

Chapter 2

Economic Impact of Infections and Antibiotics

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Burden of Diseases and Epidemiologic Transition

Epidemiologists have described disease's impact in different ways. Mortality analysis was the most important approach until the 1980s decade. In the 1990s, the World Bank commissioned the original Global Burden of Disease (GBD) study which was published in the World Development Report 1993: "Investing in Health." This GBD study served as the most comprehensive effort to systematically measure the world's health problems, generating estimates for 107 diseases and 483 sequelae [1]. The GBD is a measurement of impact of disease combining years of life lost to premature mortality plus years of life lost to time lived in states of less than full health, measured by disability-adjusted life years (DALY). "One DALY can be thought of as one lost year of 'healthy' life. The sum of these DALYs across the population, or the burden of disease, can be thought of as a measurement of the gap between current health status and an ideal health situation where the entire population lives to an advanced age, free of disease and disability" [2, 3]. The causes of disease were grouped into three by the Global Burden of Disease study: (a) communicable, perinatal, maternal, and nutritional conditions, (b) noncommunicable diseases, and (c) injuries [4].

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Furthermore, in 1972, Abdel R. Omran posited the theory of epidemiologic transition, which described the complex change in patterns of health and disease and the interactions between those patterns and their demographic, economic, and socio-logic determinants and consequences. One of the five basic propositions that support the theory is that pandemics of infection are gradually displaced by degenerative and man-made diseases as the chief form of morbidity and primary cause of death [5].

Despite the evident predominance of chronic diseases as a cause of death in 2015, infectious diseases still persist among the top ten causes. In 2015, for instance, lower respiratory infections caused 3.2 million deaths out of the 56.4 million deaths registered worldwide in that year. The death rate from diarrheal diseases almost halved between 2000 and 2015, but still caused 1.4 million deaths in 2015. Similarly, tuberculosis killed fewer people during the same period, but is still among the top ten causes with a death toll of 1.4 million. HIV/AIDS is no longer among the world’s top ten causes of death when all countries are considered, but is still among the top ten in developing countries, killing 1.1 million people in 2015 [6]. The GBD 2015 showed that progress was slower for several causes, such as lower respiratory infections and nutritional deficiencies, whereas deaths increased for others, including dengue and drug use disorders [7].

It is possible that environmental factors, like warmer temperatures, produce an increase in the importance of other infectious diseases such as those transmitted by mosquitoes. Dengue already produces more than 390 million cases every year around the world, and its burden of disease is probably underestimated due to constraints in the resources used for surveillance in developing countries. Malaria continues to ravage some developing countries especially in Africa, Asia, and South America, and emerging resistance to treatment with artesunates may hamper control efforts in the future. Recently, it has been estimated that there are around 400 million cases of malaria every year [8–10].

Figures 2.1 and 2.2 show the evolution of deaths and DALYs in the world between 1990 and 2015. Table 2.1 describes the relationship between the income level of the countries and the mortality profile. In the low-income countries, the

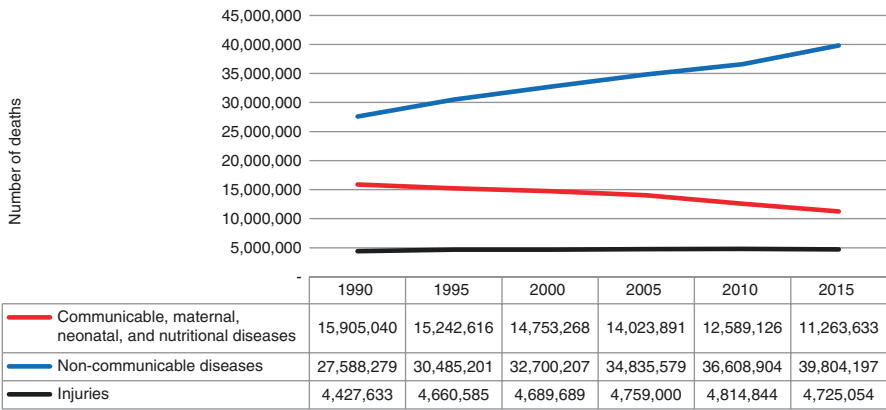


Fig. 2.1 Deaths by three groups of causes for the burden of disease in the world (1990–2015). Source: Made by the authors based on [11]

