

Update on Antibacterial Resistance in Low-Income Countries: Factors Favoring the Emergence of Resistance

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Abstract: Antimicrobial resistance has increased drastically in recent years in the developing countries, and it has rapidly become a leading public health concern. The prevalence of antimicrobial resistance varies greatly between and within countries and between different pathogens. However, overall a trend to the increase of the resistance to those antimicrobial agents more often used in these countries has been observed. Several factors can contribute to the rapid emergence and dissemination of antimicrobial resistance. In this paper, the current antimicrobial resistance in different microorganisms from different countries as well as the factors contributing to the emergence and spread of resistance in developing countries will be reviewed.

Keywords: Antimicrobial agents, resistance, developing countries, enteric pathogens, *M. tuberculosis*, *S. pneumoniae*, *S. aureus*.

INTRODUCTION

Antimicrobial resistance has increased drastically in recent years in both developed and developing countries and it has rapidly become a leading public health concern. The prevalence of antimicrobial resistance varies greatly between and within countries and between different pathogens. Multiresistant microorganisms, which in developed countries would result in the selection of an alternative treatment and hence increased expenses, in poor countries may cause infections that due to practical purposes are untreatable. Several factors can contribute to the rapid emergence and dissemination of antimicrobial resistance. Among these, inadequate access to all antimicrobial agents and health care system, poverty and malnutrition and the abuse of antibiotics should be highlighted. According to some estimates, as much as 50% of antibiotic use is inappropriate because the uses do not benefit the patients. These uses do increase selection pressure for the emergence and spread of antibiotic-resistant bacteria. The emergence of multi-drug-resistant isolates in tuberculosis, acute respiratory infections and diarrhea, often referred to as diseases of poverty, has had its greatest toll in developing countries. The epidemic of HIV/AIDS, with over 30 million cases in developing countries, has greatly enlarged the population of immunocompromised patients. In this paper the current antimicrobial resistance in different microorganisms from different countries as well as the factors contributing to the emergence and spread of resistance in developing countries will be reviewed. However, it is important to mention that the quality of the

microbiological data derived from developing countries is the highly variable. Often, the methods used in the laboratories are poor or not described; no systems for quality control are in place, with small numbers of key pathogens and use of inadequate antimicrobial susceptibility testing panels.

ENTERIC PATHOGENS

Escherichia coli

These microorganisms are associated with both extraintestinal and intestinal infections; among the former, the urinary tract infections are the most prevalent. Currently, six different pathotypes of *E. coli*, with different virulence traits, causing intestinal infections are accepted. These have been termed as enterotoxigenic *E. coli* (ETEC), enteroaggregative *E. coli* (EAEC), enteropathogenic *E. coli* (EPEC), diffuse adhering *E. coli* (DAEC), enteroinvasive *E. coli* (EIEC), and enterohemorrhagic *E. coli* or verotoxigenic *E. coli* (EHEC/VTEC) [1, 2]. EIEC and EHEC have a lower prevalence as a cause of diarrhea in developing countries compared to the other pathotypes [2]. In addition, recent data suggest that in patients with infection caused by enterohemorrhagic *E. coli* O157:H7 the treatment increases the risk of the hemolytic uremic syndrome [1].

Uropathogenic *E. coli*. There is not much data concerning antimicrobial resistance in bacteria causing urinary tract infections (UTI) in developing countries. In some of these countries and mainly in rural areas, many patients cannot afford medical expenses, therefore they undergo urine analysis only in case of repeated or complicated UTI and this can create a bias in the data generated. In a report from Dakar (Senegal) [3], on analyzing 1010 non-duplicate *E. coli* from 2004 to 2006, the resistance to amoxicillin was 73%, amoxicillin-clavulanic acid (67.5%), trimethoprim-sulfamethoxazole (68%), whereas the

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resistance to nalidixic acid, norfloxacin and ciprofloxacin was 23.9%, 16.4% and 15.5%, respectively. Most of the strains were susceptible to gentamicin, nitrofurantoin and fosfomycin (respective susceptibility rates, 6.2%, 10.1%, and 0.7%). Only 38 (3.7%) out of 1010 *E. coli* isolates produce extended-spectrum beta-lactamases. Similar levels of resistance (over 73% for ampicillin and 63% for co-trimoxazole) have been reported for uropathogenic *E. coli* from other developing countries (Table 1) [4-8]. In a study performed in Madagascar, 3.1% of the *E. coli* harboured extended-spectrum beta-lactamases. However, higher rates of resistance to cefotaxime (46% among *E. coli*, and 51% among *Klebsiella*), suggesting production of extended-spectrum beta-lactamase, have also been reported in developing countries [9]. In addition, these strains frequently show coresistances to other classes of antibacterial agents. The resistance to ciprofloxacin is very variable ranging from 8% in Central African Republic to 72% in India. The high level of resistance in this country is likely associated with the consumption of this antimicrobial agents in these countries.

Enterotoxigenic *E. coli*. ETEC are an important cause of diarrhea among children in the developing world [1, 10]. Contaminated food and water are the usual sources for ETEC. In some countries such as in Egypt, ETEC may account for 70% of all first episodes [11]. A statistically significant difference between the dry and rainy season was found in a study performed in Tanzania, being more prevalent during the rainy season [12]. During the rainy season there is an enhanced contamination of surface water with fecal material and the surface water can thus become heavily contaminated [13]. Overall, the percentages of resistance of ETEC bearing the stable (ST) or labile (LT) toxins or both are very similar, with figures above 40% for ampicillin, tetracycline, and trimethoprim-sulfamethoxazole. Chloramphenicol shows activity against ETEC with percentages of resistance ranging from 13 to 57% (Table 1). Both enterotoxins and genes encoding resistant determinants can be located in a conjugative plasmid [14], suggesting that antibiotic selective pressure could result in a wider distribution of ETEC [15]. There are no significant statistical differences among the different geographical areas analyzed. Similar levels of resistance were observed among these recent reports and previously published studies in the 1980s [12,16]. Nalidixic acid or ciprofloxacin show the best activity against these microorganisms. However, a trend to a rise in quinolone resistance has recently been described, possibly following the increase in the use of quinolones for other diseases resistant to quinolones, mainly in India [17]. Nalidixic acid was introduced a few years ago as the firstline therapy for shigellosis in some areas of India and therefore ETEC strains resistant to nalidixic acid are now emerging.

Enteroaggregative *E. coli*. EPEC, DAEC and EAEC can be distinguished according to their patterns of adherence to HEp-2 cells. EPEC forms a microcolony-forming pattern, DAEC a diffuse adherence pattern and EAEC a aggregative or "stacked-brick" pattern. Long time ago, Nataro and colleagues showed significant association of EAEC with diarrhea in Chilean children [18]. EAEC has been related to persistent diarrhea in children in developing countries likely associated with biofilm production [19]. The prevalence of EAEC as a cause of diarrhea in children has been found

higher during the dry season than in the rainy season [20]. Multidrug resistant EAEC have been reported in Kenya, Nigeria, Tanzania, Peru, and Thailand (see Table 1) [12,16,21-23]. In almost all studies the percentages of resistance to ampicillin, chloramphenicol, tetracycline and co-trimoxazole were above 50%. In an unpublished study, we have recently found 5 EAEC clinical isolates causing diarrhea in patients returning from India, which were resistant to third generation cephalosporins, and this resistance was associated with the presence of the *bla*_{CTX-M-15} gene in isolates from the Middle East and from India [24, unpublished data].

