Antimicrobial resistance in developing countries. Part I: recent trends and current status

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The global problem of antimicrobial resistance is particularly pressing in developing countries, where the infectious disease burden is high and cost constraints prevent the widespread application of newer, more expensive agents. Gastrointestinal, respiratory, sexually transmitted, and nosocomial infections are leading causes of disease and death in the developing world, and management of all these conditions has been critically compromised by the appearance and rapid spread of resistance. In this first part of the review, we have summarised the present state of resistance in these infections from the available data. Even though surveillance of resistance in many developing countries is suboptimal, the general picture is one of accelerating rates of resistance spurred by antimicrobial misuse and shortfalls in infection control and public health. Reservoirs for resistance may be present in healthy human and animal populations. Considerable economic and health burdens emanate from bacterial resistance, and research is needed to accurately quantify the problem and propose and evaluate practicable solutions. In part II, to be published next month, we will review potential containment strategies that could address this burgeoning problem.

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Introduction

The control of infectious diseases is seriously threatened by the steady increase in the number of microorganisms that are resistant to antimicrobial agents. Resistant infections adversely affect mortality, treatment costs, disease spread, and duration of illness.[1] Initially, organisms resistant to multiple drugs were found mostly in hospitals, where antimicrobial agents are used most extensively, but resistance is currently found almost as frequently in the community. Community-acquired infections—particularly respiratory and gastrointestinal infections, the leading causes of death in the USA before the advent of antibiotics—continue to be the leading cause of death in developing countries.[2] Furthermore, resistance has severely compromised our ability to cure those infected, especially in developing countries where availability of antibiotics and cost of therapy are critical constraints in public-health settings.

Multiple studies have indicated that resistance may be increasing in developing countries. The burden imposed by antimicrobial resistance on human health and quality of life is large but difficult to quantify with precision. In many instances, the data available are not amenable to accurate quantitative assessment, particularly in countries whose systematic surveillance systems are absent or rudimentary. Thus, conclusions must be drawn from point-prevalence assessments or even case studies. Here, we piece together the available information to build a picture of the situation for the most common bacterial pathogens in developing countries. In part II of this review, to be published next month, we will review potential containment strategies that could address this burgeoning problem.

Antimicrobial resistance in enteric pathogens

Diarrhoeal disease is one of the most important causes of illness and death in young children in developing countries.[3] Diarrhoea also affects adults, particularly those visiting or migrating from non-endemic areas. Most diarrhoea episodes are potentially self-limiting. Antimicrobials can shorten the course of bacterial enteritis; however, they generally do not have an effect on viral and non-infectious diarrhoeas, which account for 10–70% of all episodes.[4] Unfortunately, antimicrobial misuse is too commonly associated with enteric infections. Consequently, in cases for which antimicrobials are indicated, resistance increasingly precipitates chemotherapeutic failure.

Salmonella enterica serotype Typhi

Approximately 16 million cases of typhoid fever and more than 580 000 attributable deaths occur globally each year.[5] Potential underestimates of population-based incidence in developing countries range from 150 to more than 1000 cases per 100 000 people annually.[6] In recent years the emergence and global dissemination of *Salmonella enterica* subspecies *enterica* serotype Typhi (*S typhi*) resistant to ampicillin, chloramphenicol, and co-trimoxazole (trimethoprim-sulphamethoxazole)—multidrug-resistant typhoidal strains—has posed major public-health problems in developing countries, and over the past decade it has assumed epidemic proportions in south Asia.[7,8] The emergence of multidrug-resistant *S typhi* has been associated with an increase in the reported severity of disease.[9] Both the delay in institution of appropriate therapy as a direct result of resistance and the increased severity of disease may have contributed to the higher morbidity and mortality of multidrug-resistant *S typhi*. Shortly after the emergence of multidrug-resistant *S typhi* in south Asia, case fatality rates approaching 10% (close to the 12·8% recorded in the pre-antibiotic era) were reported.[10] Even in relatively advanced health-care systems, multidrug-resistant *S typhi* has been associated with case fatality rates as high as 1·5%.[11] Multidrug-resistant *S enterica* serotype Paratyphi (*S paratyphi*) infections have also

emerged as a public-health problem in Asia in recent years.