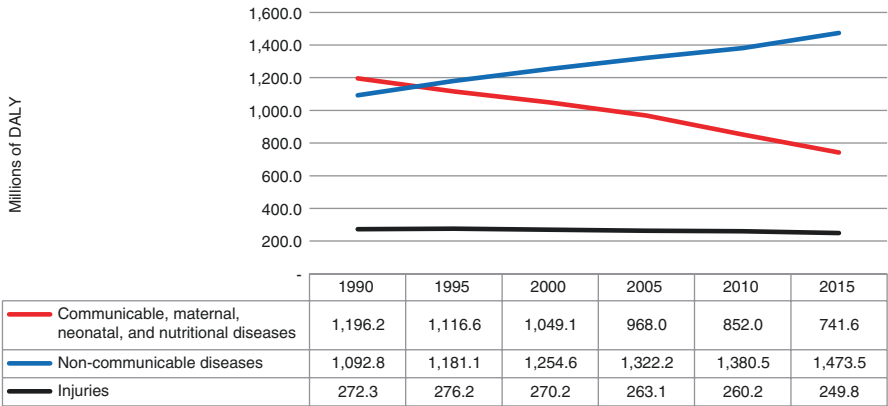


Fig. 2.2 DALYs (disability-adjusted life years), number by three groups of causes for the burden of disease in the world (1990–2015). Source: Made by the authors based on [11]

Table 2.1 Deaths and rate of death per 100,000 persons by group of causes of burden of disease (1990 and 2015)

Causes	1990 # deaths	%	2015 # deaths	%	1990 death rate ×100K	2015 death rate ×100K
Communicable, maternal, neonatal, and nutritional diseases	15,897,278	33.2	11,256,802	20.2	1655.5	767.2
High income	553,365	1.2	662,512	1.2	54.0	53.8
Upper middle income	2,781,060	5.8	1,515,225	2.7	135.9	59.0
Lower middle income	9,433,235	19.7	6,266,103	11.2	494.6	213.9
Low income	3,129,618	6.5	2,812,962	5.0	971.0	440.5
Noncommunicable diseases	27,569,752	57.6	39,769,287	71.3	2058.5	2131.3
High income	7,707,293	16.1	9,512,701	17.1	752.2	772.7
Upper middle income	10,794,811	22.5	14,956,504	26.8	527.7	582.6
Lower middle income	7,891,774	16.5	13,228,217	23.7	413.8	451.6
Low income	1,175,874	2.5	2,071,865	3.7	364.8	324.4
Injuries	4,425,110	9.2	4,721,926	8.5	351.0	259.8
High income	640,312	1.3	639,782	1.1	62.5	52.0
Upper middle income	1,868,549	3.9	1,690,063	3.0	91.3	65.8
Lower middle income	1,541,313	3.2	1,899,523	3.4	80.8	64.8
Low income	374,936	0.8	492,559	0.9	116.3	77.1
Total	47,892,140	100.0	55,748,016	100.0	4065.0	3158.3

Source: Made by the authors based on [11]

causes of death from infectious diseases predominate, while chronic and degenerative diseases are most frequent in high-income countries. However, in both groups of countries, there is a decrease in the proportion of communicable or infectious diseases as causes of death between 1990 and 2015.

Taking into account two of the most important groups of infectious diseases (diarrhea, lower respiratory infections, other common infectious diseases, and meningitis), the percentage of change (decrease) is variable with the level of income, and as expected, the changes in developed countries (high income) were much lower during the period (see Table 2.2 and Figs. 2.3, 2.4, 2.5, 2.6, and 2.7).