One alternative for the treatment of enteritis caused by EAEC is the use of quinolones. However, they are not recommended for children. Although ciprofloxacin is recommended as the drug of choice to treat traveler's diarrhea, high percentage of resistance to this antimicrobial agents has been reported in ETEC and EAEC isolated from travellers to North Africa and India, reflecting the current situation in these countries [17].

Enteropathogenic *E. coli*. EPEC causes diarrhea in infants in developed and developing countries as well as in travelers [2, 12, 25]. The percentages of antimicrobial resistance are similar to those described for the other diarrheagenic *E. coli*, with a level of resistance above 23% to ampicillin, tetracycline, and trimethoprim-sulfamethoxazole, moderate resistance to chloramphenicol, and almost no strains resistant to quinolones (see Table 1). Although antibiotics are often used to treat enteritis caused by EPEC, there is no definitive evidence that treatment shortens the clinical course.

***Shigella* spp.**

Infections caused by *Shigella* species are an important cause of diarrheal diseases, in both developing and developed countries. Worldwide, it is estimated that shigellosis causes around 600,000 death per year, two-thirds of the deceased being children under 10 years of age. *Shigella dysenteriae* and *Shigella flexneri* are the predominant species in developing countries, whereas *Shigella sonnei* is predominant in industrialized countries [26]. *Shigella* spp. are transmitted from person to person, although food and water can also be contaminated. Infection is possible due to the low inoculum required (as few as 10 microorganisms). The percentages of resistance to several antimicrobial agents in the three main species of *Shigella* isolated from different geographical areas (mainly developing countries) are shown in Table 1 [16, 27-33]. Overall, *S. flexneri* and *S. dysenteriae* are more resistant than *S. sonnei*, at least when ampicillin and chloramphenicol were tested. The prevalence of resistance to ampicillin for *S. sonnei* ranges from a low of 0% in Calcutta (India) to a high of 62% in Vietnam [28, 33]. Similarly, the rate of chloramphenicol resistance is very wide, being from 0% in Western Kenya or Tanzania to 44.3% in Korea [30, 32, 34]. In most of the geographical areas analyzed, the resistance to trimethoprim-sulfamethoxazole in three species of *Shigella* ranged from 55 to 100%, and was higher than that previously reported, showing a trend to an increase in resistance to these antimicrobial agents in *Shigella* spp clinical isolates. However, most of the scientific literature on antimicrobial

Table 1. Antimicrobial Resistance in Enteric Pathogens Isolated in Developing Countries

Bacteria/Country	AMP	CHL	TET	SXT	CTX	CFR	NAL	CIP	Ref.
UPEC									
Central African Republic	80	---	---	80	0	0	9	8	[4]
India	85	---	---	74	---	---	---	72	[5]
Madagascar	74	---	---	69.5	3.1	3.1	25	16	[6]
Nicaragua	74	---	---	63	---	0	---	30	[7]
Senegal	73	---	---	68	3.5	---	24	16	[3]
Sudan	75	---	---	67	---	19	6	---	[8]
ETEC									
Tanzania	84	25	68	79.5	---	---	2.3	0	[12]
Thailand	54	13	43	51	---	---	3	2	[16]
Vietnam	71	57	---	71	---	---	14.3	7.1	[16]
EAEC									
Kenya									[21]
Nigeria	81	46.5	95.4	74	---	---	0	0	[22]
Tanzania	83	57	88	91	---	---	1.5	0	[12]
Vietnam	90	87	---	92	---	---	19	0	[16]
EPEC									
Tanzania	90	33	81	90	---	---	0	0	[12]
Uruguay	100	27	23	42	---	---	---	0	[25]
Vietnam	82	64	---	84	---	---	24	10	[16]
<i>Shigella flexneri</i>									
Brazil	100	---	---	55	---	---	0	---	[27]
India	87	58	100	100	---	---	21	0	[28]
Indonesia	90	83	94	80	---	---	---	0	[29]
Kenya	94	90	99	88	---	---	2	0	[30]
Rwanda	83	80	---	75	---	---	0.5	0	[31]
Tanzania	92	92	99	92	---	---	0	0	[32]
Thailand	82	61	96	86	---	---	0	0	[16]
Vietnam	85	85	---	85	---	---	0	0	[33]
<i>Shigella sonnei</i>									
India	0	25	100	100	---	---	25	0	[28]
Indonesia	27	17	83	76	---	---	---	0	[29]
Kenya	5	0	98	100	---	---	0	0	[30]
Rwanda	13	7	---	38	---	---	0	0	[31]
Tanzania	25	0	100	100	---	---	0	0	[32]
Thailand	4	3	92	97	---	---	0	0	[16]
Vietnam	70	40	---	90	---	---	5	0	[33]
<i>Shigella dysenteriae</i>									
India	100	80	100	100	---	---	60	0	[28]
Indonesia	100	100	100	100	---	---	---	0	[29]
Kenya	98	100	100	95	---	---	0	0	[30]
Rwanda	100	100	---	68	---	---	20	0	[31]
Tanzania	100	100	100	100	---	---	0	0	[32]
Thailand	0	0	33	0	---	---	0	0	[16]
Vietnam	50	17	50	50	---	---	0	0	[33]

(Table 1) contd....

Bacteria/Country	AMP	CHL	TET	SXT	CTX	CFR	NAL	CIP	Ref.
<i>Salmonella other than typhi</i>									
Brazil	62	43	88	78	---	---	18	---	[40]
Kenya	53	36	59	53	---	---	7	0	[30]
Morocco	37	---	---	---	0	---	25	12.5	[41]
Thailand	28	26	59	37	---	---	21	<1	[16]
Vietnam	3	7	13	10	---	---	0	0	[16]
	AMP	A/C	TET	ERI	AZIT	NAL	CIP	Ref.	
<i>Campylobacter spp.</i>									
Indonesia	65	---	65	0	---	---	35	[29]	
Kenya	---	---	2	48 ^a	---	26	7	[30]	
Thailand	---	---	---	---	6	73	77	[16]	
Vietnam	---	---	---	---	0	7	7	[16]	

UPEC = Uropathogenic *E. coli*; ETEC = enterotoxigenic *E. coli*; EAEC = enteroaggregative *E. coli*; EPEC = enteropathogenic *E. coli*. AMP = ampicillin; CHL = chloramphenicol; TET = tetracycline; SXT = co-trimoxazole; CTX = cefotaxime; CFR = cefuroxime; NAL = nalidixic acid; CIP = ciprofloxacin; A/C = amoxicillin/clavulanic acid; ERI = erythromycin; AZIT = azithromycin.

resistance in *Shigella* spp do not analyze the epidemiological relationship among the isolates. Nonetheless, a predominant multiresistant clone is probably responsible for this high frequency of resistance [32]. Although no resistance to fluoroquinolones, such as ciprofloxacin, has been detected, the percentage of resistance to nalidixic acid ranges from 0% in several geographical areas to 100% in strains of *S. sonnei* in Korea [34]. However, the latter figures may be attributed to the spread of a resistant clone. Moreover, a trend to quinolone resistance has been observed in *S. dysenteriae* strains isolated in Burundi [35] Although the level of resistance to nalidixic acid can be as high as 25% in some countries such in India [36], the level of resistance to ciprofloxacin remains very low. An association between fluoroquinolone resistance acquisition and decrease of colonization/invasion of the intestinal epithelia in *Salmonella*, which may explain the above mentioned situation, has recently been reported [37].