Resistance among *S typhi* isolates from Africa has been less frequently and less systematically studied. Available reports appear to suggest that although resistance is common in some areas, it has yet to emerge in others. *S typhi* isolates recovered in Dakar, Senegal, between 1987 and 1990 and between 1997 and 2002, for example, remained almost universally sensitive to co-trimoxazole, ampicillin, chloramphenicol, and tetracycline and resistance to nalidixic acid, cefotaxime, and the fluoroquinolones remained to be detected.[12]

There is some evidence that the shift to previously second-line and third-line drugs for treating typhoid fever and other infections could, in the long term, herald a decline in multidrug-resistant strains or at least resistance to former first-line drugs.[13] Figure 1 shows the epidemiological pattern of *S typhi* isolates from children in Karachi, Pakistan, with a gradual reduction in multidrug-resistant isolates to a stable figure of about 20%. By contrast, data on antimicrobial use from a comparable time period suggests a steady reduction in the use of first-line antibiotics, especially chloramphenicol, at a population level in Karachi.[14] Although there is no evidence of a direct correlation between these two events, these data indicate that environmental antimicrobial pressure may have an important role in determining the overall emergence and dominance of resistant clones of organisms. However, nalidixic acid-resistant strains respond poorly to ciprofloxacin and have become common in parts of Asia.[15,16]

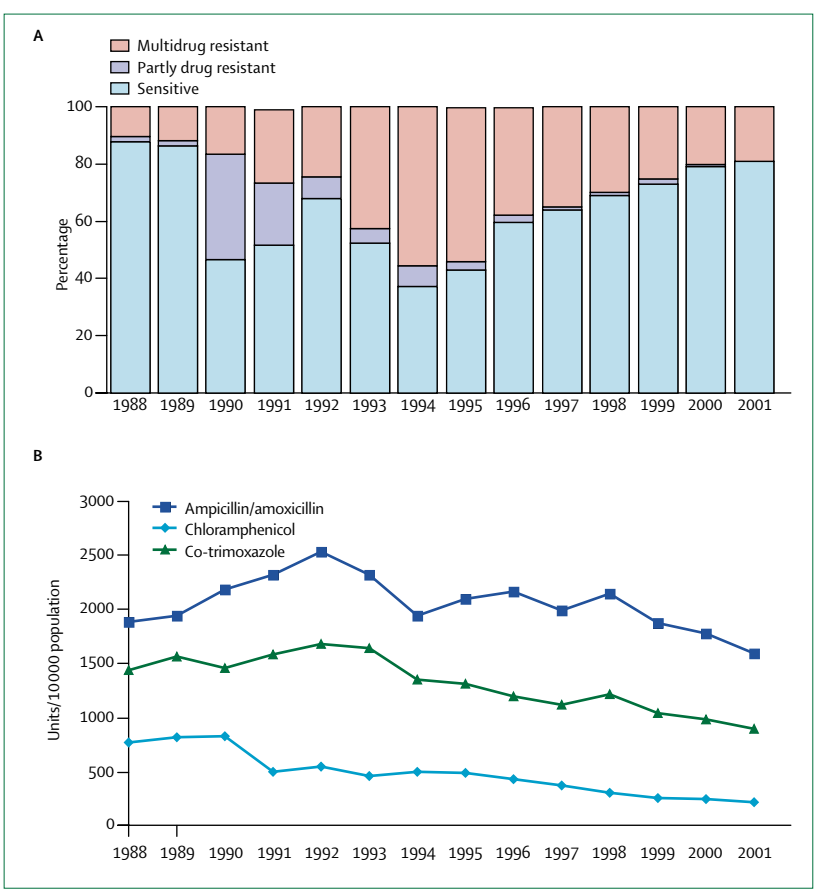

Figure 1: **(A) Antimicrobial resistance patterns among *S typhi* isolates from children presenting at the Aga Khan University Hospital, Pakistan (1988–2001); and (B) antimicrobial sales data for Karachi (units/10 000 population) in the same period[14]**

A gradual decline in the isolation of multidrug-resistant *S typhi* paralleled slight but steady reductions in first-line antimicrobial drug consumption.