Table 2.2 DALYs, rate of death per 100,000 persons by group of causes of burden of disease and income countries (1990 and 2015)

Diseases	1990	2015	%
Diarrhea, lower respiratory infections, and other common infectious diseases	67,954.9	20,421.4	−69.9%
World Bank high income	733.7	609.2	−17.0%
World Bank upper middle income	4823.7	953.2	−80.2%
World Bank lower middle income	17,761.0	4861.8	−72.6%
World Bank low income	34,164.8	10,702.3	−68.7%
Global	10,471.7	3295.0	−68.5%
Meningitis	5235.7	2397.7	−54.2%
World Bank high income	54.5	20.0	−63.3%
World Bank upper middle income	285.2	76.2	−73.3%
World Bank lower middle income	1096.7	466.4	−57.5%
World Bank low income	3095.9	1490.7	−51.9%
Global	703.5	344.5	−51.0%

Source: Made by the authors based on [11]

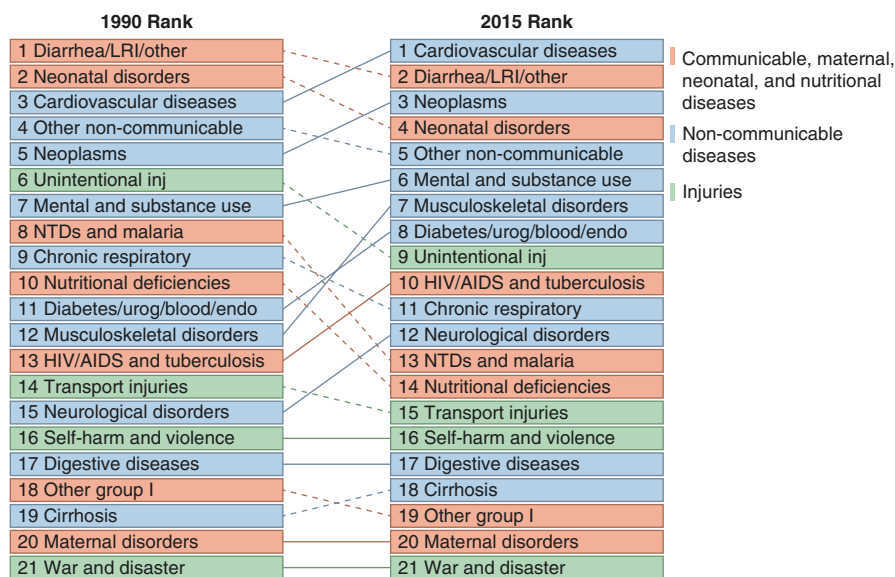


Fig. 2.3 DALYs per 100,000, both sexes and all ages in all countries. Source: Made by the authors based on [11]

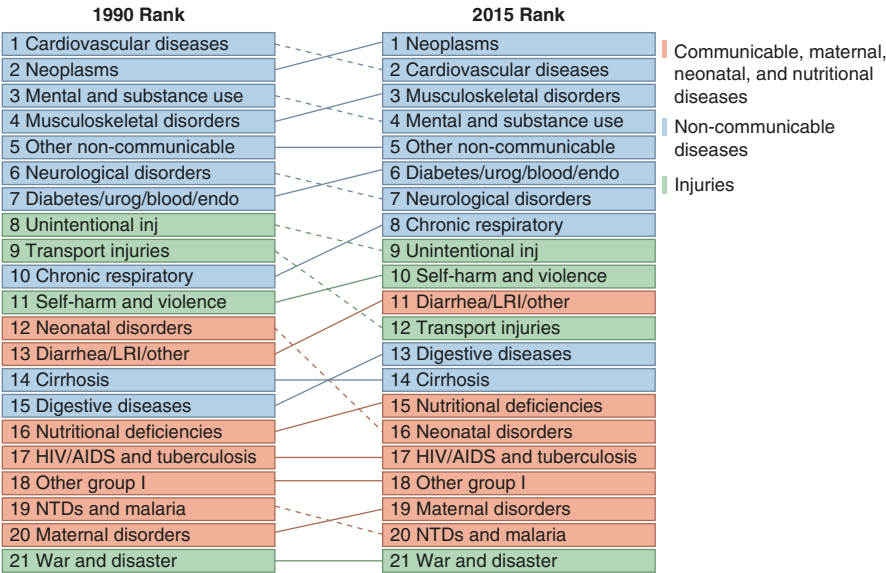


Fig. 2.4 DALYs per 100,000, both sexes and all ages in high-income countries. Source: Made by the authors based on [11]