***Salmonella* spp.**

Salmonella gastroenteritis is a well-known disease that occurs throughout the world. In industrialized nations, this large group of organisms is the most common cause of outbreaks of food associated diarrhea [38]. *Salmonella* is transmitted to humans by ingestion of the microorganism in contaminated food, although fecal-oral transmission from person to person has also been described [38].

Between 1980 and 1984, the susceptibility data for *Salmonella* strains from different tropical countries were compiled to predict significant patterns or trends [39]. The percentages of resistance to ampicillin, tetracycline, chloramphenicol, and trimethoprim-sulfamethoxazole were quite variable, with the lowest rates found in Sri Lanka, the percentages ranging from 3% (resistance to chloramphenicol) to 10% (resistance to trimethoprim) [39]. In recent studies (Table 1), the resistance to the above-mentioned antibiotics among *Salmonella* spp. has also varied among the different developing countries, with Vietnam

showing the lowest rate [16]. The resistance to fluoroquinolones is very wide going from 0% in Vietnam to 21% in Thailand two neighbouring countries (see Table 1). However, in a recent study a reduced susceptibility to ciprofloxacin (MIC, 0.125 to 1 mg/L) in non-typhoid *Salmonella* isolates was commonly observed in Taiwan (48%) and Thailand (46%) [42]. Meanwhile reduced susceptibility to ceftriaxone (MIC, 2 to 8 mg/L) remained uncommon in Asia, except in Taiwan (38%) or in *S. Typhimurium* (25%) from all countries suggesting the potential implications of ESBLs [42]. Antibiotic therapy is not recommended for most uncomplicated cases since infection is most often self-limited [38]. The administration of antimicrobial agents may prolong shedding, and antimicrobial resistance to all agents that have been used for treatment has been seen. Antibiotics should be considered for infants of less than 2 months of age, the elderly, and patients with sickle cell disease, advanced HIV infection, high fever, evidence of focal infection outside the gastrointestinal tract, or bacteremia. When therapy is indicated, the choice of agents includes a third generation cephalosporin or one of the fluoroquinolones.

***Campylobacter* spp.**

Campylobacter species associated with gastrointestinal infectious diseases include *Campylobacter jejuni*, *Campylobacter coli*, *Campylobacter lari*, and *Campylobacter upsaliensis*. The most common species implicated are *C. jejuni* and *C. coli*. *C. jejuni* is a common cause of diarrhea throughout the world. *Campylobacter* spp. are found in foods primarily of animal origins, particularly poultry. The resistance frequency to ampicillin and tetracycline in *C. jejuni* is usually very high (Table 1) [16, 29, 30]. Macrolides, either erythromycin or azithromycin, are the most active antibiotics against *C. jejuni*. Among 15 of 16 Peruvian children presenting with *C. jejuni* related dysentery, stool became normal within 5 days when treated with erythromycin, in contrast to only 6 of 12 children who received placebo [43]. Studies in adults with enteritis caused

by *Campylobacter* have indicated that treatment with either ciprofloxacin or azithromycin shortened the duration of symptoms [44]. In general, resistance to fluoroquinolones in *C. jejuni* goes from 7% to 77% in some areas such as Thailand, Mali, and Burkina-Faso [16, unpublished data] (Table 1). These high figures are similar to those found in some industrialized countries. At the end of the 1980s, several studies showed minimal resistance to fluoroquinolones among *Campylobacter* species [45]. Recently, there has been a trend toward an increased frequency of quinolone resistance concomitant with the increased use of fluoroquinolones in humans and animals [46].

Few years ago, if antimicrobial therapy was indicated for *Campylobacter* infections, azithromycin and fluoroquinolones were considered the drugs of choice. Since the symptoms of *Campylobacter* enteritis are clinically indistinguishable from those of enteritis caused by other bacteria, most physicians prescribed fluoroquinolones empirically, which covered all bacterial enteropathogens. However, due to the rapid increase in the isolation of fluoroquinolone-resistant *Campylobacter* strains, erythromycin should currently be considered as the drug of choice to treat *Campylobacter* infections. The severity of the illness may be lessened by the early administration of antibiotics during the course of the disease. Antimicrobial treatment may be appropriate for patients with high fever, bloody stools, and more than 8 stools within a 24-hour period. Immunocompromised hosts and patients with bacteremia should also be treated [47].

Other Enteric Bacteria

Although *Vibrio cholerae* infections are important in some endemic areas, they have often been described as cause of outbreaks in Asia, Africa and South America. Historically, epidemics have been due to serogroup O1 strains. In the early 1990s, a new serotype strain, Bengal O139, began a new wave of cholera epidemics. The primary treatment of cholera is oral rehydration to replace the massive fluid loss that occurs. Antibiotics are also recommended to shorten the duration of illness and bacterial shedding. Currently, the treatment of choice is tetracycline, although trimethoprim-sulfamethoxazole or a fluoroquinolone may also be used. However, some isolates causing outbreaks as well as sporadic strains have been shown to be tetracycline or trimethoprim-sulfamethoxazole resistant [48]. Ciprofloxacin possess excellent activity against *V. cholerae* O1 and O139 serogroups, and it is an effective treatment of cholera in adults and children. However, in Calcutta, India, the incidence of nalidixic acid resistance among *V. cholerae* O1 strains was low (<10%) before 1993 and increased to 100% in 1999 [49, 50].

Other potential bacterial pathogens, including *Aeromonas* spp, *Plesiomonas shigelloides*, and *Yersinia enterocolitica* are known to cause diarrhea in developing countries at a low prevalence. Among the *Aeromonas* genospecies, those considered for clinical relevance are *Aeromonas hydrophila*, *Aeromonas caviae*, and *Aeromonas veronii* biotype *sobria*. Nearly all the studies in developing countries on the prevalence of *Aeromonas* spp. as a cause of diarrhea have been reported from children. *A. veronii* biotype *sobria* and

Aeromonas caviae are most frequently related to diarrhea in children in developing countries [51]. Several outbreaks have been reported from developing countries. One reported from India in children admitted to the hematology-oncology unit, who developed acute diarrhea by *A. veronii* biovar *sobria* [52]. *Aeromonas* spp show high levels of resistance to nalidixic acid and ciprofloxacin in India [53]. *P. shigelloides* have been suggested, but not firmly established, as a cause of gastrointestinal infection. These microorganisms have been found to be part of the normal gastrointestinal flora in up to 3% of individuals. The microorganism is variably susceptible *in vitro* to chloramphenicol, tetracycline, trimethoprim-sulfamethoxazole, aminoglycosides, fluoroquinolones, imipenem, and third generation cephalosporins, and is naturally resistant to several antimicrobial agents such as penicillins, and some cephalosporins such as cefoperazone, ceftazidime, and cefepime [54]. *Y. enterocolitica* are isolated as the cause of diarrhea in developing countries, but the infection appears to occur predominantly in cooler climates. Therefore, there are not many reports on the antimicrobial susceptibility of this microorganism as a cause of diarrhea in developing countries. All the isolates causing traveller's diarrhea, which can mimic the microbiota of developing countries were resistant to ampicillin, but susceptible to tetracycline, nalidixic acid, and ciprofloxacin. Resistance to chloramphenicol and trimethoprim-sulfamethoxazole was less frequent (8%) [Vila *et al.* unpublished data].