Multidrug-resistant non-typhoidal salmonella

Most non-typhoidal salmonella infections manifest as potentially self-limiting diarrhoea. However, antimicrobial resistance—which is at least as common as, and sometimes more prevalent than in *S typhi*—is clinically relevant because 3–10% of these infections can progress to life-threatening bacteraemia, particularly in young children and HIV-infected people.[17,18] In Indonesia, Tjaniadi and colleagues[19] observed that although *S typhi* and *S paratyphi* isolates recovered between 1995 and 2001 were universally susceptible to commonly used antimicrobials, *Salmonella enteritidis* isolates were resistant to most of the antimicrobials tested, with the exception of the fluoroquinolones.[19] Similarly, although a small Zimbabwean study reported much lower rates of resistance among *S enteritidis*,[20] more than 50% of non-typhoidal salmonella isolates from children in Kilifi, Kenya, were multidrug resistant.[21] The potential consequences of these pockets of multidrug-resistant salmonella could be increased health costs even if infection rates are not increased. In a controlled study, Martin and co-workers[22] found that patients infected with multidrug-resistant *S enterica* serovar Typhimurium were more likely to be hospitalised than those infected with susceptible strains. This finding was true for patients infected with the notorious DT104 type (OR 2·3, $p<0·003$) as well as non-DT104 strains (OR 3·6, $p<0·005$). The authors estimated that more than 60% of hospitalisations occurred as a direct result of multidrug resistance.[22] Multidrug-resistant salmonella from other serovars has also been documented—eg, *S enterica* serovar Cholerasius from Taiwan.[23]

Shigella flexneri and *Shigella dysenteriae* type I

Shigella flexneri is responsible for most of the sporadic bacillary dysentery cases in developing countries, and infections can be fatal, particularly in young children.[24,25] *Shigella dysenteriae* type I, the aetiological agent of epidemic dysentery and the most virulent serotype, has been responsible for outbreaks in Africa, particularly those associated with civil conflict,[26–28] and—a matter of deep concern—is re-emerging in parts of Asia.[24] Most shigella infections are treated empirically, and therefore an understanding of resistance patterns is important for management. Empirical treatment has been compromised in large part by emerging resistance and inadequate surveillance to monitor trends.[29]

Resistance of shigella to ampicillin, tetracycline, co-trimoxazole, and chloramphenicol has also become widespread in Africa, even though these drugs are still used for first-line chemotherapy for dysentery in many parts of the continent.[30] The introduction of nalidixic acid has been followed by emergence of resistance to this agent,[30] and fluoroquinolones—the only recourse for resistant infection—are not within the reach of much of the population. Reports from areas as diverse as India,[31,32] Vietnam,[33] Kenya,[25] Nigeria,[30] Sudan,[34] and Brazil[35] appear to indicate that the situation is similar in much of the developing world. Of concern is the occurrence of isolates with intermediate sensitivity to newer quinolones in parallel with the emergence of quinolone resistance in salmonella.[31] Although quinolone resistance is rare, given the wide availability and use of oral quinolones at a population level, it is generally believed that widespread occurrence of resistance is only a matter of time.

The emergence and spread of *S dysenteriae* type I resistant to co-trimoxazole, ampicillin, tetracycline, chloramphenicol, and increasingly nalidixic acid in the past two decades means that these inexpensive and widely available antimicrobials can no longer be used empirically.[25,26,34,36–40] The alternatives—ciprofloxacin and ceftriaxone—are relatively expensive and not always available at short notice, and resistance to them has also emerged.[32]

Vibrio cholerae

In spite of improved understanding of the transmission, pathogenesis, epidemiology, and ecology of pandemic cholera, periodic and often devastating outbreaks continue to occur in Asia, Africa, and South America. Each year 5–7 million people contract cholera, which kills about 100 000 of them.[41] Cholera can be managed by rehydration alone, but antimicrobial therapy helps shorten the course of the disease and, importantly, breaks the transmission cycle during epidemics. Although it can be argued that resistance may have limited consequences for appropriately managed individual patients, the potential costs arising from new cases as a result of epidemic spread may be very high.[42]

Antimicrobial-resistant *Vibrio cholerae* O1 and, to a lesser extent, O139 isolates are becoming increasingly common.[42–45] In the USA, where cholera is imported from developing countries, the number of isolates resistant to at least one agent rose from 3% in 1992 to 93% in 1994.[46] Of concern is resistance to tetracycline and other agents used for empirical management of the disease in children, for whom tetracycline is contraindicated, or in cases where tetracycline is not available. Resistance patterns in *V cholerae* often mirror those in other enteric pathogens and commensals from the same area.[47,48] This mirroring is potentially because the organisms are under identical selection pressure, but also could be due to the sharing of some resistance genes horizontally.[49,50]