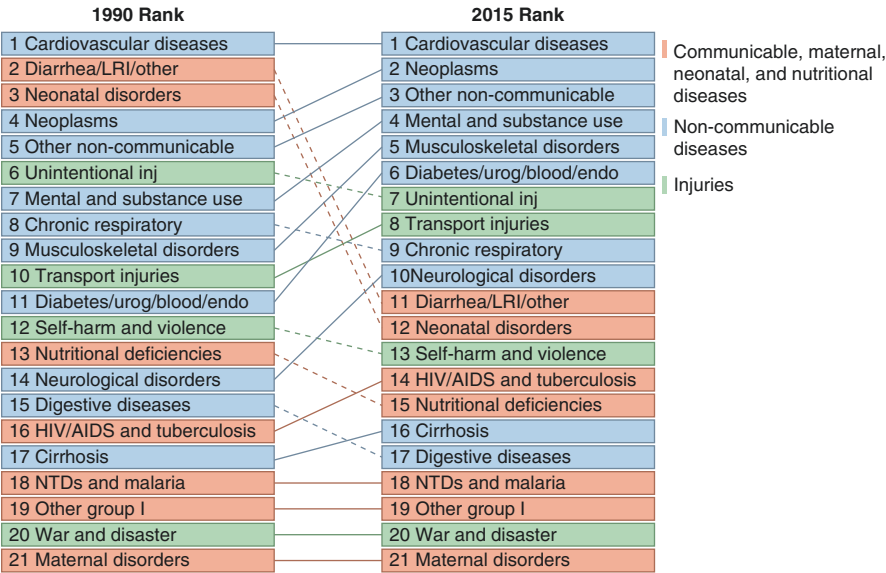


Fig. 2.5 DALYs per 100,000, both sexes and all ages in upper-middle-income countries. Source: Made by the authors based on [11]

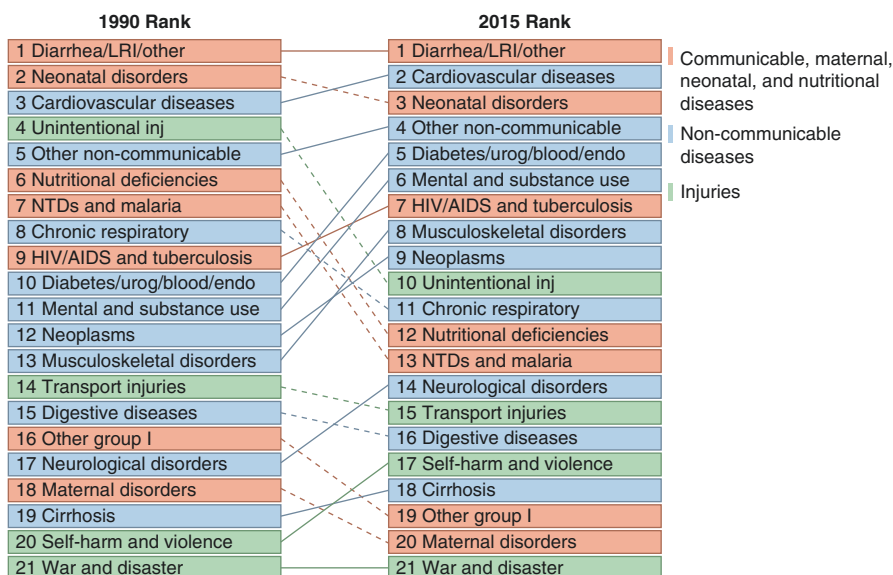


Fig. 2.6 DALYs per 100,000, both sexes and all ages in lower-middle-income countries

