


# Diarrheal Diseases: A Review on Gastroenteritis Bacteria Global Burden and Alternative Control of Multidrug-Resistant Strains

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## Abstract

Diarrheal diseases represent a significant and pervasive health challenge for humanity. The aetiology of diarrheal diseases is typically associated with the presence of enteropathogens, including viruses, bacteria and parasites. The implementation of preventive measures, including the maintenance of good food hygiene, effective water sanitation, and the development of rotavirus vaccines, has resulted in a notable reduction in the prevalence of the disease. However, the emergence of bacterial multidrug resistance due to the past or present inappropriate use of antibiotics has rendered bacterial infections a significant challenge. The objective of this review is threefold: firstly, to provide an overview of diarrheal diseases associated with bacteria; secondly, to offer a concise analysis of bacterial multidrug resistance on a global scale; and thirdly, to present the potential of filamentous fungi as an alternative solution to the challenge posed by multidrug-resistant strains. *Campylobacter* spp. is the most dangerous bacteria, followed by *Shigella* spp. and *Vibrio cholerae* in all age groups combined. However, *Shigella* spp. was the deadliest in children under five years of age and, together with *E. coli*, are the most antibiotic-resistant bacteria. With their highly developed secondary metabolism, fungi are a reservoir of natural bioactive compounds.

## Keywords

Diarrheal Disease, Bacteria, Multidrug Resistance, Fungal Metabolites

## 1. Introduction

One of the fundamental daily habits of human beings is nutrition. It is a

fundamental process that is essential for growth and development. However, it can also act as a source of disease. Food intended for consumption can become contaminated with pathogenic agents, including bacteria, viruses, parasites and prions, through a number of accidental or unhygienic practices. Once contaminated, these unsafe foods create a vicious circle of foodborne illness, with a particular impact on infants, young children, the elderly and the sick [1]. Annually, 600 million individuals contract illness as a result of consuming contaminated foodstuffs [2]. One of the most prevalent manifestations of foodborne illness is diarrhea. This results in considerable fluid loss and dehydration, which can have significant or even fatal consequences if fluids are not replenished [3]. The primary agents responsible are rotavirus, which is more prevalent in children under the age of five, and enterobacteria, which are observed in all age categories [4]-[6]. Following the introduction of the rotavirus vaccine in 2006 [7], a reduction in the incidence of infection and a decrease in the number of severe cases have been observed [8]. In the case of bacteria, the administration of antibiotics has been combined with oral rehydration salts (ORS). However, there has been an increase in the number of bacteria strains that are resistant to antibiotics [9] [10]. The cases of extended-spectrum  $\beta$ -lactamase-producing bacteria and methicillin-resistant *Staphylococcus aureus* (MRSA) serve as a prime example of this phenomenon [11] [12]. Previous reviews of bacteria responsible for diarrheal diseases have focused on cases of diarrhea in children and the germs associated with their gastroenteritis. This analytical review complements these previous works by generalizing the statistics on diarrhea in both children and adults on the one hand and the resistance of the bacteria involved to antibiotics by region of the world. The importance of the danger posed by the rapid evolution of resistance to antibiotics in bacteria responsible for gastroenteritis has become a global public health priority. In light of the aforementioned circumstances conducive to mortality, it is imperative to invest in the research of new potentially active substances that will serve as precursors to the development of new drugs. Despite the availability of numerous resources for the design of new therapeutic products, natural products are always preferred to synthetic ones.

The fungal kingdom represents one of the most significant sources of natural products with diverse structures and biological activities. It is estimated that 40% of biologically active natural products produced by microorganisms are produced by fungi [13]. In their natural habitat, fungi typically find themselves in a competitive environment with other microorganisms. In their pursuit of space and nutrients, fungi secrete secondary metabolites that function as weapons against competitors [14]. The exploitation of this scenario led to the discovery of penicillin by Sir Alexander Fleming, thereby substantiating the antibacterial potential of fungi [15]-[17]. The production of the antibacterial molecule by fungi is one aspect of the process; its isolation is another. As a result of technological advances and the growth of OMICS sciences, a number of approaches have been developed to facilitate the isolation of the most effective natural product [18]. The objective of this

review is threefold: firstly, to provide an overview of diarrheal diseases associated with bacteria at all age; secondly, to offer a concise analysis of bacterial multidrug resistance on a global scale; and thirdly, to present the potential of filamentous fungi as an alternative solution to the challenge posed by multidrug-resistant strains.

## 2. Materials and Methods

Our literature search was based on: 1) publications from 2008 to 2023 on statistical data relating to diarrhoeal diseases associated with bacteria. The following keywords were used: “diarrhoeal diseases”, “gastroenteritis”, “chronic gastrointestinal” with references to “morbidity”, “mortality”, “*Shigella*”, “*Escherichia coli*”, “*Salmonella*”, “*Campylobacter*”, “*Vibrio cholerae*”, “*Clostridium*”, “enterobacteria”, “transmission”, “multidrug resistance”; and 2) publications on antibacterial activity of fungi on enterobacteria. The following keywords were used: “antibacterial activity”, “filamentous fungi”, “gram-negative bacteria” with references to “*Shigella*”, “*Escherichia coli*”, “*Salmonella*”, “*Campylobacter*”, “*Vibrio cholerae*”, “multi-resistant enterobacteria”. The search engines Google scholar, Scopus and Pubmed were used for the searches. Only open access articles were used for this study. The bibliographic summary was based on 79 articles. Medians were calculated and histograms plotted using Microsoft Office Excel 2010. Graphical representations of the geographical distribution of multidrug-resistant bacteria were produced online using the Institute of Health Metrics Evaluations (IHME) visualisation tool (<https://vizhub.healthdata.org/gbd-results/>).