Tjaniadi and colleagues[19] found that resistance to tetracycline, ampicillin, chloramphenicol, and co-trimoxazole remained rare in Indonesia between 1995 and 2001. *V cholerae* O1 strains resistant to any of these agents represented 10% or less of isolates. Resistance among non-O1, non-O139 *V cholerae* was slightly more common but much less so than with other enteric pathogens, including *Vibrio parahaemolyticus* and *Shigella* spp.[19] However, these reassuring trends are not representative of other areas. There have been reports from India, Vietnam, and sub-Saharan Africa describing *V cholerae* strains resistant to co-trimoxazole and other antimicrobials, in some cases including tetracycline.[48,51–53] Many recent outbreaks have been caused or exacerbated by war and consequent civil displacement, accounting for more deaths than the conflicts themselves.[26,54,55] As with epidemic dysentery, management of cholera outbreaks due to resistant strains has invariably been problematic, and lives are lost before the susceptibility pattern of the causative strain is known. Where resistance is confirmed or suspected, the recourse is nalidixic acid or the more expensive fluoroquinolones. As with other organisms, resistance to these agents has emerged among *V cholerae*.[56] Also important are suggestions that although they effect a more rapid cure than tetracyclines,[42] quinolones induce the SOS DNA-damage response in *V cholerae* and consequently promote horizontal transfer of conjugal resistance determinants.[57]

Other diarrhoeal pathogens

Antimicrobial resistance appears to have become more prevalent with time in other diarrhoeal pathogens, such as *Campylobacter* species, enterotoxigenic *Escherichia coli*, and emergent diarrhoeal pathogens.[47,58–60] Hakanen and co-workers[61] studied antimicrobial resistance in *Campylobacter jejuni* isolates from Finnish travellers returning from different parts of the world. They observed a statistically significant increase in fluoroquinolone resistance rates between 1995–97 and 1998–2003 ($p<0\cdot01$). In isolates from Asia, these rates increased from 45% to 72%; in those from Africa, rates increased from 17% to 38%. Reports suggest that enteroaggregative *E coli*, an emerging pathogen frequently resistant to multiple antimicrobials, is one of the most commonly isolated diarrhoeal pathogens from children, travellers, and AIDS patients.[62–64] Studies that have examined enteroaggregative *E coli* for susceptibility have always found that these strains have acquired resistance to multiple antibiotics.[62,64]

Antimicrobial resistance in respiratory pathogens

Streptococcus pneumoniae

Acute respiratory bacterial infections kill more than 3 million children in developing countries each year, and up to 70% of these infections are estimated to be caused by *Streptococcus pneumoniae*.[65,66] *S pneumoniae* is also the

most common cause of otitis media, bacteraemia, and bacterial meningitis in children. Adults infected with HIV are also at risk of pneumococcal infection. *S pneumoniae*, as well as other major bacterial respiratory pathogens (eg, *Haemophilus influenzae* and *Moraxella catarrhalis*), can colonise without causing disease. Typically, more than 50% of children in developing countries are colonised before they are 6 months old, compared with much lower rates in developed countries, where colonisation tends to occur later in life.[66] In children, nasopharyngeal carriage often precedes symptomatic infection, and a history of penicillin use, particularly subtherapeutic regimens, has been found to predispose them to resistant infection.[67]

The emergence and clinical relevance of penicillin-resistant *S pneumoniae* were recognised in South Africa with the identification of strains that were inhibited only by higher-than-usual concentrations of penicillin and caused meningitis that was refractory to penicillin.[68,69] Laboratories now routinely distinguish sensitive strains from those with intermediate and high-level resistance by simple testing with an oxacillin disk or by dilution or gradient-diffusion testing. However, some of those distinctions may be made less important by growing evidence that penicillin or other beta-lactam antibiotics do cure the far more common lung or bloodstream infections with intermediate-resistant pneumococci.[70]

