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FEATURES OF THE ECONOMIC IMPACT OF ANTIMICROBIAL RESISTANCE ELUCIDATED IN SCIENTIFIC PUBLICATIONS

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Summary
Objectives. Highlighting the particularities of the economic impact of resistance to antimicrobial preparations and establish the methodologies used in estimating the antimicrobial resistance burden exposed in scientific publications.
Methods. The current study is a synthesis with the evaluation of 19 scientific articles selected from PubMed. The review of the scientific publications included in the study has revealed that the economic impact of antimicrobial resistance entails a series of costs, assignable to hospitals, to patients and to society as a whole.
Results. The most common approach applied in the analyzed publications consists in referring to antimicrobial resistance as an externality. Studies performed on the basis of a hospital, focus mainly on the direct costs induced by antimicrobial resistance. Studies that analyze the economic impact of the antimicrobial resistance on a global level or the macroeconomic one, offer forecasts regarding the main macroeconomic indicators – global domestic product, international trade, livestock production etc., on the basis of different scenarios of development of antimicrobial resistance. About a third of the scientific articles focus not only on measuring the impact of antimicrobial resistance, but also suggest policies, mechanisms and instruments to diminish antimicrobial resistance spread and, thus, decrease the costs associated with antimicrobial resistance.
Conclusions. The wide spread of antimicrobial resistance in time will increase the economic burden, by increasing healthcare costs, decreasing labor productivity and Gross Domestic Product, livestock production and external trade, and inducing not only quantitative, but also qualitative effects on global economy. Developing countries face deeper problems regarding the economic impact of antimicrobial resistance, it is observed especially on macroeconomic level.
Keywords: antimicrobial resistance, economic impact, patients, public health

Introduction

Antimicrobial drugs are designed to eliminate the most sensitive bacteria, but at the same time some bacteria are able to survive and adapt by acquiring "resistance genes", either by mutating existing genes or by acquiring new genes [1]. Spontaneous evolution, bacterial mutation, and passage of resistant genes through horizontal gene transfer contribute significantly to antimicrobial resistance [2].

The development of resistant bacteria is a natural phenomenon that is exacerbated and accelerated by the inappropriate use of antimicrobials in the fields of human and animal health.

Improper and unjustified use of antimicrobial preparations has led to the emergence of resistant bacterial strains. In viral infections, the use of antimicrobial drugs is unnecessary and sometimes even harmful, as it increases resistance.

Drug-resistant infections occur when pathogens change in ways that make antimicrobial preparations ineffective. As a result, the pathogens survive and continue to spread. When infections can be treated with antimicrobials, people can be cured and further spread of bacteria in the population can be easily controlled. This has saved hundreds of millions of lives since the widespread use of these "miracle drugs" began more than 70 years ago. Loss of drug efficacy due to resistance to antimicrobials is on the rise in both developing and developed countries. If this trend continues uncontrollably, the world will face a reality in which many infectious diseases have "no treatment and no vaccine." [3].

Among the factors that accelerate the rate of antimicrobial resistance (AMR) are: misuse and overuse of antimicrobials, over-the-counter use, use of antimicrobials in agriculture and animal husbandry, rising income levels that increase purchasing power, modern and easy travel routes (through exposure to resistant pathogens), gaps in knowledge of proper use and resistance to antimicrobials [21].

Currently, treatment for many infections (pneumonia, tuberculosis, sepsis, gonorrhea) has become difficult and sometimes impossible because antimicrobial drugs are losing their effectiveness. New antibiotics are being developed, but none of them are considered effective against the most resistant bacteria [4].

Globally, there were approximately 4.95 million deaths associated with antimicrobial resistance in 2019 [5].

Antimicrobial resistance is a global problem that threatens not only public health but also the economic development and security of states [1, 5]. Global scenarios predict that AMR could cause about 10 million deaths by 2050 [6]. The World Bank estimates that global healthcare costs will increase due to AMR by 2050 to one trillion US dollars [7].

The multifactorial threat of antimicrobial resistance has led to various complex issues affecting countries around the globe. The impacts found in bibliographic sources can be classified into three different perspectives: patient, healthcare and economic [2].

The impact of antimicrobial resistance on human life, health systems and economies is considerable and will continue to grow [2, 8]. Estimates of economic effects are published and the findings are worrying. For example, the annual cost to the US health care system has been estimated at 21-34 billion USD, and more than 8 million additional days in hospital [9]; in the European Union antimicrobial resistance costs around 1.5 billion Euro per year [8].

Medical costs are only part of the economic equation, beside this, when assessing the financial impact, it must be taken into account the decrease in employment and income and the increase in healthcare spending. EU estimates that resistance to antimicrobials causes about 600 million days of lost productivity each year, while in Thailand some researchers estimate that AMR leads to a loss in productivity that accounts for 2 billion USD per year [10].

According to the World Bank, in case the spread of AMR is not limited, annual costs could become as massive as those of the global financial crisis that began in 2008. Moreover, sustainable development goals for 2030 – such as eradicating poverty and hunger, ensuring a healthy life, reducing inequalities and revitalizing global partnerships – are likely to remain unfulfilled [3].