## 3. Results and Discussion

### 3.1. Global Burden of Bacteria-Related Diarrhoeal Diseases

Diarrheal diseases represent a significant public health concern. Notwithstanding the considerable strides made in modern medicine and the plethora of strategies devised to curtail infection, the mortality rate associated with diarrheal diseases caused by bacteria has exhibited only a modest decline over time. Annually, gastroenteritis bacteria are responsible for billions of infections, with a high morbidity rate and a relatively high mortality rate [19] [20].

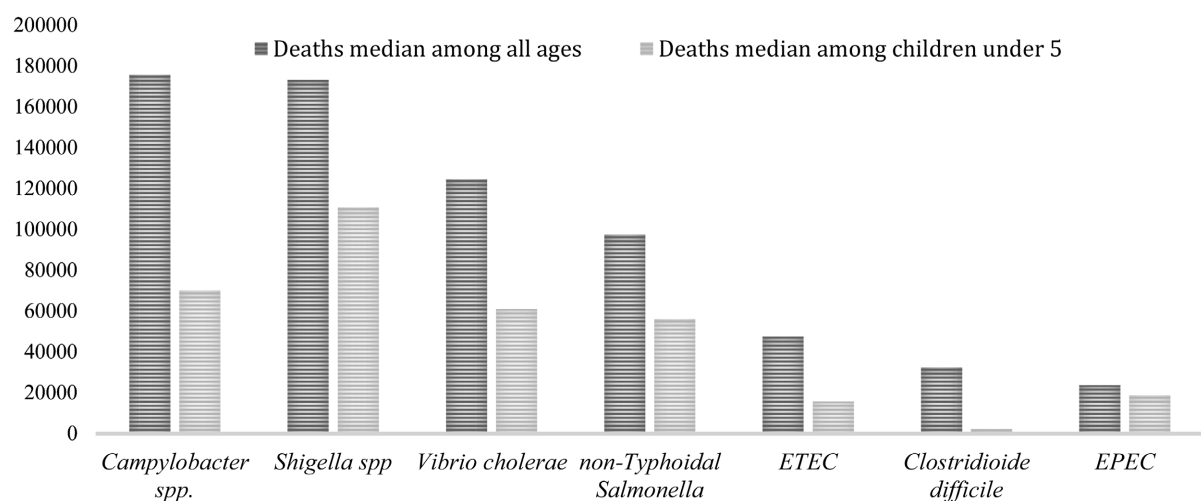
In Benin, diarrhea represents one of the most significant causes of morbidity on a daily basis. As indicated by data from the Ministry of Health, diarrheal diseases are less fatal than malaria or anemia. However, they have a significant economic and public health impact on the population. As indicated by the World Health Organization (WHO), diarrheal diseases represent the second leading factor contributing to reduced life expectancy, with a reduction of 1.97 years following lower respiratory tract infections, which result in a reduction of 2.09 years. This fact cites diarrheal diseases among the causes of premature death in countries with a low sociodemographic index (SDI) [2].

The most common bacteria associated with diarrhea, according to the Global Burden of Disease study, are *Campylobacter* spp., *Shigella* spp., *Vibrio cholerae*,

non-typhoidal *Salmonella*, enterotoxigenic *Escherichia coli* (ETEC), enteropathogenic *Escherichia coli* (EPEC) and *Clostridioides difficile*. Globally, *Shigella* spp. [21] [22], non-typhoidal *Salmonella* [23] [24] and *Campylobacter* spp. [25] [26] were the leading causes of diarrheal mortality [27]. The most recent data from the Institute of Health Metrics Evaluation (IHME) indicate that *Campylobacter* spp. is the most dangerous bacteria, followed by *Shigella* spp. and *Vibrio cholerae* across all age categories (Figure 1). Nevertheless, *Shigella* spp. is responsible for most deaths in children under five years of age (Figure 1). These observations are consistent with those of the Global Enteric Multicenter Study (GEMS). The findings of this study indicate a significant correlation between *Shigella* spp. and an elevated risk of mortality in children under five years of age [28]-[30]. It is the primary cause of mortality in regions with low and moderately low SDI, followed by *Vibrio cholerae* and non-typhoidal *Salmonella* (Table 1) [31]. A substantial proportion of the global burden of diarrheal disease is attributable to death rates from diarrheagenic *Escherichia coli*, particularly in low SDI regions (Table 1). *Clostridioides difficile* is the most under-recorded bacterial species associated with gastroenteritis and diarrhea worldwide. But it is mainly known for causing intestinal infections, often after the use of antibiotics, which can lead to symptoms such as severe diarrhea, abdominal cramps and, in serious cases, complications such as toxic megacolon. It is particularly prevalent in regions with a high socio-demographic index (Table 1).