There are no international standards for *S pneumoniae* surveillance, but hospital-based drug resistance reports of pneumococcal respiratory tract isolates in developing countries reveal several general trends (table). Strains fully susceptible to penicillin, once nearly universal, have declined to a half to two-thirds of strains in many countries and to less than a quarter in some. At the same time, *S pneumoniae* resistance to macrolides and to co-trimoxazole has increased, the latter especially in HIV-positive patients taking it for prophylaxis, and resistance to tetracycline or chloramphenicol has fluctuated widely. Data suggest that penicillin and erythromycin resistance is an emerging problem in community-acquired *S pneumoniae* in Asia, Mexico, Argentina, and Brazil, as well as in parts of Kenya and Uganda.[71–77] Rising resistance to each drug has been accompanied by a growing percentage of strains resistant to many or all of them (table) and the emergence of resistance to the fluoroquinolones.[78–80] Surprisingly, low levels of resistance have been found in rural India, the Dominican Republic, and isolated rural African communities.[81–84] However, this observation should not lead to complacency. In many parts of Asia, temporal trends have shown an increase in resistance over the past decade as increased access to antibiotics without control of over-the-counter use has led to some of the highest rates of resistance in the world.[84]

The relation between antimicrobial use and pneumococcal resistance is well established in developed countries.[85,86] Numerous lines of evidence suggest the same relation in developing countries, but direct evidence is hampered by the lack of corresponding data on antimicrobial use. The exposure of pneumococci to antimicrobials is not simply a function of a lack of public sector control over drug availability. India, a large country with scant control over antibiotic prescribing, has very low rates of resistance among systemic isolates of pneumococci, at least in rural areas.[87] These low rates exist despite wide antibiotic availability, probably because poverty limits the duration of antibiotic exposure.

An association between infection with HIV and pneumococcal resistance is likely explained by the higher exposure of these patients to hospitals and antibiotics given as treatment or prophylaxis, and the documented propensity of HIV-infected adults to infection and re-infection with paediatric pneumococcal serotypes that are often antibiotic resistant.[88–90] The transmission of resistant strains from children to adults was suggested by anecdotal reports as far back as the 1980s[91] but is strongly supported by the impact of conjugate pneumococcal vaccine in reducing antimicrobial resistance among adult pneumococcal bacteraemic isolates in the USA.[92] The association of HIV infection with paediatric serotypes and pneumococcal antimicrobial resistance suggest the potential utility of this approach to reduce the burden of pneumococcal antimicrobial resistance in developing countries, where the burden of disease is overwhelmingly associated with HIV infection in both children[93] and adults.[94]

Worldwide, *S pneumoniae* resistance has been marked by the dissemination of successful multidrug-resistant clones, which belong to 10% of the 90 *S pneumoniae* serotypes.[95] A clone of Spanish origin, Spain 23F-1, that is resistant to penicillin, chloramphenicol, tetracycline, and erythromycin has, since its original description,[96] been isolated in other parts of Europe, the USA, South and Central America, South Africa, and east Asia.[72,97,98] It is likely that Spain 23F-1 is even more widespread and that the absence of reports from other areas reflects the lack of laboratories capable of delineating resistant pneumococcal clones, not the absence of the organisms themselves. Other globally disseminated, multidrug-resistant *S pneumoniae* include specific clones within serotypes 3, 6A, 6B, 9N, 9V, 14, 19A, and 19F.[97] Over time, these clones have become the predominant isolates from infected patients in both developed and developing countries.[72,98–100] Spread of some pandemic clones has continued, even in areas where successful interventions have reduced selective pressure from antimicrobial use.[101] With increasing international travel, the potential of these strains to reach areas where resistance is uncommon can no longer be considered remote. The appearance of fluoroquinolone resistance in pandemic multidrug-resistant clones is another area of concern.[102,103] A global network—the Pneumococcal

Molecular Epidemiology Network—has been established to support researchers in identifying the emergence of these clones in both developed and developing countries.[97]

Mycobacterium tuberculosis

Mycobacterium tuberculosis kills more people worldwide than any other infectious bacterial species, and one-third of the world's population is believed to be infected.[104,105] Resistance in *M tuberculosis* presents an unusual paradigm—resistance can readily emerge in the treated individual and compromise his or her own chemotherapy. By contrast, in many other bacterial pathogens, acquisition of preselected resistant bacteria—or horizontal acquisition of preselected resistance genes by infecting bacteria—is the principal means by which the individual is affected.[106] If antituberculous treatment is conducted using standard multidrug regimens, the emergence of clinical drug resistance will be prevented, even though spontaneous mutations to single-drug resistance in the infecting strain occasionally occur.