The aim of the research is to highlight the particularities of the economic impact of resistance to antimicrobial drugs and establish the methodologies used in estimating the AMR burden exposed in scientific publications.

Material and methods

A selective systematic search was performed in PubMed for the period January 1, 2017 - December 31, 2021, using the Boolean AND operator to facilitate the search (by narrowing the search field). Publications from the last 5 years have been taken into account to ensure the analysis focused on the contextual literature describing current models of economic impact of resistance to antimicrobial preparations. The search was limited to articles describing scientific research published in English. We used the following keyword combinations to identify research articles (economic interventions) AND (antimicrobial resistance); (economic impact) AND (antimicrobial resistance); (cost-effectiveness) AND (antimicrobial resistance); (cost quantification) AND (antimicrobial resistance); (Economic evaluation) AND (antimicrobial resistance); (economic burden) AND (antimicrobial resistance).

Study selection

The search for scientific articles resulted in 1458 publications, of which 796 publications were excluded after the titles and abstracts were read and analyzed in relation to the inclusion criteria; 213 titles were excluded due to lack of full text, 32 publications were excluded due to duplication, 398 articles – due to eligibility. Thus, 19 articles met the inclusion/exclusion criteria and were taken over in full for review (Figure 1), their metadata and .pdf documents have been uploaded to Reference Management Software – Mendeley (version 21.01.2021).

The full texts of the extracted studies were evaluated according to the inclusion criteria. There was no disagreement among reviewers during the study selection process.

Inclusion criteria:

- specific information on the association between economic aspects and antimicrobial resistance,
- the association between resistant bacteria and financial impact,
- full-text articles,
- papers published in English,
- studies published between 01.01.2017-31.12.2021.

Exclusion criteria:

- articles on symptoms, antimicrobial treatment, but without an economic approach on antimicrobial resistance/ unrelated to economic impact,
- articles that measure cost-effectiveness in case of diseases not implying antimicrobial resistance,
- research on parasites, viruses and fungi,
- abstracts published in conference proceedings, reviews, letters to the publisher, correspondence, editorials, comments and case reports.

Data extraction

Data from eligible papers were extracted using a standardized spreadsheet in Excel (Microsoft Office Excel 2016).

Data extracted from articles included year, country, context/ perspective, participant characteristics, efficiency data source, efficiency reference, cost source, treatment, cost-effectiveness of therapy, cost measurement, types of costs, total cost, cost-effectiveness analysis, incremental cost-effectiveness, economic forecasts on the national level, economic models used to approach the economic impact of AMR, instruments and mechanisms implied in management of economic impact of AMR.

Data synthesis

The data extracted from the publications included in the study were analyzed and summarized using narration, tables. The information has been grouped and described in the following sections:

✓ Antimicrobial resistance as an economic externality,
✓ The macroeconomic and global impact of AMR,
✓ The microeconomic impact of AMR.

The scientific publications that met the inclusion criteria were grouped according to the level of economic impact of AMR reflected in the study. As a result we obtained:

- 5 studies that had a global and macroeconomic (on the level of national economy and society as a whole) approach of AMR's impact,
- 2 studies that mentioned only the global effects of AMR,
- 1 study that referred to both global and microeconomic impact of AMR,
- 4 studies with only a macroeconomic approach of AMR impact,
- 1 study with both a macro- and microeconomic approach to AMR impact,
- 6 studies that treated the economic impact of AMR only from a micro level (entire hospital, intensive care unit, other hospital units).