### 3.2. Bacteria-Related Diarrhoeal Disease: Management

Interventions for diarrheal diseases can be divided into two categories: preventive and therapeutic. Preventive measures to reduce exposure to enteric pathogens include improvements to the quality of drinking and cooking water, the quantity of water available for personal and domestic hygiene, safe food storage, hand washing and the sanitary disposal of faecal waste. These may include wastewater



Source: IHME, Global Burden of Disease (2019) results. Consulted 15/11/2023.

Figure 1. Burden of bacteria responsible for diarrhea.

**Table 1.** World burden of diarrheal disease by SDI region.

Location	etiological agents	Deaths median among all ages	Death range among all ages	Deaths median among children under 5	Death rage among children under 5 years
Low SDI countries	<i>Shigella</i> sp.	105,954.5	(37,681 - 174,228)	79,571	(25,713 - 133,429)
	<i>Vibrio cholerae</i>	96,139.5	(51,140 - 161,138)	52,228	(21,892 - 82,564)
	<i>Campylobacter</i> sp.	78,879.5	(23,874 - 133,885)	46,089.5	(15,272 - 76,907)
	Non-typhoidal <i>Salmonella</i>	59,152.5	(2839 - 115,465)	40714	(2839 - 78,589)
	Enterotoxinogenic <i>Escherichia coli</i>	16,925.5	(6593 - 27,252)	9296.5	(2988 - 15,605)
	Enteropathogenic <i>Escherichia coli</i>	14,893.5	(6160 - 23,626)	12643	(4904 - 20,382)
	<i>Clostridioides difficile</i>	492.5	(220 - 765)	131	(40 - 220)
Low middle SDI countries	<i>Campylobacter</i> sp.	70,814	(15,790 - 125,839)	18,927	(6649 - 31,205)
	<i>Shigella</i> sp.	27,442	(15,747 - 39,127)	22,361.5	(6523 - 38,200)
	Non-typhoidal <i>Salmonella</i>	23,388.5	(825 - 45,952)	9637	(825 - 18,449)
	<i>Vibrio cholerae</i>	22,537	(13,605 - 31,469)	7530	(4050 - 11,010)
	Enterotoxinogenic <i>Escherichia coli</i>	22,520	(7829 - 37691)	4650	(1498 - 7802)
	Enteropathogenic <i>Escherichia coli</i>	5689	(2575 - 8803)	4071	(1595 - 6547)
	<i>Clostridioides difficile</i>	1400.5	(846 - 1955)	386.5	(186 - 587)
Middle SDI countries	<i>Campylobacter</i> sp.	20,255.5	(4531 - 35,980)	5051	(1699 - 8403)
	<i>Shigella</i> sp.	16,960.5	(6105 - 27,816)	7686	(2613 - 12,759)
	Non-typhoidal <i>Salmonella</i>	12,624	(530 - 24,718)	4574	(530 - 8618)
	Enterotoxinogenic <i>Escherichia coli</i>	6528	(2496 - 10,560)	1567.5	(450 - 2685)
	<i>Vibrio cholerae</i>	5671.5	(3613 - 7730)	1680	(895 - 2465)
	<i>Clostridioides difficile</i>	5013	(3721 - 6305)	1215	(692 - 1738)
	Enteropathogenic <i>Escherichia coli</i>	2863.5	(1220 - 4507)	2009.5	(737 - 3282)
High middle SDI countries	<i>Clostridioides difficile</i>	4882.5	(4100 - 5665)	752	(231 - 521)
	<i>Shigella</i> sp.	3198	(1046 - 5350)	794.5	(235 - 1354)
	<i>Campylobacter</i> sp.	2456.5	(468 - 4445)	433.5	(127 - 740)
	Non-typhoidal <i>Salmonella</i>	2007.5	(62 - 3953)	464	(62 - 866)
	Enterotoxinogenic <i>Escherichia coli</i>	1033	(375 - 1691)	160.5	(48 - 273)
	<i>Vibrio cholerae</i>	702.5	(380 - 1025)	130.5	(63 - 198)
	Enteropathogenic <i>Escherichia coli</i>	267	(122 - 412)	317	(61 - 256)
High SDI countries	<i>Clostridioides difficile</i>	20,635.5	(17,623 - 23,648)	154	(128 - 180)
	<i>Campylobacter</i> sp.	2609.5	(349 - 4870)	11.5	(3 - 20)
	Non-typhoidal <i>Salmonella</i>	1767	(2 - 3532)	20.5	(2 - 39)
	Enterotoxinogenic <i>Escherichia coli</i>	830	(339 - 1321)	10	(3 - 17)

## Continued

<i>Shigella</i> sp.	788	(228 - 1348)	15.5	(4 - 27)
Enteropathogenic <i>Escherichia coli</i>	50.5	(20 - 81)	3	(1 - 5)
<i>Vibrio cholerae</i>	34.5	(16 - 53)	7.5	(3 - 12)

Note: the classification of bacteria by SDI region and from most to least recurrent bacteria in each SDI region. Source: IHME, November, 15<sup>th</sup> 2023.

treatment by a filtration system or boiling or the use of water purification tablets to inactivate microbial pathogens [32]. Nevertheless, it is crucial to situate the water source at a safe distance from latrines.