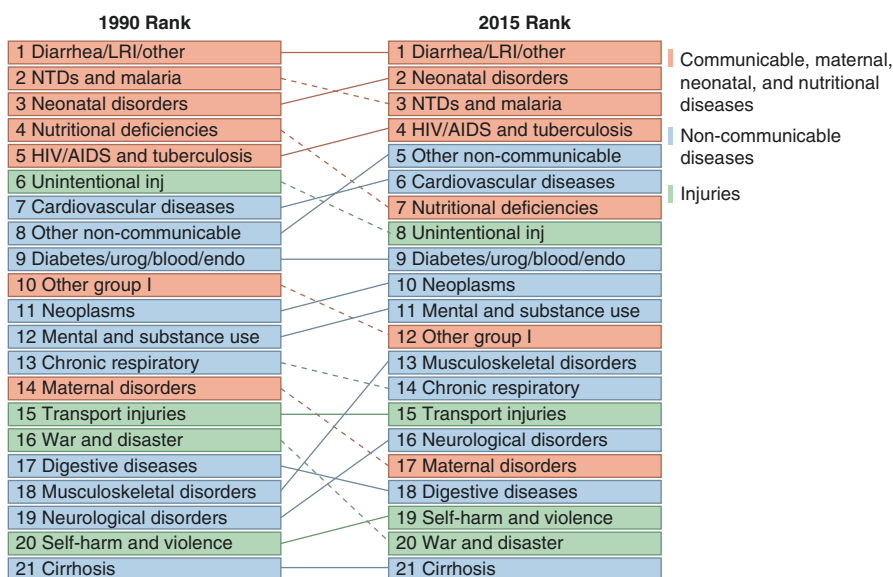


Fig. 2.7 DALYs per 100,000, both sexes and all ages in low-income countries. Source: Made by the authors based on [11]

Antibiotic Consumption and Inappropriate Use

The era of antibiotics started in 1928 with the discovery of penicillin fungus by Sir Alexander Fleming at St Mary's Hospital, London. He discovered that it produced a substance (penicillin) that killed the bacteria he was examining. The development of new antibiotics allowed the effective treatment of deadly illnesses such as pneumonia, tuberculosis (TB), and infections associated with the care of childbirth [12].

Although the antibiotics have reduced the burden of common infectious diseases and become essential for many medical interventions, antibiotic resistance is the main challenge of both research and treatment of infections [13]. Today, the world calls for greater research and production of new antibiotics [14]. There is a lot of evidence on the decline in the frequencies of infectious diseases, and probably antibiotics have played a very important role in this. Although antibiotics appear at the beginning of the twentieth century, it was only halfway through this that antibiotic therapy was consolidated.

Over the past decade, the prevalence of antibiotic resistance has increased alarmingly worldwide, prompting the General Assembly of the United Nations to label this problem as the greatest threat to human health, sustainable development, and security [15]. Inappropriate empirical antibiotic treatment for severe infections is associated with increased mortality. Superfluous treatment is associated with resistance induction [16]. The inappropriate use of antibiotics represents a risk for individual health and a waste of health resources [17].

Antimicrobial resistance represents arguably the greatest current public health threat. If the increase in drug resistance is not slowed, modeling suggests that from the current 700,000 deaths annually, deaths attributed to drug-resistant infections by 2050 will surpass 10 million [12]. The cost to global economic output is estimated at US\$100 trillion [18]. Overuse of antibiotics, the main driver of resistance, pervades all of society. High levels of animal protein production through intensive farming have long been supported by the use of subtherapeutic concentrations of antibiotics to promote growth and reduce the time to market and by a wide-scale treatment (metaphylaxis) of healthy fed animals with antibiotics to prevent infections [18].