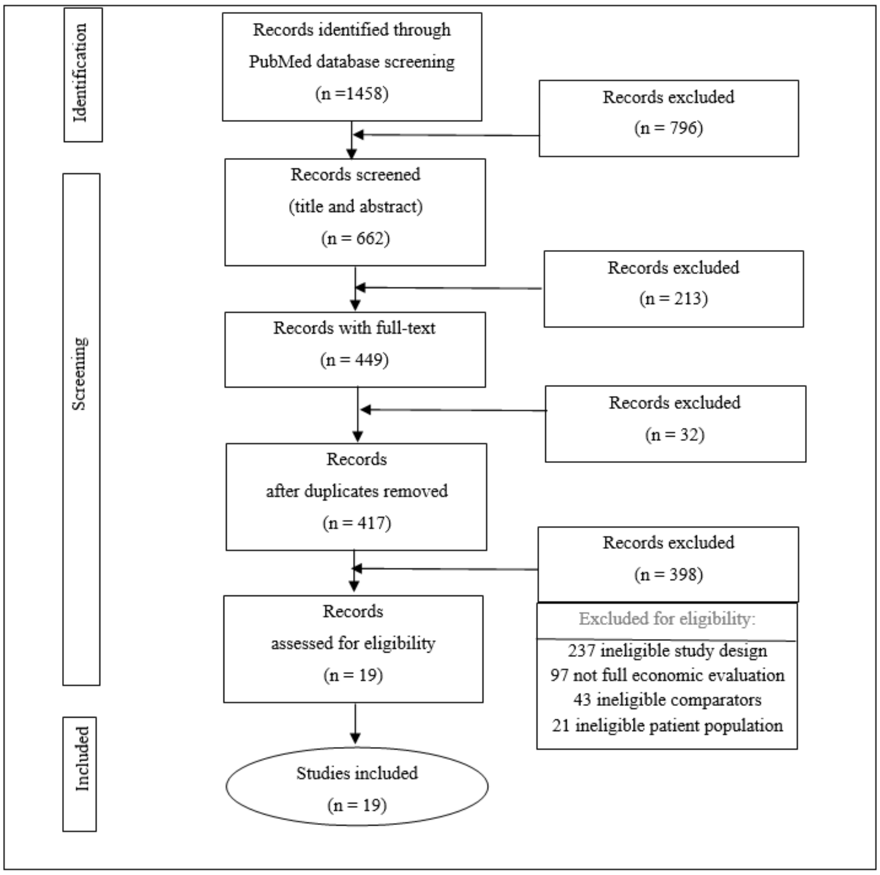

Figure 1. *Search results and the process of selection and inclusion of publications in study*

We underlined those studies that treated AMR as an economic externality, reflecting the main ideas behind this approach.

Further, we grouped and analyzed the studies within each section according to the type of effects they analyzed:

- decline in Global Domestic Product,
- increase in healthcare expenditures,
- decline in labor offer,
- decrease in labor productivity,
- increase in global poverty,
- decrease in global trade and exports,
- decrease in livestock production.

Some studies had made their own forecasts related to the global impact of AMR, others cited the reports made by World Bank, OECD and other sources.

Studies reflecting the microeconomic impact of AMR were analyzed according to information provided on costs of AMR (total hospital costs, patient costs, length of stay in the hospital, costs of antibiotics, cost-effectiveness of therapy with different combinations of antimicrobials). However, the studies that treated the microeconomic impact of AMR were more heterogeneous in approaching the costs and cost-effectiveness of therapy, since each study analyzed the costs of AMR caused by a specific group of bacteria. We focused mainly on the costs reflected by the following types of gram-negative bacteria - *P. aeruginosa, E. coli, K. pneumoniae, A. baumannii, S. aureus.*

The next step of data synthesis included identifying and describing the strategies and mechanisms to reduce the negative economic impact of AMR, that were suggested by authors of publications included into research.

Results

Out of 19 publications chosen for analysis, 9 studies have treated the economic impact of antimicrobial resistance (AMR) on the microeconomic level, focusing on the hospital costs (direct, indirect and total hospital charge, including the cost of antibiotics, the costs of stay and the cost of all other medical services provided); 9 studies had examined the effects of AMR on macroeconomic level, offering forecasts on evolution of such indicators as Global Domestic Product, trade (exports, mainly), labor productivity, labor supply, health care costs; 8 studies comprised an analysis on AMR impact on global level, pointing out the evolution of such phenomena as rise in poverty, decrease in Global Domestic Product, loss of capital, decrease in livestock, in exports, in labor offer and labor productivity etc. (Table 1).

Studies in the sphere of economic impact of AMR underline various approaches towards treating the concept and economic nature of AMR.

Antimicrobial resistance as an economic externality

Several studies included into research have treated the AMR as an economic externality, meaning that part of the cost is hidden and cannot be quantified timely and correctly. This approach emphasizes that there is a challenge in assessing the economic burden of AMR, especially due to multiple ways of influencing the economy – through the loss of labor productivity, Gross Domestic Product (GDP) decrease, external trade decrease, etc. Estimates of costs primarily focused on costs incurred by health care systems

Table 1
Global, macroeconomic and microeconomic levels discussed in the publications chosen for the present study

Nr.	Authors	Year of publication	Global level	Macro level (national economies, society)	Micro level (hospital, intensive care unit, other hospital units)
1	Basetti and Giacobbe	2020		+	
2	Dadgostar	2019	+		
3	Pulingam et al.	2021	+	+	
4	Ahmed et al.	2017	+	+	
5	North	2020		+	
6	Calbo et al.	2020	+		
7	Founou et al.	2017			+
8	Dos Santos et al.	2019			+
9	Zhen et al.	2019	+		+
10	Shrestha et al.	2018		+	+
11	Smallwood et al. 11	2019			+
12	Ahmad and Khan	2019	+	+	
13	Leal et al.	2017		+	
14	Regea	2018	+	+	
15	Jit et al.	2020		+	
16	Huebner et al.	2019			+
17	Ait Ouakrim et al.	2020	+	+	
18	Wozniak et al.	2019			+
19	Nathwani et al.	2019			+

Source: *elaborated by authors on the base of cited publications*

and not society, have focused on current rather than future potential costs [12].

Evaluating the economic impact of AMR should consider the specificity of each bacteria producing resistance, treatment procedures, individual characteristics of patients and associated costs. To reduce consumption of antimicrobials among patients and influence prescribers' choice authorities can introduce regulation, charges or taxes on the use of antimicrobials, and the right to trade permits or licenses [12], these mechanisms will have an economic impact, too. In the meantime, there are opportunity costs of committing resources to introducing new antimicrobials to replace old, ineffective ones, in exchange to other public health initiatives [12].