NON-FERMENTATIVE GRAM-NEGATIVE BACTERIA

Pseudomonas aeruginosa and *Acinetobacter baumannii*

P. aeruginosa are mainly found in moist environments (respiratory equipment, sinks, tap water,...), whereas *A. baumannii* can survive in dry environments more than 20 days, a feature likely associated with the production of biofilm (Vila *et al.*, Unpublished data). The most important part of the infections caused by these microorganisms takes place in intensive care units. Late-onset ventilator-associated pneumonia is likely the most frequent infectious diseases caused by these microorganisms in both developed and developing countries. However, considering *A. baumannii* many times it is not easy to differentiate between colonization and infection. In a recent paper [55], the antimicrobial resistance of different microorganisms causing hospital-acquired pneumonia in 10 Asian countries was analyzed. The resistance of *P. aeruginosa* to ceftazidime ranged from 3 to 48%, from 3 to 35% for imipenem, from 4 to 44% for ciprofloxacin and from 2 to 30% for piperacillin-tazobactam. Meanwhile, the resistance of *A. baumannii* to imipenem and ciprofloxacin ranged from 2 to 77% and 23 to 92%, respectively. Multidrug resistant *P. aeruginosa* has also been shown in Cameroon [56], where 41.2% of the clinical isolates showed resistance to at least four antimicrobial agents. The SENTRY Program findings in the Latin American region were in agreement with previous local studies, demonstrating that increasing resistance to commonly used anti-pseudomonal agents is a major therapeutic issue. Furthermore, the report clearly indicates that antimicrobial resistance among *P. aeruginosa* isolates in Latin American countries has increased significantly over a relatively short time period. This upward trend may reflect differences in antimicrobial prescription practices and/or a

more frequent dissemination of MDR clones in the countries participating in the SENTRY Program [57].

A. baumannii can be considered as the paradigm of multiresistant bacteria. It is highly prevalent in different Asian as well as South America countries, however, little attention has been given to the prevalence of this microorganism in Africa. Special mention is needed for some panresistant *A. baumannii* strains. For instance, 18.3% of *Acinetobacter* isolated in Korea were resistant to all antimicrobial agents tested [58], whereas 6% of the analyzed clinical isolates in Taiwan showed this panresistant phenotype. In India, *Acinetobacter* has been found to be an important nosocomial pathogen in intensive care units demonstrating extended drug resistance, thus, resistant to all antimicrobial agents but colistin [59]. According to the SENTRY reports, resistance rates for *A. baumannii* are higher in Latin American countries than in the USA or Europe. The prevalence of carbapenem resistance in *A. baumannii*, across Latin America in the SENTRY database in 2001, was estimated at 25% [57]. The emergence of panresistant *A. baumannii* clinical isolates makes new therapeutic alternatives necessary [60].

Global dissemination of eight carbapenem-resistant *A. baumannii* lineages has recently been shown, illustrating the success this organism has had in epidemic spread. Among these different lineages, European clone II was disseminated to the USA, Europe, Israel, Asia, Australia and South Africa [61].

GRAM-POSITIVE COCCI

Streptococcus pneumoniae

According to a recent estimate, in the year 2000 approximately 14.5 million episodes of serious *Streptococcus pneumoniae* infections occurred causing about 826,000 deaths in children below 5 years of age. Consequently, *S. pneumoniae* alone accounted for 11% of deaths in this age group. Not surprisingly figures are heavily skewed towards the developing world: 61% of the 735,000 victims (not co-infected with HIV) came from 10 African and Asian countries [62]. However, serious, life threatening infections are not the only problems associated with *S. pneumoniae* exhibiting increasing drug resistance: acute otitis media is the commonest disease following the colonization of the upper respiratory tract [63], and this pathogen is the most frequent isolate from the middle ear worldwide [64].

Most concerns related to the decreased antibiotic susceptibility in *S. pneumoniae* have been centered on two groups of drugs, i.e. beta-lactams and macrolides. This holds true even in the light of accumulating proof showing that most non-meningitis infections due to beta-lactam intermediately resistant strains respond well to increased doses of the drugs. This resulted in the recent re-evaluation of the interpretation criteria of beta-lactam breakpoint values for *S. pneumoniae* distinguishing between central nervous system isolates (with MIC values for parenteral penicillin, susceptible: ≤ 0.06 g/L, resistant ≥ 0.12 g/L) from those recovered from non-meningitis cases (susceptible: ≤ 2 g/L, intermediate: 4, resistant ≥ 8 g/L with similar changes for cephalosporins, as well) [65]. Caution should always be

exercised when comparing results obtained by testing respiratory and invasive, particularly meningitis isolates. However, these changes in interpretation criteria further emphasize the need for careful interpretation of data. Earlier studies may have applied more stringent criteria to respiratory isolates as well, using the formerly accepted, general ≥ 2 g/L breakpoint value for resistance. This may have resulted in over-estimating real incidences of resistance among non-meningitis isolates while underestimating them among strains isolated from the central nervous system. The effect of different interpretation criteria was clearly shown recently by Hsieh Y-C *et al.* [66] reporting on sterile-site isolates recovered from over 500 invasive disease episodes in Taiwan during 2007. While 67.8% of the isolates were non-susceptible to penicillin using the meningitis criteria, only 7.7% fell into this category with the non-meningitis breakpoints. Corresponding figures for ceftriaxone were 50.5% and 14%, respectively.

Large scale antibiotic surveillance projects such as the PROTEKT or GLOBAL studies [67, 68] revealed a considerably uneven distribution of penicillin resistance among *S. pneumoniae* isolates. According to the former study, more than a third of all respiratory tract isolates had reduced susceptibility to penicillin. However, respective figures from South Africa, the Far East and from the Middle East, i.e. regions with several developing countries, were much higher, being 74%, 63% and 54%, respectively [67]. Similarly, skewed distribution of penicillin non-susceptibility towards developing regions was found by the GLOBAL study [68].

It is noteworthy that incidence figures exhibit not only a variation between areas of the world, but also remarkable variations exist within the regions. This was shown among respiratory tract [69, 70] and mixed [71] isolates in South America, among mixed [71] and invasive [72, 73] isolates in Africa, the Mediterranean region [74] and the Arabian Peninsula [75-77]. Notably, trends may differ in distinct parts of the same region: between 2003 and 2005 a more than 50% decrease in the proportion of non-susceptible invasive strains was observed in Egypt, while an increase from 12.8% to 24.3% was experienced during the same time in Turkey. Due to the relatively low number of isolates involved in these studies, however, further, extensive surveillances should exclude timely, quickly reversible fluctuations [74].