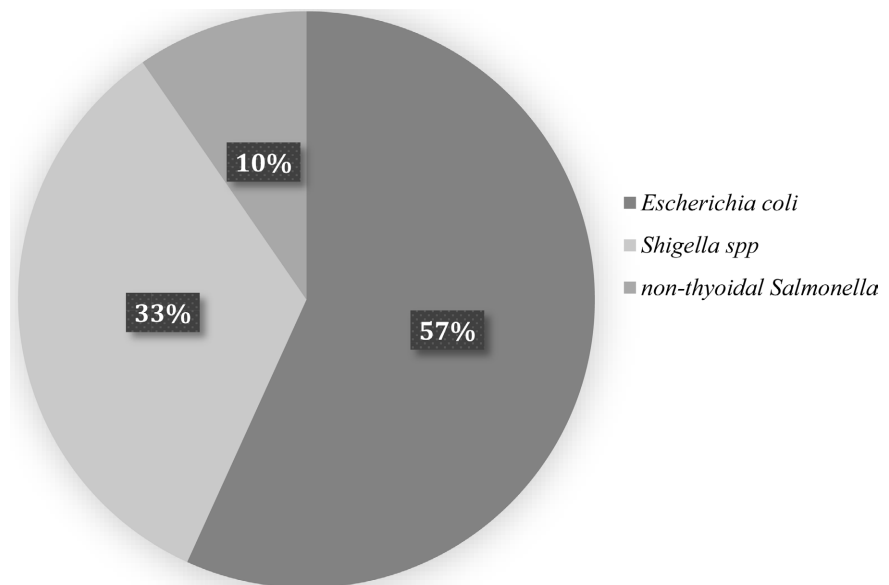
Given that dehydration is the most common complication of the disease, therapeutic intervention is primarily focused on reversing this dehydration. This practice is fundamental to the treatment of pediatric patients. An oral rehydration solution (ORS) is employed for this purpose. The solution is composed primarily of sodium, chloride, and glucose. The global distribution of this solution has contributed to a reduction in the number of deaths among children caused by diarrhea [33]. The World Health Organization (WHO) recommends zinc supplementation in conjunction with oral rehydration therapy for children, given the considerable zinc losses that occur during childhood diarrhea. In Bangladesh, a combination of oral rehydration solution (ORS), zinc and vitamin A was found to be highly effective in reducing the number of deaths caused by diarrhea in children [34]. In instances of severe dehydration, which is frequently observed in hospital settings in tropical countries, intravenous fluid replacement is employed as a treatment modality [4]. An antibiotic is incorporated into the oral rehydration treatment regimen.

A meta-analysis of randomized controlled trials has demonstrated that antibiotic therapy is an effective intervention for reducing the duration of illness caused by bacteria. The current drugs used to treat diarrhea and gastroenteritis caused by bacteria are metronidazole (nitroimidazole), azithromycin (macrolide), ciprofloxacin (quinolone), amoxicillin/clavulanic acid ( $\beta$ -lactam) and ceftriaxone ( $\beta$ -lactam) [35]. The aforementioned pharmaceutical agents may be administered in combination, according to the physician's diagnosis, with the objective of achieving the most favorable outcome [36]. In particular, quinolones (ciprofloxacin) remain efficacious in instances of *Shigella* spp. infections; however, due to the emergence of multidrug resistance, azithromycin represents a viable alternative [37]. In the case of *Campylobacter* infections, treatment within four days of the onset of symptoms may result in improved outcomes with gentamicin. However, it should be noted that azithromycin and erythromycin are already prone to multidrug resistance [38]. The majority of non-typhoidal *Salmonella* infections are self-limiting. Nevertheless, in view of the potential risk of bacteremia in specific patient groups, treatment may be warranted for those at high risk, including children under one year of age, adults over 60, and individuals with underlying immunodeficiency. Similarly, resistance to quinolones is now prevalent in the treatment

of *Campylobacter* infections. In such cases, azithromycin may be a superior option [39]. Nutrition also plays a role in the treatment of foodborne bacterial disease. Nutritional support can be considered both a therapeutic and a preventive measure. Malnutrition is both a consequence and a risk factor for diarrheal disease [40]. Nutritional support during diarrhea and nutritional rehabilitation during convalescence enhance resistance and facilitate recovery from subsequent episodes of diarrhea [33].

### 3.3. Gastroenteritis Bacteria: The Danger of Multi-Resistance

The ongoing prevalence of foodborne diseases attests to the persistent challenge of effectively controlling enterobacteria, despite advancements in prevention and treatment strategies. The principal concern pertaining to food-borne bacterial diseases is the rising incidence of bacterial resistance to antibiotics [41]. As indicated by data from the Institute for Health Metrics and Evaluation, the multidrug-resistant gastroenteritis bacteria that are responsible for the greatest number of deaths globally are *Escherichia coli*, *Shigella* spp., and non-typhoidal *Salmonella* (Figure 2). *E. coli*, all categories combined, is the main cause of death due to antibiotic resistance with a rate of 57% (mean value 58,702.5) deaths in 2019. The second bacteria responsible for gastroenteritis causing the most deaths due to multi-resistance to antibiotics is *Shigella* spp. (33%); then in third position is non-typhi *Salmonella* (10%) (Figure 2).