A simple model to estimate the magnitude of the negative externality associated with antimicrobial use in healthcare facilities was proposed based on the following ideas: a dose-response relationship between antimicrobial consumption and the emergence of resistance would be calculated, using multivariate time series analyses, considering different factors of medical nature. The obtained coefficients would prove that temporal variations in the volume of administered antimicrobials result in temporal variations in the incidence of AMR. To register the changes it would take at least 2 years of observations, to compare the costs of implementing the policy with the savings due to reduced AMR [13].

Another argument in favor of treating AMR cost as an externality is the fact that the key cost driver in healthcare expenditures is the estimation of a bed-day cost, treated as an accounting cost (spending related to treat a case of AMR) as well as an opportunity cost (showing the value of freeing up a hospital bed for an alternative use) [13].

From the societal perspective, disease not resulting in hospitalization becomes important because it still results in productivity losses, even if direct healthcare costs are low. Patients with AMR are administrated AMR tests, that are expensive and/or empirically prescribed antibiotics that are costlier and have worse side effects than first-line antibiotics [14].

The macroeconomic and global impact of AMR

Ten out of 19 studies included into research, focused on the macroeconomic consequences, i.e. treated the AMR as a factor of influence over national economy. Some studies only provided the World Bank forecasts data, The Organization for Economic Co-operation and Development Reports data, Research and Development Corporation (RAND Corporation) Report data that estimated global or regional economic impact of AMR and offered forecasts.

A significant loss of capital due to AMR by 2050, ranging from 300 billion USD to 1 trillion USD is indicated by Pulingam et al. (2021) [15]. A decrease is registered in GDP by 1% and in the same time by 5-7% for developing countries, by 2050 (Table 2). The economic burden is considered to be higher for low- and middle- income countries, especially in

South-Eastern Asia and Africa, due to the fact that inadequate treatment options and late identification of AMR imply the necessity to abandon the first treatment prescriptions and use second- or third-line antibiotics which are often more expensive. Thus, AMR results in a significant increase in extreme poverty due to a disproportional impact of AMR on different groups of countries.

One instrument to counteract the spreading of AMR are rapid microbiological tests for the diagnosis of bloodstream infections due to multidrug resistant gram negative bacteria. These tests may be used to anticipate diagnosis, treatment, and infection-control measures for patients with AMR. There are several factors that affect the clinical outcomes, antimicrobial use, and cost-effectiveness of such rapid tests. They are:

(i) the specific of local microbiological epidemiology;

(ii) the local prevalence of antimicrobial resistant bacteria;

(iii) the local therapy protocols;

(iv) and the laboratory staff availability on night and weekend shifts [16].

A continuous rise in AMR by 2050 would lead to a loss of 10 million human lives and an annual reduction of 2-3.5% in Gross Domestic Product, raising the cost of AMR up to 100 trillion USD (see Table 2). In the meantime, in the US, the estimated cases in hospitalized patients in 2017 were 323 700, with 10 600 estimated deaths and 1.7 billion of attributable healthcare costs [17].

The estimated annual direct and indirect costs of antimicrobial resistance counts for $55 billion in the US. It is also projected that by 2050, 10 million lives a year and a cumulative USD $100 trillion of economic output will represent a potential loss due to the increase in AMR [12] (Table 2).

Data from the OECD Report reveal that by 2050, the cumulative cost of AMR to the health care system of those countries is expected to reach $134 billion [18] (Table 2).

The World Bank forecasts by 2050 point out two scenarios – the optimistic and the base-case one (Table 3). As we can see from the Table 3 the range of variation is quite large, underlining the high economic impact of AMR on global production.

The forecasts on global GDP, trade and level of poverty are mentioned by Ahmed et al. (2017), pointing out that the losses in GDP during 2015-2050 may increase up to 85 trillion USD and $23 trillion in global trade. By 2050, the cost of AMR in GDP could range from 1.1 percent (low case) to 3.8 percent (high case) [19]. AMR will increase poverty, especially in developing countries, because these countries have less controlled prescribing habits of antimicrobials. The authors point out that under the high level of AMR scenario, by 2030, an additional 24.1 million people would be extremely poor, of whom 18.7 million live in low-income countries. In general, developing countries will be hurt the most, especially those with the lowest incomes [19].

The impact of low, middle, and high cases of antimicrobial resistance on various macroeconomic indicators is presented in Table 4. As we observe, the most significant impact of AMR will occur in more deaths due to AMR, thus a decrease in labor supply, and a rise in extreme poverty. A reduction in livestock production as well as global restrictions on livestock trade will affect global economy, determining shifts in global production structure.