Antibiotic-resistant infections add considerable and avoidable costs to the already overburdened US healthcare system. In most cases, antibiotic-resistant infections require prolonged and/or costlier treatments, extend hospital stays, necessitate additional doctor visits and healthcare use, and result in greater disability and death compared with infections that are easily treatable with antibiotics. The total economic cost of antibiotic resistance to the US economy has been difficult to calculate. Estimates vary but have ranged as high as \$20 billion in excess direct healthcare costs, with additional costs to society for lost productivity as high as \$35 billion a year (2008 dollars) [19].

There are less evidence on the burden and cost of antibiotic resistance in developing countries. Alsan et al. [20] analyzed the data from the World Health Organization's antibacterial resistance global surveillance report and assess the amount of out-of-pocket spending and copayment requirements for public sector drugs employed in treating bacterial-resistant infections in low- and middle-income countries (LMIC). They found a strong correlation between increases in the value of out-of-pocket spending and the increase in bacterial-resistant isolates [20].

Bhutta [21] reports that common bacteria producing severe disease among children in developing countries, *Streptococcus pneumoniae* and *Haemophilus influenzae*, have increased their resistance levels to cheap antibiotics such as penicillin and co-trimoxazole. This should have a huge impact on the precarious budget of developing countries' health services because more expensive antibiotics need to be used to treat infections by those bacterial agents [21].

In Colombia, Lemos et al. [22] were able to demonstrate an increase in clinical adverse events as well as a statistical significant increase in economic costs among patients infected with carbapenem-resistant *Acinetobacter baumannii* compared to those infected by a multisensitive strain of the same bacteria. In average, being infected with a resistant *Acinetobacter* increases hospital costs by 1.6 even after controlling by the type of infection, severity of illness, age, and other characteristics [22]. Other studies in Colombia found increase in costs for nosocomial pneumonia and urinary infections compared to patients that do not acquire nosocomial infections [23, 24]. Similar results have been found in other studies in other Latin-American countries [25, 26].

In the USA, the CDC estimates that gaps in knowledge of antibiotic resistance are based on limited national, state, and federal capacity to detect and respond to urgent and emerging antibiotic resistance threats, even for critical pathogens of concern like carbapenem-resistant *Enterobacteriaceae* (*cre*) and *Neisseria gonorrhoeae* [19]. In addition, it states that there is no complete knowledge of the domestic incidence, prevalence, mortality, and cost of antibiotic resistance.

Antibiotic drug consumption is a major driver of antibiotic resistance. Variations in antibiotic resistance across countries are attributable, in part, to different volumes and patterns for antibiotic consumption [13]. An estimated 80% of all antibiotics are used in the community, where prescribing and purchasing of antibiotics without prescription are common, especially in low- and middle-income countries (LMICs). In many countries at all economic levels, clinicians have incentives to overuse antibiotics. The confluence of patients with serious medical conditions, interconnectedness of hospitals through mobile patient populations, and high density of antibiotic use make hospital antibiotic use disproportionately important [27].

Between 2000 and 2010, consumption of antibiotic drugs increased by 36% (from 54.0 to 73.6 billion of standard units). Brazil, Russia, India, China, and South Africa accounted for 76% of this increase. In most countries, antibiotic consumption varied significantly with season. There was increased consumption of carbapenems (45%) and polymyxins (13%), two last-resort classes of antibiotic drugs [13].

Increasingly, numerous publications describe the inappropriate use of antibiotics. In the USA, the Centers for Disease Control and Prevention (CDC) has campaigned to reduce inappropriate antibiotic prescribing for more than 20 years, yet antibiotic prescriptions for acute respiratory tract infections, which generally do not require antibiotic treatment, have decreased only modestly for children and not at all for adults [28].

The Economic Burden

In 2015, the World Bank estimates for the world gross domestic product (GDP) in billions of current dollars is 74,152.4 [29]. The high-income countries with 16.2% of the world population have 63.9% of GDP with \$39,939 per capita, and the health expenditure was 12.3% of GDP [30]. The low-income countries have 8.7% of the world’s population and only 0.5% of GDP and the mean of health expenditure is 37 dollars per person. Latin-American and Caribbean countries have 8.6% of world’s population, 7.1% of GDP, and the mean of health expenditure is 714 dollars per person. In 2015, the US healthcare spending increased to 5.8% to reach \$3.2 trillion or \$9990 per person and more than 17% of GDP as health expenditure [31] (see Table 2.3).