Mostly, the Far Eastern region is hit by the problem of beta-lactam resistant pneumococci, in general, and it is the same region where the most extensive regional variations have been noticed. In an ANSORP (Asian Network for Surveillance of Resistant Pathogens) study collecting strains from 14 centers in 11 countries in 2000 and 2001, 29.4% of the isolates were resistant to penicillin and a further 23% exhibited intermediate susceptibility [78]. However, while in Vietnam 71.4% of all isolates were resistant (with Korea being the second with 54.8% resistance), no resistant isolates were found in India or in the Philippines. Furthermore, no direct correlation between the rates of intermediate resistance and that of full resistance was observed. In Sri Lanka, the intermediately resistant strains represented 71.4% of all isolates and 14.3% were resistant, while in Vietnam, extremely high figures of resistance (i.e. 71.4%) were

supplemented with a further 20.6% of intermediately resistant isolates only [78].

Recent studies noted further significant increases in penicillin resistance in some areas of the region, notably in Taiwan [66] and in China [79] and most of the regional differences have recently been confirmed [80].

Extended spectrum cephalosporins, particularly cefotaxime and ceftriaxone, are often the drugs of choice to treat invasive *S. pneumoniae* infections, meningitis in particular. Overall, in Asia 0.9% of the strains were found to be ceftriaxone resistant, although all the isolates came from four countries, i.e. Korea and Vietnam, 3.2-3.2% each, Malaysia (2.3%), and China (1.8%) [78]. A few years later no further increase was noted in the regional rate of ceftriaxone resistance (0.6%) (according to “non-meningitis” criteria), although only 83.1% of the isolates exhibited full susceptibility while 16.3% were intermediately resistant [68]. Recently, unpublished observations from the CDC of Taiwan were cited providing figures of about 65-70% resistance to penicillin (compared to the 38.6% seen previously – [78]) and a 38% resistance to ceftriaxone, although no specifics on breakpoints used or on the source of isolates were provided [80].

The remarkable country-to-country variation observed for beta-lactam resistance was also present for macrolides. While isolates from Vietnam, South Korea and Taiwan had over 80% erythromycin resistance rates, the Philippines, Sri Lanka, Saudi Arabia and in particular in India, it remains below 20%, actually being below 2% in the latter country [76]. According to the PROTEKT study some countries of South-East Asia had an outstandingly high erythromycin resistance rate, around 80%, with South Africa (about 54%) and Southern-Europe (\approx 37%) following [78].

Although in general, strains resistant to either macrolides or to penicillin are more likely to be resistant to the other drugs, or to other classes, co-trimoxazole, in particular [74, 78, 79, 81] the link is not direct. When comparing isolates from 9 study centers in 8 cities of China the rate of erythromycin resistance was found to be uniformly high, the lowest rate among the centers being 86.1%. While the rates of cefaclor resistance were also comparatively even (above 65% in all but one center), penicillin resistance varied between 31 and 89.6%, resistance to amoxicillin/clavulanic acid between 0 and 52.2% and ceftriaxone resistance between 0 and 62.7 % [78]. Nevertheless, it is clear that multidrug resistance (MDR) is an increasing problem, in particular, in developing countries usually most burdened by non-susceptibility to individual drugs [74, 78, 79, 81]. Once studied, MDR strains in developing countries are often found to represent global clones, such as Taiwan^{19F}, Spain^{9V} and England¹⁴ in South Africa [82] or Taiwan^{19F} and Spain^{23F} in Asia [78].

Increased use of the conjugated pneumococcal vaccine may have a beneficial effect on the rate of antibiotic resistant strains in the developing countries as it had in some industrialised parts of the world [83-88]. This anticipation is based on the fact that several serotypes of the heptavalent PCV7 vaccine (containing serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) often exhibit a high level of resistance [89, 90]. Two problems, however, may interfere with this effect of the

vaccine. First, the composition of PCV7 is based on prevalence data collected in developed countries and its current composition may not cover serotypes in other regions of the world to the same extent. Furthermore, non-PCV7 “replacement” serotypes with frequent high level of resistance, e.g. 19A, could occupy the niche created by the suppression of previously dominating vaccine-serotypes [91]. In some developing regions this non-PCV7 serotype is already well represented [79, 80, 92, 93]. Introduction of broad-coverage of vaccines (i.e. PCV10 or 13) is likely to provide solutions to these problems – provided financial constraints permit their wide-spread use.

Enterococcus

Relatively little is known about the glycopeptide resistance of *Enterococcus* isolates from the developing countries. A recent study identified vancomycin resistant enterococci (VRE) as the only drug resistant pathogen among isolates from ICUs from 18 developing countries which did not exceed the incidence seen in the respective data from surveys in the US [94]. However, from the sparse data available it seems that the problem is clearly emerging particularly in the developing countries of Asia [95-98], Latin America [99, 100] and Africa [101]. A SENTRY study found 10.3% of *E. faecium* and 0.4% of *E. faecalis* resistant to vancomycin in the Asia-Pacific region [102]. The frequency of VRE among enterococci exhibits considerable variation between countries, but usually remains below to what has been found in the US. Nevertheless, alarmingly high figures from some countries have been reported, such as recently in Teheran with overall 12% vancomycin resistance among all enterococci, 6% among *E. faecalis* and 22% among *E. faecium* [103].

Local outbreaks of VRE could be linked to inappropriate use of glycopeptides, as recently reported from Thailand [104], and could be controlled by strict measures, even with limited resources, as in an oncology ward from South Africa, facing a multi-clonal outbreak [105]. Lineages, such as Clonal Complex 17 (CC17) causing the majority of hospital outbreaks has spread globally [106] and is now being isolated from epidemics of developing countries as well [107]. Locally, (and also globally) increased or inappropriate use of glycopeptides can contribute to local emergence or spread of VRE [104,108]. Little is known about the contribution of environmental and animal strains to human infections in these countries. Some of the few studies having addressed this issue found a very high rate of VRE among animal (equid) isolates [109], but their impact on human morbidity is still to be investigated.

Staphylococcus aureus

Morbidity and mortality rates in high-income countries due to antibiotic resistant *Staphylococcus aureus*, methicillin resistant strains (MRSA) in particular, have attracted considerable media and public attention. This has accompanied, and to some extent even triggered, professional efforts to understand the reasons for these epidemics and to control them [110]. Irrespective of the success of these efforts, the existence of the problem has been well appreciated and documented in industrialized parts of the world. In the developing countries, however, diseases such as HIV, tuberculosis, malaria, and various enteric and

pneumococcal infections have been considered to be more important causes of morbidity and mortality than infections due to *S. aureus* [111, 112] (and to most antibiotic resistant organisms in general). This, in the past, has considerably limited the attention paid to the emergence and spread of resistance of this pathogen in low income areas [111, 112].

While the rate of MRSA in some of the developing countries might still be lower than the burden in countries with higher quality health care infrastructure [113], this is rather an exception than a rule for most developing areas. Strikingly higher figures for the rate of MRSA among *S. aureus* ICU isolates (80,8%) were observed in the developing countries than in the reports from the US, which already perceived as being heavily burdened by the problem itself (52.9%) [111].

Furthermore, mortality-related figures due to *S. aureus*/MRSA infections are clearly higher in developing countries. In a recent study analyzing data of 98 patients with *S. aureus* bacteremia in a large regional hospital in Northeast Thailand found that the all-cause, and particularly attributable mortality rate was almost twice as high (52% and 44%) as cited by some studies from the US. While strains acquired in the community were uniformly sensitive to methicillin, 28% of the hospital acquired or health care-related infections (54% of all cases in the study) were caused by MRSA [111]. It is interesting to note that contrary to what has been observed in high income countries, in territories with limited resources invasive cases due to *S. aureus* are more common in the neonatal age [114, 115].