Projections of economic influence of AMR were made according to the classification of countries by income. Four categories of groups were used in the forecasts – low income, lower middle income, higher middle income and high-

Table 2

Articles that analyze or underline the impact of AMR on GDP

Nr.	Authors	The impact of AMR on GDP
1.	Pulingam et al. (2021)	a loss of capital due to AMR by 2050, ranging from 300 billion USD to 1 trillion USD. A decrease in GDP by 1% and in the same time by 5-7% for developing countries, by 2050.
2.	Calbo et al. (2020)	annual reduction of 2–3.5% in Gross Domestic Product, rising the cost of AMR up to 100 trillion USD
3.	Leal et al. (2017)	by 2050 a cumulative USD $100 trillion of economic output will represent a potential loss due to the increase in AMR.
4.	Ait Ouakrim et al. (2020)	Annual global GDP fall by 2030 – $1 trillion Annual global GDP fall by 2050 – $3.4 trillion
5.	Ahmed et al. (2017)	Decline in GDP: low-income countries – 5.6% middle-income countries – 4.4% high-income countries – 3.1% Total decline – 3.8% Absolute value of decline – 6.1 trillion dollars
6.	Regea (2018)	a decrease from 2 till 3.5 percent in global Gross Domestic Product (GDP), and in the same time a 100 trillion USD decrease by 2050
7.	Dadgsotar (2019)	decrease in GDP (5-7% by 2050),
8.	Zhen et al. (2019)	Loss of GDP due to AMR 1.1-3.8%. The major loss in GDP will be registered by low- and middle- income countries. Countries in Sub-Saharan Africa may have a GDP loss of 0.1-2.5%

Source: *elaborated by authors on the base of cited publications*

Table 3

Projections of GDP decrease by 2030 and by 2050

	Annual global GDP fall by 2050	Annual global GDP fall by 2030
The optimistic scenario of low AMR impacts	1.1%,	$1 trillion
The base-case scenario of no AMR	3.8%	$3.4 trillion

Source: *elaborated by the authors on the base of [18]*

Table 4

The economic impact of AMR in low, middle and high cases

Scenarios	*Declines in labor supplies*		*Fall in labor productivity*	*Reduction in livestock production*	*Reduction of real global exports*	*Global restrictions on livestock trade*	*Impact on extreme poverty (mln people)*
	resulting number of deaths for workers	resulting number of deaths for working population					
low case	11 million	18 million	by 1.5%	by 3%	by 1.1%	by 5%	6,9
middle case	74 million	117 million	by 3%	by 5%	-	by 10%	18,4
high case	137 million	214 million	by 4,5%	by 7%	by 3.7%	by 15%	28,3

Source: *performed by author on the base of [19]*

Table 5

Projections regarding the impact of AMR over different groups of countries

Groups of states by income	*Rise in health care cost*	*Decline in GDP*	*Decline in exports*	*Decline in livestock production*	*Rise in health care expenditures*
low-income	5.4%,	5.6%	5.2%	11.1%	25.3%
lower middle-income	4.2%,	4.4%	4.2%	7% - 9%	15% -16%
higher middle-income	6.1%,				
high-income	12.7%.	3.1%	3.1%	6%	6.2%
Total decline	-	3.8%	3.7%	7.6%	8%
Absolute value of change	-	minus 6.1 trillion dollars	minus 1.7 trillion dollars	-	0.33 trillion dollars

Source: *elaborated by authors on the base of [19]*

Table 6

Forecasts of AMR impact on GDP evolution, global poverty, livestock output, world trade and health care costs

Scenarios	*GDP*	*Livestock output*	*Health care costs (USD)*	*Global trade*	*Global poverty*
	decrease, %	decrease,%	increase, %	decrease, %	increase, *(mln people)*
low impact of AMR	1,1%	2,6%	300 billion	1,1%	28,3
high impact of AMR	3,8%	7,5%	1 trillion	3,8%	-
Impact over low income countries	5%				26,3

Source: *elaborated by authors based on [20]*

income countries (see Table 5). Thus, the most significant economic impact of AMR will touch low-income countries, generating a very high increase in the level of health care expenditures, due to a rise in health care costs, in the social sphere and a decline in GDP, exports and livestock production in the economic sphere.

The same forecasts on GDP evolution, global poverty, livestock output, world trade, as well as health care costs are revealed by Ahmad and Khan (2019) [20]. Comparing the data from Table 6 to the data identified by Ahmed et al. (2017), we can observe that they present similar economic trends [19].

Beside this, Ahmad and Khan focus on average hospital settings due to treatment of patients with AMR, showing that this expenditures will rise from 10 000 USD to 400 000 USD. In the meantime, the US burden of AMR is estimated to 55 billion USD, of which 20 billion USD are generated by health services. Lost labor productivity per year represents 35 billion USD, entailing both an economic and a social cost [20].

The estimates of national, multinational and global effects of AMR presented by Jit et al. (2020) include: increased treatment cost, reduced productivity and labor supply as a result of higher morbidity and premature mortality, reduced intersectoral transactions and trade, etc. The fall in labor supply is estimated to induce an economic cost up to 6,8 trillion USD per year in 40 years and 3,5 trillion USD in 30 years [14].

Some data regarding the forecasts of human losses due to AMR – 10 million annual deaths, and thus, a huge loss of labor force is given by Regea (2018). Beside, the mentioned author gives a a forecast of a decrease from 2 till 3.5 percent in global Gross Domestic Product (GDP), and in the same time, a 100 trillion USD decrease by 2050, rise of 6.2 to 18.7 million in the number of extremely poor people by 2030. By 2030 the number of extremely poor people will be higher than 6,2%, reaching an upper limit of 18,7 million lives of extremely poor people [21].