Table 2.3 Gross domestic product, population, and health expenditure in the world (\$US currents)

Countries groups	GDPpc 2015	% Population	% GDP	Health expenditure pc 2014	Health exp % GDP 2014
World	10,093	100.0	100.0	1061	9.9
High income	39,939	16.2	63.9	5251	12.3
OECD members	36,091	17.5	62.4	4735	12.4
IDA and IBRD total	4447	84.2	37.1	274	5.9
Low and middle income	4345	83.8	36.1	267	5.8
Middle income	4776	75.2	35.6	292	5.8
IBRD only	5566	61.6	34.0	349	6.0
East Asia and Pacific	9512	31.0	29.2	643	6.9
Upper middle income	7901	35.3	27.6	518	6.2
Europe and Central Asia	22,112	12.4	27.1	2420	9.5
North America	54,831	4.9	26.4	8990	16.5
United States	56,116	4.4	24.3	9403	17.1
European Union	32,005	6.9	22.0	3613	10.0
East Asia and Pacific (excluding high income)	6488	27.7	17.8	334	5.3
East Asia and Pacific (IDA and IBRD countries)	6557	27.4	17.8	334	5.3

(continued)

Table 2.3 (continued)

Countries groups	GDPpc 2015	% Population	% GDP	Health expenditure pc 2014	Health exp % GDP 2014
Euro area	34,182	4.6	15.6	4135	10.4
China	8028	18.7	14.8	420	5.5
Lower middle income	2002	39.8	7.9	90	4.5
Latin America and Caribbean	8364	8.6	7.1	714	7.2
Europe and Central Asia (IDA and IBRD countries)	7538	6.2	4.6	603	6.4
Middle East and North Africa	7407	5.8	4.2	433	5.3
Europe and Central Asia (excluding high income)	7034	5.6	3.9	570	6.4
South Asia (IDA and IBRD)	1542	23.7	3.6	67	4.4
South Asia	1542	23.7	3.6	67	4.4
Sub-Saharan Africa	1588	13.6	2.1	98	5.5
Sub-Saharan Africa (IDA and IBRD countries)	1588	13.6	2.1	98	5.5
Sub-Saharan Africa (excluding high income)	1587	13.6	2.1	98	5.5
Central Europe and the Baltics	12,403	1.4	1.7	953	6.8
Low income	618	8.7	0.5	37	5.7

The International Development Association (IDA) is the part of the World Bank that helps the world's poorest countries. International Bank for Reconstruction and Development (IBRD). IBRD was established to function as a self-sustaining business and provide loans and advice to middle-income and credit-worthy poor countries

Source: Made by the authors based on [29]

With respect to prescription drugs in 2015, the US healthcare spending was \$324.6 billion (10%). Although the growth in 2015 was slower than the 12.4% growth in 2014, spending on prescription drugs outpaced all other services in 2015 [31].

According to the study “Outlook for Global Medicines through 2021” [32] with a rate of growth between 4 and 7%, the global medicine spending will reach nearly \$1.5 trillion by 2021 on an invoice price basis, up to nearly \$370 billion from 2016. This growth will be driven by new medicines in hepatitis and cancer (see Fig. 2.8) [32].

For the other side, infections and antibiotics are substantial health and economic burden to healthcare system, as well as to patients and their families. Two cost types are important: the direct medical costs linked to attention process, for one side, and the indirect cost related to the lost productivity, on the other side.

