p. 1. This includes working out the details with regard to the differing legislative competences.

129 See Cunningham, Old cure revived to help fight against antibiotic-resistant superbugs, The Sydney Morning Herald, 09.01.2023.

130 See instead of many: Haarhof, Antibiotikresistenzen: Phagen – auf dem Weg zur Zulassung?, Tagesspiegel Background Gesundheit & E-Health, 20.12.2022.

131 Haarhof, Antibiotikaresistenzen: Phagen – auf dem Weg zur Zulassung?, Tagesspiegel Background Gesundheit & E-Health, 20.12.2022.

132 See e.g.: Haarhof, Antibiotikresistenzen: Phagen – auf dem Weg zur Zulassung?, Tagesspiegel Background Gesundheit & E-Health, 20.12.2022 and Cunningham, Old cure revived to help fight against antibiotic-resistant superbugs, The Sydney Morning Herald, 09.01.2023.

133 See e.g.: Cunningham, Old cure revived to help fight against antibiotic-resistant superbugs, The Sydney Morning Herald, 09.01.2023.

such partnerships should not be limited to the elimination of trade barriers but also involve investment support and cooperation in the field of knowledge exchange. Creating new and stable supply chains will thus require the long-term effort and commitment of policy-makers and the private sector on both sides. At the same time, the creation of new dependencies must be avoided, requiring a balanced portfolio of partners to provide a hedge against country-specific regulatory and societal risks.

In light of the time needed for creating new stable supply chains for antibiotics, the stockpiling of essential antibiotics in the EU could represent an important complementary measure in the short to medium term. In a comparison of available options, incentivizing private stockpiling by EU-internal distributors appears to be the most effective way. In doing so, regulation needs to ensure that economic actors are sufficiently rewarded for the societal benefit of ensuring availability in times of crisis through stockpiling. At the same time, such a regulation should not be too detailed regarding the specific types of antibiotics stockpiled, thus allowing actors to respond flexibly to product innovation and changing market needs. Foremost, it is important that stockpiling does not conflict with the goal of reducing the overuse of antibiotics in the EU. Promotion mechanisms thus also need to be calibrated with respect to systemic consumption incentives.

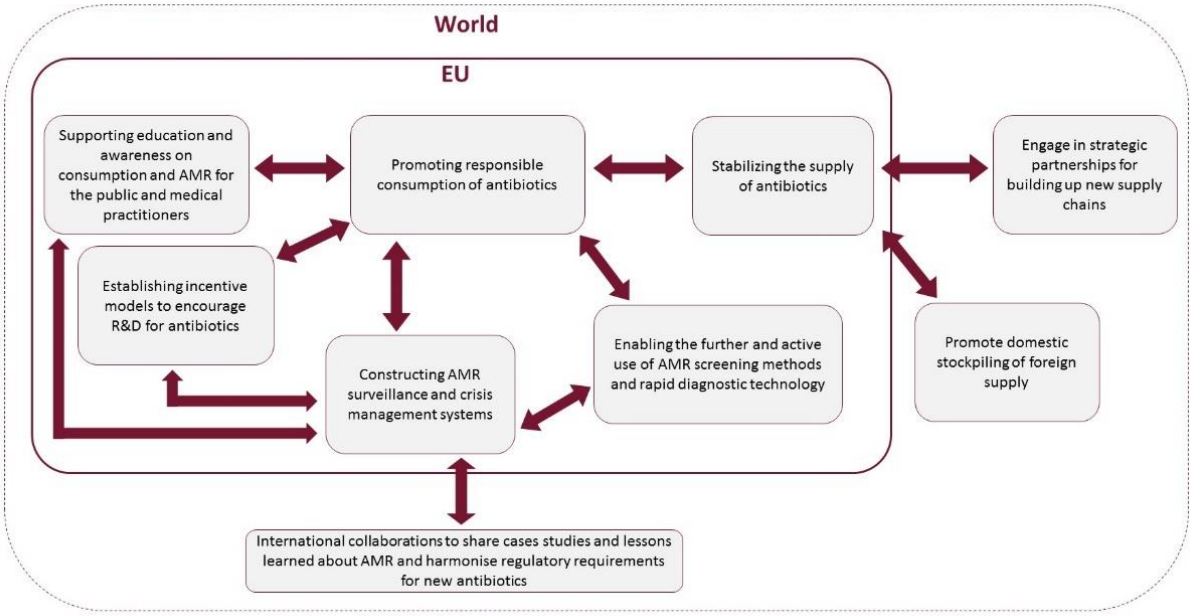
A reduction in consumption is required. Several measures are needed simultaneously, involving stakeholders at different levels, to address this multidimensional problem. Individual citizens, healthcare professionals, Member States and the EU including the EMA all have an important role to play. The problem cannot be resolved by these actors, acting alone, so collaboration among them will be necessary. Actions should target responsible consumption through, for example, the training of healthcare professionals, the production of guidelines by e.g. professionals in Member States and awareness campaigns. Individual citizens are also responsible for unnecessary consumption and educating themselves on the issue may have an impact on reducing consumption levels.

The societal benefit of producing new types of antibiotics lies mainly in the option of having them available when the existing ones fail. However, production “for the shelf” does not provide sufficient private return as availability as such is not rewarded. Currently available tools at EU level are principally based on time-limited financing programmes which are paid out to researchers, companies, Member States, and others mostly in form of grants (“pushing” innovation). These tools are focused on selective, individual projects rather than establishing a system for continuous innovation. There is a need to create an incentive system which fosters continued innovation and the development of new antibiotics and alternatives. Most prominently discussed as new incentives are a “voucher model” and a “subscription model”. Both have their merits, as they try to overcome the current situation but the devil will be in the detail. The optimal or most reasonable option for Europe is likely to be a combination which allows for competition. Any model will need close cooperation between the EU and the Member States.

The upcoming Commission proposal for a reform of EU pharmaceutical law – expected in March – presents an ideal opportunity to address the issues at hand in a comprehensive public discussion, because there is no single solution, close cooperation between the EU and the Member States is required and any bundle of measures will come at some form of (economic) cost.

8. Appendix

Antibiotics are a multi-perspective challenge indeed, which means that cooperation on all levels is needed and that there is no single solution to the urgent challenges ahead. See the following for a graphical representation:



Source: own depiction, based on the figure found atAMR Alliance Japan, (2023), Our policy recommendations.

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