Negative impact on the trade is also mentioned by Regea, (2018) – antibiotic resistance from food products causes their rejection, thus EU registers around a third of rejections and US counts for a fifth of rejections of aquaculture products originary from Vietnam, China, Thailand, Bangladesh, and Indonesia [21].

The same economic effects of AMR are identified by Dadgostar (2019):

- elevation of rate of poverty,
- extending economic gap between the developed and developing countries,
- decreased labor income,
- loss of labor productivity caused by sickness and premature death,
- decrease in global exports,
- decreased production and trade of livestock, increasing prices of proteins,
- decrease in GDP (5-7% by 2050),
- the cost of AMR in the US – 55 billion USD,
- loss of productivity in the US – 35 billion USD [2].

Beside forecasts regarding the decrease in GDP, labor productivity and trade, a particular attention is paid to the impact of AMR on livestock production (Table 7).

The large use of antimicrobials in the agriculture sector, leading to a decrease in treatment efficiency, and possible bans on imports, due to high concentration of antimicrobials in meat and other animal production, will affect the structure of external trade.

The microeconomic impact of AMR

Eight studies out of 19 that were comprised into research had shown a wide variety of microeconomic costs occurring due to AMR. Such costs include: cost of bed day, the cost of medical products administered by the hospital or bought by ambulatory patient, laboratory diagnosis of AMR, costs of associated procedures, staff time, etc. Some studies referred to mechanism preventing or decreasing costs associated with AMR – such as permits to prescribe antibiotics, tax on antibiotic consumed, bureaucratic regulation and antimicrobial stewardship programs [14].

The study performed by Founou et al. (2017) analyzed the published literature on the clinical and economic impact of AMR in developing countries (Thailand, China, Turkey,

Table 7

Articles that analyze or underline the impact of AMR on animals / livestock

Nr.	Authors	The impact of AMR on animals/livestock
1	Ahmad and Khan (2019)	Alteration of gut microbiome of an animal, which makes it susceptible to other infections and affects health, imposing costly treatment
2	Pulingam et al. (2021)	Decrease in efficiency of treatment of livestock, increase in the infection rate and the spread of the infection; rise in the price of protein sources, including meat, egg and milk supplies; Decrease in the yield of livestock in low and middle income countries – 11% of loss in livestock production by 2050 and financial loss in animal production
3	Ahmed et al. (2017)	Global restrictions on livestock trade – low case 5%, middle case 10%, and high case 15%. Trade reductions from a "fear factor" will further reduce livestock production, especially for the low-income countries. Reduction in livestock production: - the decline in livestock production by 2050 is 11.1% for low-income countries, 7-9% for middle-income countries, and about 6% for high-income countries. The global decline is 7.6%. Trade in livestock and livestock products are vulnerable to AMR not only because of impacts on productivity of untreatable disease but also because the "fear factor" results in disruptions of trade (such as bans on imports) in response to disease outbreaks.
4	Regea (2018)	Antibiotic residues found in animals or meat of animals can impose rejection of imports/exports, affecting the trade of countries
5	Dadgostar (2019)	The increase in AMR will make treatments on animals ineffective and cause the infections to become more severe, leading to decreased production and trade of livestock, resulting in elevated prices of protein due to the decrease in protein sources such as milk, egg, and meat. The increase in AMR can lead to a shortage of protein. The most drastic impact of AMR will be registered in low-middle income countries – under conditions of the same rate of growth of AMR an 11% loss in livestock production is forecasted by the World Bank by 2050.

Source: *elaborated by authors on the base of cited authors*

Table 8

The longest periods of stay identified by the study, for different bacteria

Country	Bacteria	Length of stay (days)	
		Case group	Control group
Brazil	*P. aeruginosa*	43	43,1
China	*Enterococcus*	37	17
Thailand	*E. coli* and *K. pneumoniae*	26	26
Thailand	*A. baumannii*	51	41
Turkey	*S. aureus*	50,3	32,7

Source: *elaborated by authors on the base of [22]*

Colombia, Malaysia, India, Mexico, Jordan, Palestine, Senegal). The study outlined that AMR had an impact on hospital costs, through an increase in length of stay of the patient at the hospital. The study comprised infections with *S. aureus, A. baumannii, K. pneumoniae, P. aeruginosa, Enteroccocus* and *E. coli* that determined longer length of stay in hospital. The longest period of stay in the hospitals in case groups are presented in the table below [22].

Overall healthcare costs associated with resistant infections in case groups were 8,107.375 USD, in comparison to control groups in which the overall healthcare costs amounted to 5,469.487 USD. Of the countries comprised in the study, the highest costs were identified in Turkey – 35 277 USD, Thailand – 11773 USD and Colombia – 11822 USD.

The review performed by Dos Santos et al. identified eight studies that evaluated the cost-effectiveness of different treatments for CRKP (carbapenem resistant *Klebsiella pneumoniae*) infections. The results of their research demonstrated that there is no gold standard treatment for CRKP infection. Studies comprised comparisons in terms of cost and clinical effectiveness of several antimicrobials, as piperacillin-tazobactam, ceftriaxone-metronidazole, amoxicillin, ertapenem, nitrofurantoin ofloxacin and levofloxacin [23].