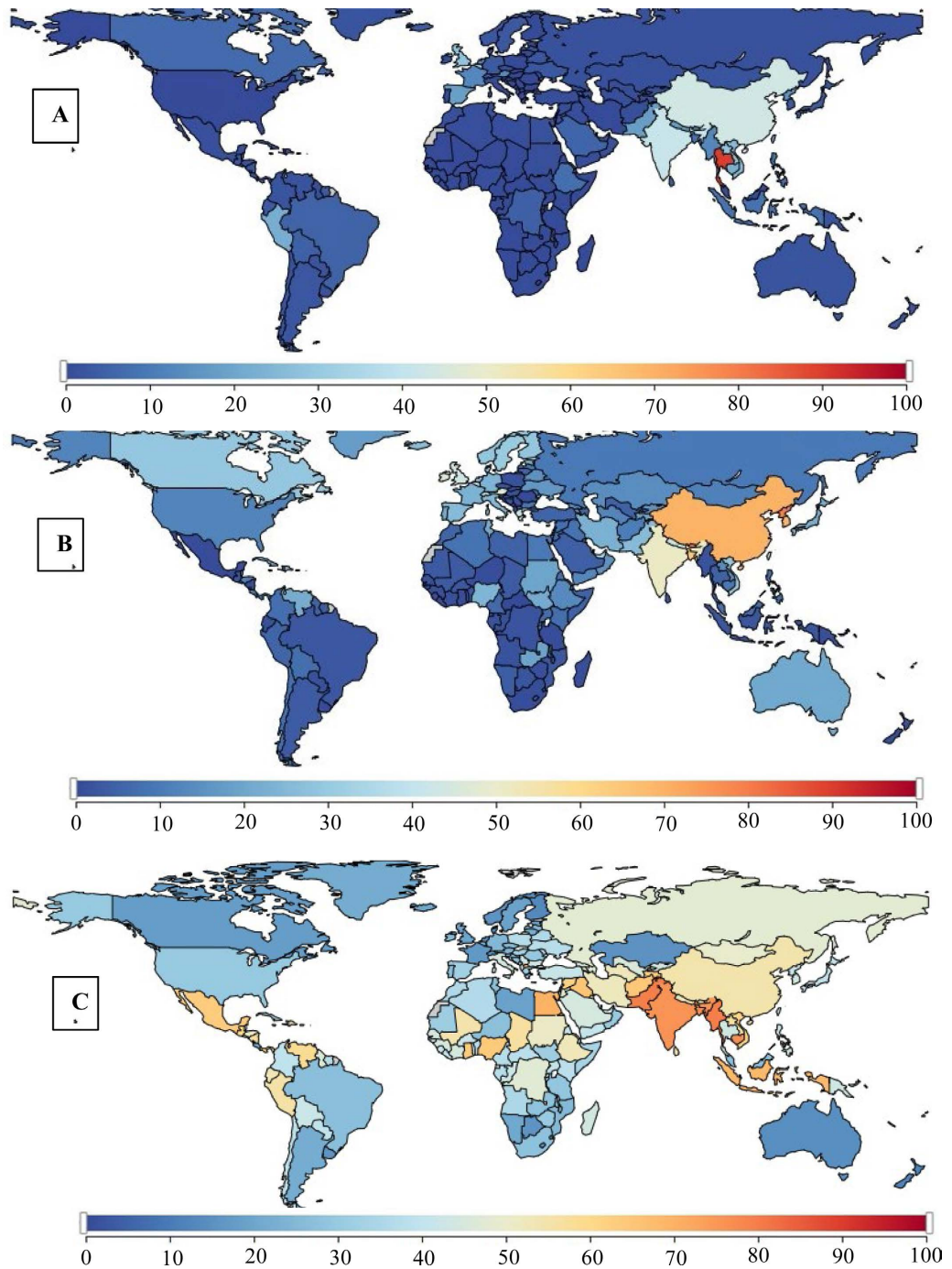


Source: IHME, Global Burden of Disease (2019) results. Consulted 15/11/2023.

**Figure 2.** Death associated to main antimicrobial multi-resistant enterobacteria causing diarrhea in world.

Fluoroquinolones, which have historically demonstrated efficacy against a diverse range of bacterial pathogens, are gradually exhibiting reduced activity against these organisms. A reduction in the susceptibility of non-typhoidal

*Salmonella* to fluoroquinolones has been documented in multiple studies conducted in various African countries [42]-[47]. China and India are the countries most affected by fluoroquinolone-resistant non-typhoidal *Salmonella* (Figure 3A). An analogous situation has been observed in the case of *Shigella* spp. overseas.