Figures, however, could be extremely variable within a large region, as was shown among isolates from 8 African Hospitals and Malta varying from a 4.8% rate of MRSA among *S. aureus* in Algeria to nearly 30% in Nigeria [116]. Nevertheless, in regions where data from different time-points are available for comparison, an increase in MRSA incidence has been uniformly noted [117-120].

Data from 9 Asian countries suggest that the overwhelming majority of hospital-acquired MRSA infections can be attributed to a single clone, sequence type ST239 [121,122], i.e. a genotype with an extremely broad worldwide distribution [123]. The same clone, among others, was recently found in several hospitals in South Africa and India [124, 125] indicating, as expected, that hospitals in the developing regions are not sealed off from the global trade of clones of pathogens.

Community-acquired MRSA (CA-MRSA), usually characterized by *sccmecA* types IV or V and often positive for the genes encoding for Panton-Valentine leukocidine (PVL), are having an increasingly recognized impact on the incidence of MRSA in the community, and lately also in the hospitals in several high income countries. However, very little is known about the epidemiology of CA-MRSA in the developing countries. Since invasive infections, particularly blood stream infections, are the typical clinical presentations causing the most concern of *S. aureus* infections in these regions, this might have diverted attention from infections more consistent with CA-MRSA etiology (e.g. soft tissue infections, fulminant lung infections). Few studies in low income countries accurately distinguish between community and hospital-acquired/health care-related *S. aureus*

infections. However once done, data show that the rate of MRSA in the former group is still low in developing countries, particularly among blood stream isolates [111, 112, 126-129]. Some other studies however, do present figures to the opposite [130], particularly when samples more consistent with the anticipated CA-MRSA etiology are investigated. In a recent study from India it was shown that of the 250 pyoderma cases from the community 80.8% was due to *S. aureus*, of which 10.9% was MRSA; 54.4% of the patients carried *S. aureus* in their nares, 11.8% being resistant to methicillin [131]. Among agents of community acquired thoracic empyema of children in an Indian study *S. aureus* was the most frequently identified pathogen and from 3 children MRSA was isolated [132]. Unfortunately, none of these studies has been complemented with molecular typing data to confirm typical CA-MRSA genotypes and some use only phenotypic surrogate markers, as clindamycin susceptibility, to define "community-acquired-like" isolates [133]. Furthermore, very few of the community-based studies explore previous health care exposure in case of non-nosocomial isolates. Previous connection to health care does have an impact on antibiotic resistance of subsequent isolates as repeatedly shown is industrialized countries, and in a few cases, when studied, in low income settings as well [111, 112, 127].

Increasing multidrug resistance among MRSA strains is a global problem [134] and was also found commonly in different developing countries, e.g. in Africa [116, 124, 130], in Jamaica [129] and India [120]. It is of particular concern that the emergence of mupirocin resistance (i.e. a drug commonly used to eradicate MRSA from the nares) has been reported already from several developing regions, e.g. Trinidad [135], Africa [124] and the Middle East [136]. The emergence of vancomycin heterointermediately, and intermediately resistant *S. aureus* has been reported from several Asian countries [137-139]. Recently, two vancomycin and teicoplanin resistant strains in India were isolated following vancomycin therapy [140].

OTHER CLINICALLY RELEVANT BACTERIA

Haemophilus influenzae

There are two major types of *Haemophilus influenzae* infections causing significant morbidity and mortality. The pathogen is commonly carried in the pharynx and is a frequent cause of upper respiratory tract infections: after *S. pneumoniae* it is the second most common isolate from acute otitis media cases worldwide. Most of these isolates are non-encapsulated, or express capsular types other than "b". The majority of invasive infections (meningitis and pneumonia in particular) are due to strains expressing type "b" capsular antigen (Hib). The incidence of invasive infections has been radically reduced in countries where the conjugated capsular vaccine had been used. Where introduced, the effect of vaccination programs in developing countries has been as successful as in high-income regions [141, 142], although the majority of the under-privileged areas are still far from a satisfactory level of vaccine coverage. Consequently, Hib was still estimated to cause over 8 million serious infections worldwide in 2000, in children under 5 years of age, resulting in an estimated 371,000 death, mostly in low income countries [143].

Resistance of *H. influenzae* to beta-lactams is of primary concern all over the world. However, in some developing countries increasing rates of multidrug resistance, non-susceptibility to trimethoprim/sulfamethoxazole, fluoroquinolones, and/or to chloramphenicol are emerging problems. Ampicillin resistance is common due to the production of TEM-1 or ROB-1 type beta lactamases [144, 145]. In a recent study *Sham et al.* found that in most regions of the world ampicillin resistance was below 20% and only in Asia and North America it did approach 30%, while amoxicillin/clavulanate resistance remained below 0.5% globally [68]. Although most of the local studies report similar or lower figures, some found much higher rates of ampicillin resistance, e.g. in Thailand with 48.4% of the isolates producing beta-lactamase [146], and in another study 37% ampicillin resistance among the non-typable strains [147]. In Egypt 63% of ampicillin resistance was found among isolates from meningitis cases [148]. In a recent SENTRY study of strains collected in North and Latin America the rates of ampicillin resistance were more than twice as high as those seen in Europe (41.2% and 45.5% vs 18.0%) while all strains remained susceptible to amoxicillin/clavulanic acid [149]. In some developing countries there is a clear trend in increasing resistance: among invasive isolates in rural Kenya it was found that from 100% recorded in 1994, susceptibility to amoxicillin decreased to 32.2 % by 2002. Alarming, it was accompanied by a 100% to 28.1% decrease in chloramphenicol susceptibility, and by a 66.6% to 14.8% decrease in trimethoprim/sulfamethoxazole susceptibility with 40% of the strains being MDR in 2002 [150].

Recently, a new type of beta-lactam resistance mechanism in *H. influenzae* has emerged, i.e. due to mutations decreasing the affinity of the penicillin binding proteins (PBPs) to the drug [151]. This results in the "beta lactamase nonproducing ampicillin resistant" (BLNAR) phenotype. These strains are found with varying – usually low – frequencies in Europe and in North America, but some Asian countries, particularly Japan, are heavily burdened [152-155]. BLNAR strains with decreased ampicillin susceptibility, but none expressing full resistance, were isolated from lower respiratory infections in children in Vietnam [156]. In North India 14.4% of the *H. influenzae* strains isolated from the nasopharynx of children were BLNAR (based on the lack of beta-lactamase activity), 81.8% of which expressed the "b" type capsular antigen. Although no molecular analysis to reveal the genetic basis of BLNAR was done, 9 out of the 33 BLNAR strains were fully resistant to ampicillin. In the same study resistance to chloramphenicol, erythromycin and co-trimoxazole was common, particularly among the beta-lactamase producing strains [157].

Although apparently emerging in some developing countries as well, BLNAR strains are still not uniformly present in Asia. While a high rate of beta lactamase producers among *H. influenzae* were recovered from the nasopharynx of healthy children below 5 years of age, and among isolates from invasive cases (61.5% and 55%, respectively). In Taiwan, no BLNAR were isolated [158, 159].