The evaluation of the economic burden of AMR, comparing cases when patients had antimicrobial resistant bacteria (*E. coli, S. aureus, K. pneumoniae, A. baumannii, P. aeruginosa, Enteroccoccus*) with those lacking AMR had been undertaken by Zhen et al. The study comprised a comparison of median and average costs for each group of bacteria [24]. The highest and lowest identified total hospital costs are shown in the table below.

Shrestha et al., (2018) had undertaken research to identify the costs of AMR for *S. aureus, E. coli, K. pneumoniae, A. baumannii* and *P. aeruginosa*. The approach to account for human capital loss was applied: mortality figures were converted into productivity losses. Based on a study from intensive care unit in Thailand, it was considered that a person would work for ten years more, if death wouldn't occur. Thus, the number of deaths was multiplied by ten productive years and by GDP per capita to calculate losses per one person death. These values were adjusted by the annual rate of GDP growth (1%) and a 3% discount rate.

The cost of AMR attributable to the use of a Standard

Table 9

The highest and lowest identified total hospital costs for AMR

Bacteria	Median cost in 2015 USD	
S. aureus	Max	146.716
	Min	15.763
Enteroccocus	Max	177.503
	Min	48.121
E. coli and K. Spp.	Max	96.785
	Min	11.085
E. coli	Max	21.712
	Min	4877
K. pneumoniae	Max	46.934
	Min	2139
P. aeruginosa	Max	111.871
	Min	5743
A. baumanii	Max	24.897
	Min	2558

Source: *elaborated by authors on the base of [24]*

Unit (SU) of antimicrobials administrated to the patients and a full course of eight antibiotic drug classes was calculated, by multiplying the costs of AMR, the RMf (The Resistance Modulating factor – the proportional contribution of human antimicrobial consumption towards the total cost of AMR), and the consumption of antibiotics that drive resistance in each pathogen [25].

The cost of AMR per SU of each antibiotic consumed was used to calculate the cumulative economic cost per each antibiotic consumed, including only the infections in which the particular drug class was assumed to propagate resistance [25].

This model assumes that resistance is driven exclusively by human antimicrobial consumption of antibiotics and that consumption of all drug classes contribute to resistance in all pathogens equally. The cost of AMR per person was multiplied by the number of lost years due to premature death (ranging from 5 to 20 years) to calculate the loss in human capital [25].

The results of comparison between Thailand and United States have revealed the following:

- the direct costs associated to AMR were higher in Thailand for *A. baumannii* – 29 mln. USD and for *S. aureus* in US. – 42 mln USD;
- the indirect costs were higher in Thailand for *A. baumannii* – 367 mln. USD and for *S. aureus* in the USA – 2184 mln. USD;
- total economic loss was higher in Thailand for *A. baumannii* – 396 mln. USD and for *S. aureus* in the USA – 4797 mln. USD [25].

Another study dedicated to a comparison of direct and indirect costs due to AMR was performed by Smallwood et al. The authors included into the study the costs occurring at acute care facilities. The possible future scenarios included three levels of rates: low (20%), medium (50%) and high

(100%). Costs associated to treatment of AMR at an acute center reach 10.2 million USD. The incremental cost of antimicrobial resistance represented 1.2 mln USD. At a level of AMR of 100%, the burden could rise to as much as $30 million. In case AMR is prevented, the opportunity cost would be 18 mln USD [11].

Wozniak et al. suggest calculating the hospital cost of AMR by taking into account the length of stay, in tight correlation with the time of infection and infectious status of patients [13]. Resistant infections may in fact need to be considered as additive, indicating that considering only the incremental cost of resistance compared to susceptible infection would underestimate the total costs of resistant infections.

Antimicrobial stewardship programs (ASPs) are highly recommended among measures to limit the increasing expansion of AMR. Out of 19 studies included into research, 4 studies were dedicated to ASP as mechanism to lower the negative economic impact of AMR. One of the study [17] treats superficially the economic impact of ASP programs, analyzing more deep the clinical effects of ASP, while three others [26, 27, 28] focus more on the economic effects of ASP. They focused on decreasing length of stay and readmission rate, less use of antimicrobial treatment and reducing total costs. Benefits resulting from cost savings were higher in case of hospitals with comprehensive ASPs, i.e. including both therapy review and antibiotic resistance [26, 27].

Discussions

The large number of approaches to evaluate and quantify the economic burden of AMR underline its complex nature. The relationship between antimicrobials consumption and AMR is not instantaneous, nor linear, it is more complex and dynamic, because it takes a period to develop, and the AMR may occur to another antibiotic than the one that was prescribed to the patient. Antibiotic consumption not only in case of humans, but also in agricultural use, can generate different economic impacts, making its assessment even more difficult. Beside this, the present levels of AMR may represent the cumulative effect of previous antibiotic use.