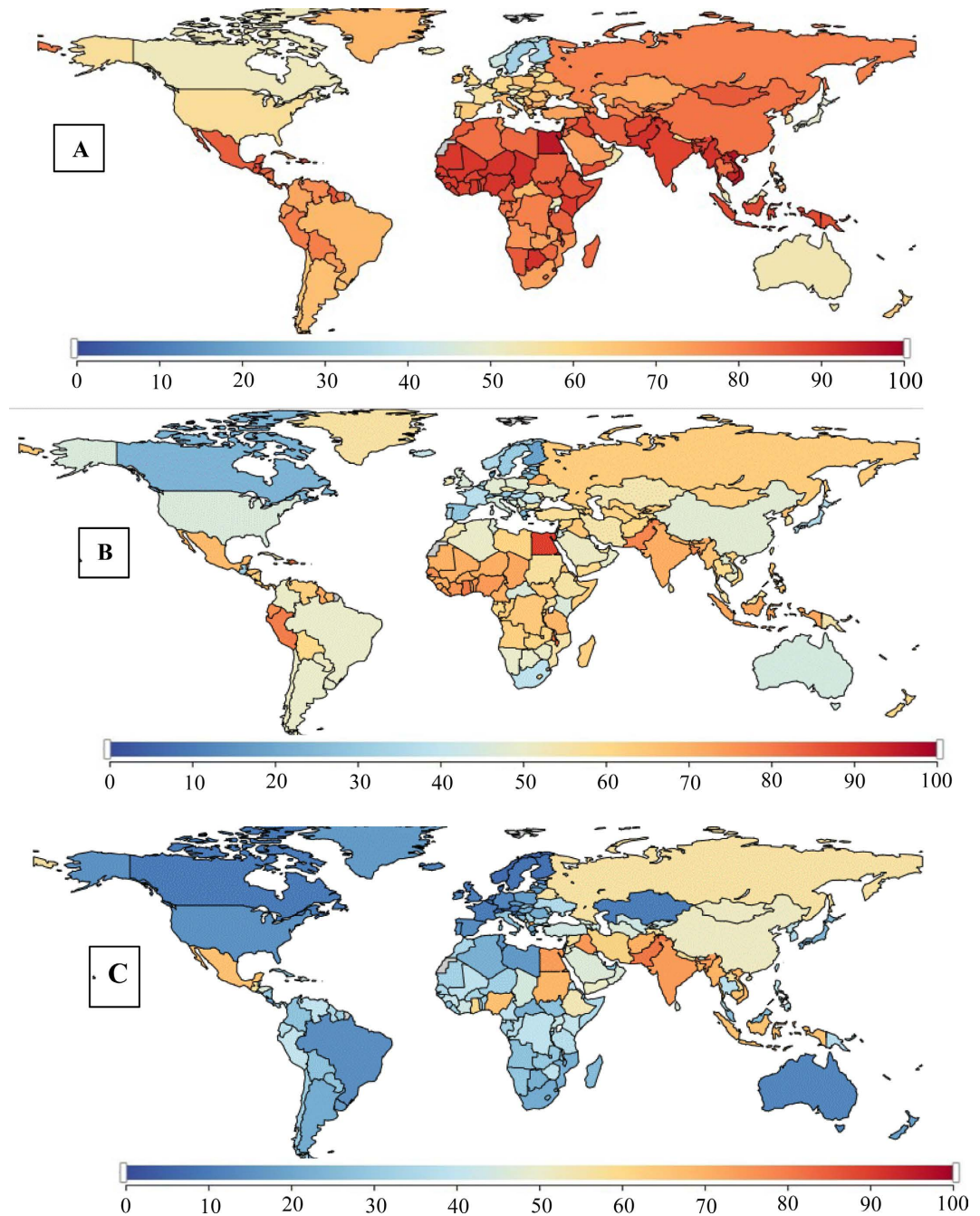


Source: IHME, Global Burden of Disease (2019) results. Consulted 15/11/2023.

**Figure 3.** Geographical distribution of gastroenteritis bacteria resistant to fluoroquinolones (in percentage). A: non typhoidal *Salmonella*; B: *Shigella* spp. and C: *E. coli*.

In France, there has been a concerning increase in the proportion of *Shigella sonnei* that is multi-resistant to ciprofloxacin, third-generation cephalosporins and azithromycin [48]. In Bangladesh, fluoroquinolone-resistant *Shigella* spp. has been the second most common cause of childhood diarrhea from 2019 to 2021, after *E. coli* [49]. As illustrated in **Figure 3B**, the proportion of fluoroquinolone-resistant *Shigella* spp. strains are notably elevated in South Asia and South-East Asia, according to IHME statistics. Fluoroquinolone-resistant *E. coli* is the most widely distributed globally (**Figure 3C**). Moreover, it is among the most prevalent strains that accumulate antibiotic resistance (**Figure 4**) [50] [51]. Aminopenicillins are the antibiotic class with the highest proportion of *E. coli* resistant globally, particularly in Africa and Asia, according to IHME (**Figure 4A**). Furthermore, the  $\beta$ -lactam resistance strain is predominantly distributed in Africa, Asia, and a few regions of Latin America (**Figure 4B**). This can be attributed to the ease with which the general population can access aminopenicillins. Third-generation cephalosporins, which are considered a mainstay for the treatment of severe infections, have already been associated with cases of resistance in bacteria such as *E. coli* (**Figure 4C**) [52]-[57].