The introduction of the PCV7 vaccine in developing countries is likely to increase the frequency of colonization of the upper respiratory tract by *H. influenzae* compared to *S. pneumoniae*. It is also anticipated that this will result in a shift towards the former pathogen as the etiological agent of otitis media, as happened in the developed nations [160]. This, together with increasing rates of BLNAR and MDR strains are likely to bring new challenges for treatment. It will be particularly difficult in countries with limited resources since therapies alternative to simple beta-lactams are often more costly [161]. The changes are affecting treatment options for invasive cases as well.

Neisseria gonorrhoeae

In 1999, the highest number of new gonorrhea cases occurred in South-East Asia (27.2 million) and in sub-Saharan Africa (17.03 million) [162]. With 1.11 million and 1.56 million new cases in Western Europe and in North America respectively, it is estimated that, all regions considered, the prevalence is at least 10 times higher in the developing world than in the industrialized countries [163].

The speed of emergence and spread of antibiotic resistance in *Neisseria gonorrhoeae* has been matched by few pathogens only. In the past 25 years, this has enforced repeated changes of paradigms in treatment and it is not unrealistic to expect the need for the next one in the foreseeable future. Following a relatively short lived use of sulfanilamides starting from the 1940s penicillin has remained the drug of choice for a long time. However, by the mid 80s chromosomal and plasmid-coded resistance mechanisms became wide-spread, frequently co-emerging with tetracycline resistance [164]. Gradually, 3rd generation cephalosporins and fluoroquinolones became the recommended therapies, substantially increasing the costs of treatment. Unfortunately, however, even the relatively cheaper oral fluoroquinolones (ciprofloxacin, ofloxacin) became obsolete in the forthcoming decade in most parts of the world. Emerging in the Pacific regions [165] and quickly spreading through Asia and to the rest of the world, fluoroquinolone resistant strains have reached very high frequencies adding to the usually wide-spread penicillin and tetracycline resistance all over the world, including developing countries [166-171]. The few localities still experiencing a low rate of ciprofloxacin resistance more likely represent exceptions than the rule [172, 173]. The emergence of multidrug resistance is favored by the fact that *N. gonorrhoeae* has a tendency to retain resistance, even if the use of the particular drugs has been discontinued [174]. As a result, resistance to multiple antibiotics became a serious challenge in several of these areas [169, 175]. Consequently, current treatment recommendations are restricted to a single class of antibiotics, i.e. cephalosporins, either as an injectable (ceftriaxone) or as an oral (cefixime) drug [176, 177].

Limitations of therapeutic options had already seriously challenged the resources of developing countries, while in some countries extended spectrum cephalosporins are not even available for gonorrhea treatment [178]. Meanwhile reports on therapeutic failures following oral (not parenteral, yet) cefixime or ceftibuten treatment have already been increasing, particularly in Asia and in the Pacific Region

[179, 180]. In some countries, like Japan, the problem has increased to the extent that oral cephalosporin therapy is not even recommended any longer [181].

Once parenteral, increased dose (i.e. 250 mg-1 g) cephalosporin regimens failed in the future, alternative treatments will be difficult to find. A possible alternative, spectinomycin, is not uniformly available. Currently, even in the developing countries, the overwhelming majority of the strains are still susceptible [166, 168, 169, 172, 180, 182], but resistance, once used extensively, develops easily [183] making the drug an unlikely candidate as the first line treatment. Azithromycin could also be used, but resistance already exists, therefore, it is also unlikely to represent a safe choice in a much feared post-cephalosporin era [164].

Mycobacterium tuberculosis

Approximately every third person around the globe is infected with *Mycobacterium tuberculosis* (MTB). According to the latest WHO, 13th annual report on the global control of tuberculosis (TB) [184] in 2007, an estimated 9.27 million new active cases of tuberculosis occurred worldwide. The incidence data are heavily distorted towards developing regions of the world: 55% of the new cases occurred in Asia and 31% in Africa. The countries with the highest total number of new cases were India (2.0 million) and China (1.3 million). Fifteen percent of all new TB cases were HIV-positive, 79% of these cases in Africa and 11% in South-East Asia. Among the 15 countries with the highest estimated TB incidence rates, 13 are in Africa, a phenomenon linked to high rates of HIV co-infection [184].

Antibiotic resistance in *M. tuberculosis* commonly emerges if the two key elements of anti-TB therapy (i.e. combination of proper drugs and long term treatment) are not strictly observed. Using multiple drugs to treat susceptible cases, theoretically, allows the survival of newly emerging resistant cells only if more than one resistance-conferring mutation occurs simultaneously in the same cell – a statistically unlikely event. Furthermore, the combination of different drugs should act at the same time on cells of the pathogen occupying different niches (e.g. cavities, caseous material, intracellular within macrophages) and exhibiting very different levels of metabolic activities. Long exposure to drugs is needed to eradicate cells with limited activity. A pan-susceptible strain gaining resistance during treatment (*acquired resistance*) usually indicates inadequacies in therapy. The rate of infection with a resistant organism is strongly influenced, beyond the comparative biological fitness, virulence and transmissibility of the resistant strains, by the level of local TB control, i.e. the number of infectious patients in the community, by the number of susceptible individuals etc. [185]. The spectrum of resistance can be broadened if patients infected with strains already resistant to some drugs still receive inappropriate chemotherapy (*amplified resistance*) [186]. This may contribute to the emergence of multi-drug - (MDR), and extensively resistant strains (XDR), respectively. MDR strains are defined as being resistant to isoniazid and rifampin, while XDR isolates gained further resistance to any fluoroquinolone and to at least one of the three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin) [187].

While there are still a few countries not reporting any MDR tuberculosis, which is truly a global problem. The most seriously affected regions are countries of the former Soviet Union and China in particular. The Global Project on Anti-Tuberculosis Drug Resistance Surveillance program recently published its report on drug susceptibility data collected between 2002 and 2007 [188]. In the 75 countries and territories providing figures on new cases of TB, the median prevalence of MDR cases was 1.6% globally. However, 12 of the 15 locations with MDR prevalence above 6% were countries of the former Soviet Union and two were Chinese provinces. The highest figures were seen in Baku, Azerbaijan (22.3%) and Moldova (19.4%). This distribution was not unlike the one seen for resistance to isoniazid alone: of the 17 settings with a prevalence of isoniazid resistance higher than 15%, 14 were former Soviet territories or located in China [187]. As expected, the median prevalence of MDR tuberculosis among previously treated cases reported from 68 countries was higher than observed among new cases (11.7%). In this comparison also, countries worst hit were those of the former Soviet Union. Of the 17 locations with MDR prevalence over 25% (i.e. every fourth case previously having received treatment is an MDR case) 9 were from Soviet republic or its territory. In some of these regions (e.g. Lithuania, Orel Oblast, Tomsk Oblast), an increase in MDR prevalence was observed during the study period. In 8 countries of the former Soviet Union approximately 10% of the MDR strains were, in fact XDR, with the highest figure (23.7%) observed in Estonia [188].