Studies aimed to determine AMR's economic impact concentrate both on the microeconomic level – i.e. a hospital, a hospital unit, intensive care units (ICU), for example, and at a macroeconomic level (the impact over the whole economy) or, even global level. Depending on the level on which the economic impact is assessed, the methodology applied can vary significantly. It can be directed towards evaluating changes in GDP, labor force, external trade, livestock production etc.

As we observe, the most significant impact of AMR will occur in higher mortality due to AMR, leading to a decrease in labor supply. To estimate the fall in labor offer, studies use the human capital method, by multiplying the years lost due to death caused by AMR, either by the average wage or by the national GDP per capita [14]. Also, AMR leads to a rise in extreme poverty. This trend is observed especially in developing countries, because they are characterized by less controlled prescribing habits of antimicrobials. A lot of studies emphasize the disproportional impact of AMR on different groups of countries.

On the one hand, the large use of antimicrobials in the agriculture sector, especially in the case of low and middle income countries, will increase the high rate of incidence of AMR and will decrease future treatment efficiency, determining a reduction in livestock production. On the other hand, a spreading incidence of AMR will generate possible bans on imports of livestock and meat, egg and milk products because of antimicrobial residues found in them. Since the export of these products represent important production sectors of low- and middle- income economies, restrictions on livestock trade can lead to serious structural disruptions in external trade, determining shifts in production structure of these countries and affect global economy.

The economic burden of AMR on households is emphasized by Jit et al (2020) – increased length of stay in hospital due to AMR leads to a growth in household out-of-pocket costs – co-payments for treatment, transport costs, caregiver accommodation costs and childcare costs. Patients and caregivers may miss work and lose income. These externality costs may be especially large for poorer categories of population [14].

Sickness, disability, premature mortality due to AMR leads to increased healthcare demand and reduced consumption. The usual spending patterns of households are changed, substituting a consumption of services like tourism and education with healthcare services, the demand for antibiotics and other AMR treatment associated medicines increases. Pandemics due to SARS Covid-19 had very eloquently proved this phenomenon.

Specialized literature attempts to perform researches regarding costs associated with AMR within hospitals / intensive care units (ICU) and other medical settings/wards. The large number of studies quantifying the economic impact of AMR refer to the hospital costs, dividing them into direct and indirect costs. These studies focus mainly on such indicators as length of stay in hospital, antibiotic costs, ICU costs, hospital costs after culture, total hospital charges, therapy, laboratory analysis costs, personnel costs, etc.

Studies focusing on healthcare expenditures associated with hospital stay have similar methodology of costs evaluation: by calculating per patient costs for a day of stay in hospital and multiplying by length of stay and number of patients with AMR. Length of stay in hospital varies significantly for cases of AMR for different types of bacteria. LOS is considered to be an important indicator of the AMR burden, this indicator is present in most of the hospital-based studies. The argument for its importance is that hospital beds are blocked by patients with longer stays due to resistant infections, and thus, cannot offer timely access to healthcare to other patients.

Also, the vast majority of the hospital-based studies have the aim to identify the differences in costs registered by case and by control groups (patients with antimicrobial resistance and patients with sensitiveness to antimicrobials, respectively). These differences in AMR costs vary significantly, depending on the type of resistant bacteria chosen for study.

Studies that estimated hospital costs due to treatment of AMR cases use descriptive statistical approaches to assess the impact of a discrete intervention on AMR prevalence or treatment cost. For example, such studies estimate a fixed ratio or describe a linear correlation between a decline of antibiotic consumption and a decrease of AMR costs as a result of introduction of a stewardship program [14]. Most hospital-based studies consider AMR costs from the perspective of the healthcare provider (e.g. the hospital providing treatment), although other perspectives are relevant to decision-makers, too, for instance costs attributable to the patient, that include not only hospital costs, but also expenditures to buy drugs or pay additional visits to the doctor, etc.

In the meantime, these studies tend to extrapolate findings from a single site to a national or even global level, however, and this is their major limitation - disconsidering existing specifics between countries and regions.

Conclusions

Antimicrobial resistance represents a serious threat for health and, in the meantime, it entails high costs, determining a raising number of reports that estimate global economic burden of AMR.

The analysis performed on the basis of review of scientific publications in the field of AMR's economic impact has revealed the following. The trend of wide spread of AMR in time will worsen the economic impact of AMR on global level, inducing not only quantitative, but also qualitative effects, like shifts in geographical distribution of GDP, deepening the economic gap between developed countries and low and middle income countries.

The effects of AMR on the global and macroeconomic level include a decrease in a series of macroeconomic indicators, such as: disposable income of households, labor productivity, labor offer, trade and livestock production, and, in the same time, an increase in healthcare expenditures and a larger prescription of antibiotics of second and third level. This explains why multiple scientific publications are aimed to study the mechanisms of diminishing the consumption of antibiotics and reducing the spread of AMR.

On the microeconomic level the impact of AMR is reflected in higher hospital costs, due to an increase in costs associated with antibiotic consumption, bed day costs, as well as increased length of stay of patients with AMR. Such studies can be accurate in hospitals with representative patient data on healthcare services costs and antibiotic susceptibility, ensuring a more precise estimation of AMR economic burden.

Ethical consideration

This systematic review of the literature has been based on published researches and therefore no ethical approval is required.

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