In Asia, the use of antibiotics in animal husbandry favors resistance to fluoroquinolones. In Africa,  $\beta$ -lactam antibiotics are the most widely used antibiotics by the population, with practices that are not recommended. On the other hand, in Europe, it is the resistance of bacteria such as shigella, caused by the use of macrolides, quinolones and cephalosporins in medicine, that is more prevalent. In America, a combination of animal husbandry and treatment techniques, combined with the medical use of different antibiotic families, does not reflect a different pattern than in other parts of the world. These different, albeit dissimilar, practices around the world are conducive to the emergence of multi-resistant strains, thanks to the transfer of resistance via mobile genetic elements between bacteria. All of this contributes to the increasing difficulty of treating bacterial infections, and the growing number of deaths caused by multi-resistant bacteria responsible for gastroenteritis (**Figure 2**). In light of the gravity of the multi-resistant strain's situation and its ramifications at the individual and collective levels, a number of recommendations have been put forth by scientific societies. One such recommendation is that of hand hygiene. This is the most straightforward method of preventing the transmission of multi-resistant bacteria, particularly within hospital settings. It is of the utmost importance that healthcare workers adhere to the established hygiene protocols [58]. Strict adherence to the aforementioned recommendations would prevent the transmission of multi-resistant strains by touch. It is as crucial for healthcare workers to practice hand hygiene as it is for any other individual in society. Nevertheless, all hygiene practices, from hand hygiene to environmental hygiene, are efficacious measures against the dissemination of pathogens. While hygiene is an effective method of preventing the transmission of microorganisms, it is not a panacea. The control of antibiotic acquisition by patients, for instance through the implementation of a prescription



Source: IHME, Global Burden of Disease (2019) results. Consulted 15/11/2023.

**Figure 4.** Geographical distribution of *E. coli* resistant to A: aminopenicillin; B: beta-lactam and C: third cephalosporins generation.

requirement prior to the purchase of antimicrobials, may prove an effective strategy for the reduction of the emergence of multi-resistant strains [59]. Such a measure would also serve to mitigate a number of the adverse consequences associated with self-medication. It is also imperative to implement active surveillance for multidrug-resistant strains in healthcare facilities. In the course of routine analysis of clinical specimens, microbiological testing laboratories are obliged to include

antimicrobial susceptibility testing in order to monitor the emergence of multi-drug-resistant strains. It is recommended that an update of the strain repertoire be conducted in the event of the emergence of new multi-resistant strains [60].

### 3.4. Fungi: A Source of Antibacterial Compounds

The emergence of new cases of fatal infections due to the accelerated development of bacterial resistance to antibiotics underscores the urgent need for the development of novel therapeutic compounds. The use of natural products for the treatment of illness is a practice that has been employed by humans for a considerable length of time. The majority of these products are derived from plants, animals, or microorganisms.

Fungi are cosmopolitan microorganisms that play a significant role in the biodegradation of organic matter. They are particularly endowed with a well-developed secondary metabolism. The compounds produced by this metabolic process are referred to as secondary metabolites [61]. These are typically produced by fungi at the conclusion of their life cycle or during the process of colonizing diverse habitats or under conditions of stress [62]. Polyketides and non-ribosomal peptides are the most commonly secondary metabolites described as possessing antibacterial activity.

Polyketides represent the largest and most structurally diverse class of fungal secondary metabolites. This impressive diversity is the consequence of the remarkable flexibility of polyketide synthases. The selection of carboxylic acid derivatives, control of polymer length, cyclisation or cleavage, as well as aromatization, oxidation, alkylation and glycosylation on polyketides produced by polyketide synthases results in a vast array of bioactive secondary metabolites. The class of metabolites in question comprises polyesters, polyphenols, macrolides (macrocyclic esters), polyenes and enediynes [63]. These are primarily produced by fungi of the genus *Penicillium* [64]. Notable examples include xanthoradones A and B, penipyranicin C and xanthoepocin. The potentiation of imipenem activity against MRSA by xanthoradones A and B was demonstrated by a reduction in the MIC value of imipenem from 16 µg/ml to 0.060 and 0.030 µg/ml, respectively [65]. Penipyranicin C is produced by *Penicillium* CAAM64, which was isolated from a hydrothermal source. It has demonstrated notable efficacy against gram-negative bacteria, particularly *Enterobacter xiangfangensis* and *Pseudomonas aeruginosa* [66]. Additionally, xanthoepocin has been identified as a potent agent against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterobacter faecium*, with an MIC of 0.313 µg/ml. Xanthoepocin is produced by *Penicillium ochrochloron* CBS 123823 [67]. It should be noted that polyketides are also produced by other fungi. This is exemplified by rubeline anthraquinone, which is produced by *Ramularia collo-cygn*, an ascomycete fungus that causes *Ramularia* plant diseases. Rubeline has been demonstrated to exhibit activity against *Bacillus subtilis* and *Enterococcus faecalis* 1528, and the multi-resistant strain, methicillin-resistant *Staphylococcus aureus* [68]. An additional illustration of antibacterial

metabolites derived from polyketides is eupenicinicol. *Eupenicillium* spp., an endophytic filamentous fungus, was the source of eupenicinicol, which demonstrated antibacterial activity against *E. coli* with a minimum inhibitory concentration of 5 µg/mL [69]. Given their provenance and structural diversity, polyketides have been demonstrated to exhibit broad-spectrum antibacterial activity and are also capable of combating multi-resistant strains.

Non-ribosomal peptides represent one of the most diverse and complex classes of secondary metabolites observed in the living world. Ascomycota are the primary producers. The biosynthesis of these compounds does not involve the usual protein synthesis machinery; instead, it is carried out by multidomain enzymes known as non-ribosomal peptide synthases.