An interesting disproportionality was found earlier by *Shah et al.* [189] collecting data from 14 Supranational Reference Laboratories (SRLs) worldwide on susceptibility tests carried out between 2000 and 2004. While the highest rate of MDR strains among all MTB tested was found in Asia (70.1%) (excluding South Korea) only 1.52% of these were XDR. On the other hand, in the Republic of Korea with a comparatively low rate of MDR (10.9%), a high percentage of these isolates qualified as XDR (15.4%). The African and Middle Eastern regions provided lower figures than the industrialized nations both in terms of MDR (23.5% vs 32.9%) as well as for XDR (0.6% vs 6.5%), respectively. Although further studies should clarify as to what extent these figures represent dissimilarities in testing and sampling methods or in real prevalences, they certainly shed light on the worldwide emerging problem of XDR TB [189].

It should be noted that even these alarming figures are likely to underestimate the problem of the emerging MDR, and in particular of the XDR epidemics. Drug resistance surveillance is seriously hampered in many countries by the technical limitations in the susceptibility testing methods available – facts most likely to affect regions having a higher prevalence of cases [190]. Even if some facilities are there, laboratories may test only one or two second line drugs and may use different methodologies [191].

For the developing countries, particularly in Asia and Africa, it is imperative to gain a better understanding of the association of HIV and MDR-TB. HIV infection clearly facilitates the progression of active diseases following primary infection, and also increases reactivation of latent cases. In both cases microbial load is amplified which is anticipated to increase drug resistant cases [187]. Statistical

data, on the other hand do not always show a clear correlation between HIV and drug resistance of TB co-infection: in 5 of the 7 regions reporting on the HIV status of MDR TB patients no significant association between MDR-TB and HIV infection was found, although none of these regions were from Africa with a high HIV burden [188]. The increased mortality among TB-HIV co-infected patients certainly warrants the extension of isoniazid chemoprophylaxis among those infected with HIV to prevent activation of latent TB, and thus indirectly having a limiting effect on the emergence of MDR cases as well [186].

Preventing the emergence of acquired and amplified resistance requires rapid and accurate diagnosis including susceptibility testing followed by a full-course treatment. Consequently, countries with limited resources are clearly disadvantaged. The DOTS (Direct Observation Treatment, Short course) program of the WHO can be instrumental in this field. Its key targets are to secure global and local political and financial commitments, assuring case detection through quality-assured bacteriology, standardized treatment with supervision and patient support, sustaining effective drug supply and management system, and monitoring evaluation system and impact measurement. Recently, building on the success of this initiative, the program was extended to target MDR case, as well (DOTS-Plus [192]).

However, preventing emergence of drug resistance alone is unlikely to solve the problem of MDR and XDR TB. Increasing number of evidence has shown that transmitted resistance is the primary mechanism for XDR-TB epidemic with 63-75% of the cases being transmitted in some outbreaks [190,193]. Interrupting the chains of transmission in the community as well as in the hospitals with well designed and affordable infection control measures has significant impact on MDR/XDR TB cases. Steps as simple and cheap as increased ventilation or rapid patient isolation in hospital settings [194,195] have a significant impact on MDR/XDR-TB transmission.

FACTORS FAVORING ANTIMICROBIAL RESISTANCE

Emergence of organisms resistant to antibiotics, either by mutations or by acquiring new genetic material by horizontal gene transfer, takes place irrespective of the presence of antibiotics. It is the exposure to drugs that provides an advantage to cells with the newly gained phenotype and promotes their expansion. Use of antibiotics, as a side effect, also gives rise to resistance – a biological price we have to pay for benefitting from the curative potential of these drugs. However, their excessive or suboptimal use creates excessive resistance – a situation we are currently experiencing all over the world.

The biological driving forces behind the wide-spread drug resistance in the developing countries are, in principle, the same as in high-income countries, only multiplied and accentuated. In these countries internationally developed and accepted guidelines related to susceptibility testing, antibiotic use and infection control may not be broadly available, not to mention the lack of financial constraints to implement them. Furthermore, due to the often lower general educational level of the population these standards are less known, less accepted and appreciated and less expected both by the providers, as well as the receivers of health care.

Underprivileged sub-populations of wealthier countries are affected by the poverty-driven constraints in antibiotic use similar to those commonly seen in developing countries [196].

Several factors favor the development of bacterial resistance to antibiotics in developing countries:

1. *Less potent activity*: Some of the antibiotics provided in developing countries have decreased potency because of degradation or adulteration of the drug, or because of the presence of a lower concentration of active substances [197-199]. For instance, substandard concentrations of ampicillin and tetracycline have been found in Nigeria [200,201]. Moreover, expired drugs, with altered or removed expiry dates, have also been detected in developing countries [202-204]. Some drugs produced in industrialized countries have been found to have expired on distribution in developing countries [205]. Finally, the antibiotics provided to these countries may be poorly transported and stored, leading to drug inactivation [206-208].
2. *Lack of diagnostic laboratories*: Most of the hospitals in developing countries do not have clinical microbiology laboratories to perform routine analyses for microbiological diagnosis. Even if some services are in place, international guidelines and quality control for susceptibility testing are often not available or require methods not affordable locally. Therefore, they have no information about either the etiology of the infectious diseases or antimicrobial susceptibility, both essential for clinical practice. Bacterial infections are often treated empirically with broad-spectrum antibiotics. For control, an accurate diagnosis including proper susceptibility data is a must, supplemented with capacities to type organism. This needs properly standardized, quality controlled methods complemented with the collection and compilation of data into appropriate databases on antibiotic resistance. A hierarchical structure of local, national, regional and supranational laboratories with well defined and controlled competences can only meet these tasks.
3. *Over-the-counter availability*: In most developing countries, antibiotics can be purchased without prescription in pharmacies, general stores, markets, and from street hawkers. Since many drugs are expensive, some patients purchase incomplete regimens whenever possible and discontinue treatment when the symptoms disappear [209]. As in industrialized countries, unnecessary prescriptions of antibiotics, mainly in cases of acute infantile diarrhea and respiratory infections, have been reported in developing countries [210-213]. Although the problem is not exclusive to the developing countries, in many hospitals in these regions antibiotic policies and infection control practices are suboptimal, nonexistent, not appropriately enforced or compromised due to the lack of resources and properly trained personnel [214].

4. *Use of antimicrobials in animals.* Although it may not seem to be an important problem in developing countries, where the practice is less applied, the excessive use of antimicrobials, especially as growth promoters in animals destined for human consumption, presents a growing risk to human health due to the emergence of bacteria resistant to the antibiotics fed to animals, which can then be transferred to humans through the food chain [215-217]. Spread of antibiotics and resistant bacteria into the environment is also a contributor to the problem.

In order to improve this situation, a better understanding of the driving forces behind inappropriate demands, medical practices should be well understood, a surprisingly under-researched area in developing countries [218,219]. Basic health education is likely to influence expectations, remove mistrust or correct unfounded beliefs concerning antibiotics [218]. Improving education among health care providers concerning prudent use of antibiotics will bring the same benefits in the developing countries [220] as has been proven repeatedly in the industrialized world.

Contribution to control the emergence and spread of antibiotic resistance in the developing countries is a gargantuan task, but it is the moral obligation of the industrialized countries to improve the well being of people living in underprivileged conditions. However, as microorganisms do not respect boundaries, it is also an interest of their very own.

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