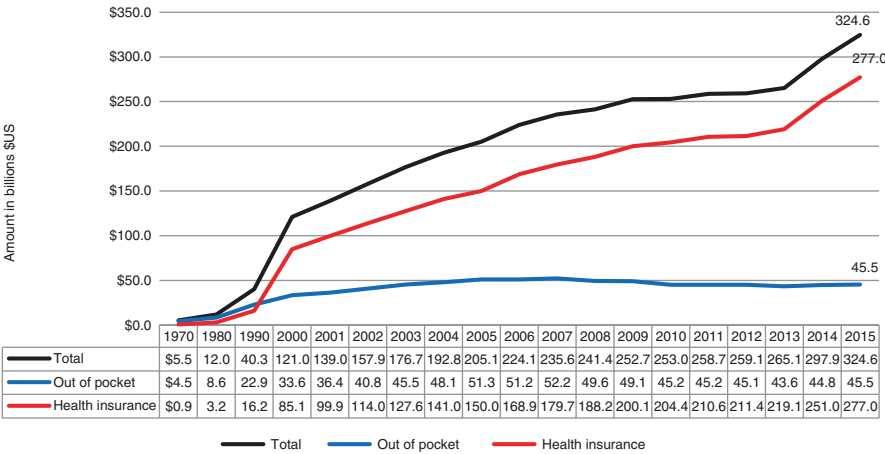


Fig. 2.8 Retail prescription drugs expenditures; by source of funds in the USA (1970–2015). Source: Made by the authors based on [33]

Table 2.4 Ten most common antibiotics prescribed to Medicare Part D beneficiaries, USA (2013)

Antibiotic	Total claims (in millions)	Total costs (in millions)
Azithromycin	6.3	\$83.10
Ciprofloxacin	5.8	\$41.50
Amoxicillin	4.5	\$24.80
Trimethoprim and sulfamethoxazole (co-trimoxazole)	3.5	\$23.90
Cephalexin	3.4	\$26.50
Levofloxacin	3.2	\$46.50
Amoxicillin and clavulanate	2.2	\$49.00
Doxycycline	2.0	\$149.30
Nitrofurantoin	1.5	\$68.90
Mupirocin	1.3	\$22.00

Source: CDC [27]

According to “Avoidable Costs in US Healthcare,” the avoidable cost opportunity from antibiotic misuse is \$35 billion, with a range from \$27 billion to \$42 billion [34]. About 95% of these costs occur in hospitals and the rest in outpatients. This economic burden is a result of antibiotic-resistant infections, longer medical treatment, expensive second- and third-line antibiotic therapies, and screening and diagnostics to detect and prevent the spread of resistant bacterial strains [34].

For 2021 expenditure antibiotics will grow between 2 and 5% and the USA will continue leading the spent [32]. Table 2.4 shows the main and most common antibiotics prescribed to Medicare Part D beneficiaries, USA, 2013 [27]. Over 54 million outpatient antibiotic claims were filed for Part D enrollees in 2013, representing more than \$1.5 billion in total antibiotic expenditures [35].

Conclusions

Infectious diseases and resistance to antimicrobials seem to have an important impact on public health in developed and developing countries. Though there are more detailed data for developed countries, scarce data from developing and LMIC also showed increase in resistance for antimicrobials and antibiotics. This trend is likely to increase in the medium term if systematic and coordinated measures to curb the trend are not implemented across the globe. Some measures proposed by experts which include increasing public awareness, improving standards of care, and the appropriate regulation of the use of such antimicrobials are all important steps [21].

Many challenges remain to improve the perspectives regarding antimicrobial resistance in developing countries. Better information systems defining the magnitude of the problem are badly needed as well as training programs to optimize treatment with antibiotics. Also, there is a need to balance antibiotic “access” as well as “excess.” Measures to regulate antibiotic availability must be accompanied by strengthening workforce capacity and drug supplies in dysfunctional health systems. The crisis of increasing antimicrobial resistance to serious and common infections is a threat to weak public health systems in developing countries, and solutions are urgently needed [21].

Three questions could be important:

1. Is the economic impact of antimicrobial resistance on the health systems well identified, especially in low- and middle-income countries?
2. How to encourage public policies of appropriate use of antimicrobial drugs to reduce the rise of resistance?
3. How to promote potential research for alternative therapies to disrupt the rise in antimicrobial resistance?

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