β-lactams represent the most extensively studied category of non-ribosomal peptides. β-lactams are among the most extensively studied fungal antibacterial metabolites. This family of secondary metabolites comprises penicillins and cephalosporins, which are produced by fungi of the genera *Penicillium* and *Acremonium*, respectively [70] [71].

Other classes of antibacterial secondary metabolites produced by fungi are cyclic dipeptides, terpenoids and isoquinoline alkaloids.

Cyclic Dipeptides are ubiquitous secondary metabolites in biological systems. They have been described as one of the oldest classes of signalling molecules and have even been found in extraterrestrial meteorites [72]. They are formed by the bonding of two amino acids. The absence of free C- and N-terminal groups in their formula means that they are resistant to human digestion. This characteristic makes them attractive for the development of protein-based drugs. Many cyclic dipeptides display biological activities such as inhibition of microbial growth and human tumor cells. For example, a single fermentation of *Aspergillus fumigatus* produced cyclic dipeptides, most of which have antibacterial activity [73].

Periconicin A and B are secondary metabolites that belong to the class of compounds known as diterpenes. Both compounds demonstrated antibacterial activity against a range of human bacterial pathogens, including *S. aureus* and *Salmonella Typhimurium* [74]. The majority of bioactive fungal terpenes and terpenoids discovered in recent years have been isolated from marine fungi and fungi associated with algae [75]. Isoquinoline alkaloids are formed from the amino acids tyrosine and methionine. The most recently described are spathulin A and B, both produced by *P. spathulatum* and active against both gram-positive and gram-negative bacteria. Spathulin B has been demonstrated to exhibit greater activity than spathulin A, with an MIC of 5 µg/mL on *E. coli* LMG15862 [76].

The diverse range of antibacterial metabolites produced by fungi can be employed as a basis for the synthesis of semi-synthetic antibacterial compounds. This is exemplified by pyrrolium indole dicationic, a synthetic antibacterial compound with MIC 250 µg/mL on *E. coli*. This compound has been shown to optimize the antibacterial activity of crude extracts of the secondary metabolite produced by *A. niger* from MIC 250 µg/mL, initially reducing the concentration to 50 µg/mL after

combining pyrrolium indole dicationic with MIC 250 µg/mL [77]. Taking into account all this research into antibacterial fungal secondary metabolites, the importance of exploring the fungal kingdom in the fight against multidrug-resistant bacteria is well established (Table 2).

**Table 2.** Fungal antibacterial metabolites and their minimum inhibitory concentration.

Fungal species	Antibacterial compound	Target bacterium	Minimum Inhibitory Concentration (MIC) or Inhibition zone (IZ)	Reference
<i>Altenaria</i> sp. SCSIOS02F49	Didenizopyrone	<i>Shigella flexneri</i> CMCC51571	15.63 µg/mL	[78]
<i>Aspergillus fumigatus</i>	Monomethyl sulochrin-4-sulfate	Methicilin resistant <i>Staphylococcus aureus</i> NRRLB-767	3.90 µg/mL	[79]
<i>Eupenicillium</i> sp. LG41	Eupenicinicol	<i>Escherichia coli</i>	5 µg/mL	[69]
<i>Nigrospora</i> sp. MA75	2,3-didehydro-19 $\alpha$ -hydroxy-14-epicochlioquinone B	<i>Escherichia coli</i> and Methicilin resistant <i>Staphylococcus aureus</i>	8 µg/mL for both	[80]
<i>Penicillium</i> sp. CAAM64	Penialidin C	<i>Vibrio cholerae</i> SG24 and <i>Vibrio cholerae</i> PC2	0.5 µg/mL for <i>V. cholerae</i> SG24 and 8 µg/mL for <i>V. cholerae</i> PC2	[81]
<i>Penicillium</i> sp. RO-11	Penipyranicin C	<i>Enterobacter xiangfengensis</i>	0.9 µg/mL	[66]
<i>Penicillium</i> sp. Y-5-2	Isocoumarins	<i>Escherichia coli</i> CMCC44102	32 µg/mL	[82]
<i>Penicillium chrysogenum</i> MTC5108	(3,10-didehydro-3[2"(3",3"-dimethyl-prop-2-enyl)-3"-indolylmethylene]-6-methyl piperazine-2,5-dione)	<i>Vibrio cholerae</i>	IZ (14 - 16 mm)	[83]
<i>Penicillium ochrochloron</i>	Xanthoepocine	<i>Enterobacter faecium</i> and methicillin resistant <i>Staphylococcus aureus</i>	0.313 µg/mL for both bacteria	[67]
<i>Penicillium spathulatum</i> EM19	Spathuline B	<i>Escherichia coli</i> LMG15862	5 µg/mL	[76]

#### 4. Conclusion

Diarrheal diseases associated with bacteria remain a significant cause of morbidity and mortality globally, with a disproportionate impact on young children in regions with low SDI. The persistence of these diseases worldwide is attributable to a number of factors, including the use of unsafe water sources, poor sanitation, and the increasing prevalence of antimicrobial resistance. One of the most significant challenges for the future is to identify a solution to the multi-resistance observed in gastroenteritis bacteria. Fungi represent a promising avenue for the discovery of new compounds that could help contain the widespread resistance to usual antibiotics. This is due to their highly developed secondary metabolism and

history as producers of antibacterial compounds.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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