A global network of 23 supranational reference laboratories for tuberculosis resistance surveillance, with four regional subnetworks, was initiated in 1994. This network, known as the WHO/International Union against Tuberculosis and Lung Disease Global Project, covers 77 countries and samples 20% of the world's population. Global reports have been issued in 1997, 2000, and 2004. The project reveals wide ranges in the prevalence of resistance to antituberculous drugs from place to place (figure 2).[105] There are at least 17 documented multidrug-resistant tuberculosis hotspots with prevalences above 3% (figure 2). The top five on the list (prevalence over 9%) are in former Soviet states and China, but hotspots exist in South and Central America, south Asia, the middle east, Africa, and Europe.[107] Cox and colleagues[108] have shown that 30–50% of isolates from previously untreated patients in the central Asian countries of Uzbekistan and Turkmenistan were resistant to at least one first-line antimycobacterial, and 10–30% were multidrug resistant.

Globally, 2 billion people may be infected with *M tuberculosis*,[109] and there are more than 8 million new cases of active tuberculosis every year. Using resistance surveys from 64 countries and data predictive of resistance rates from 72 others, Dye and colleagues[110] estimated 3·2% of all new tuberculosis cases are multidrug resistant. By these methods, an estimated 273 000 (95% CI 185 000–414 000) new cases of multidrug-resistant tuberculosis occurred worldwide in 2000. By simple extrapolation, 70 million people could be latently infected with multidrug-resistant tuberculosis, and there could be more than 1 million multidrug-resistant tuberculosis cases among previously treated patients. Despite its threatening potential, the global prevalence of multidrug-resistant tuberculosis in new patients remains less than 2%, decades after the introduction of antituberculosis drugs.[111] Animal studies[112] and molecular epidemiology analyses[113,114] suggest that multidrug-resistant tuberculosis strains might be, on average, less infectious. Unlike most bacteria, mycobacteria replicate rather slowly (and hence mutant strains are only slowly amplified) and share little, if any, genetic material horizontally. Thus, even in the absence of widespread treatment, the prevalence of multidrug-resistant tuberculosis may not necessarily explode.[114,115]

Region/ country	n	Percentage multidrug resistant defined as			
		any three drug classes excluding penicillin	any three drug classes including penicillin	any four drug classes	any five drug classes or more
Africa	540	14·3	24·8	13·5	3·3
Kenya	277	3·6	16·6	2·2	0·0
S Africa	263	25·5	33·5	25·5	6·8
East Europe	1109	10·1	11·7	6·0	1·0
West Europe	3328	14·7	18·4	11·9	4·1
Far east	730	53·2	63·2	40·6	23·0
Middle east	314	11·2	18·2	10·5	4·1
Latin America	429	13·3	20·1	12·1	1·9
Brazil	181	2·8	5·0	1·1	0·0
Mexico	248	21·0	31·1	20·2	3·2
USA	2432	16·2	25·8	15·5	7·0
All isolates	8882	17·5	23·7	14·6	5·9

Drug classes were defined as follows: beta-lactams (penicillin minimum inhibitory concentration [MIC]≥0·12 mg/L), macrolides (erythromycin MIC≥0·5 mg/L), tetracyclines (doxycycline MIC≥0·5 mg/L), phenicols (chloramphenicol MIC≥8 mg/L), folate pathway inhibitors (co-trimoxazole MIC≥1 mg/L based on trimethoprim component), and quinolones (ofloxacin MIC≥8 mg/L).

Table: **Prevalence of *S pneumoniae* resistant to three or more drug classes, Alexander Project 1998–2000[14]**

Neisseria gonorrhoeae

A sharp decline in gonorrhoea incidence has been seen in many developed countries, but *Neisseria gonorrhoeae* remains one of the most common causes of sexually transmitted disease in developing countries. Unlike many sexually transmitted diseases, gonorrhoea is treatable, but treatment has been greatly compromised by the emergence of penicillinase-producing *N gonorrhoeae* in 1976, and the subsequent emergence of strains resistant to tetracycline and spectinomycin. Between 1996 and 2001, the prevalence of penicillinase-producing *N gonorrhoeae* in Hong Kong increased from 57·2% to 81·8%.[116] Penicillin resistance among gonococci currently ranges between 9% and 90% across most of Asia and exceeds 35% in sub-Saharan Africa and the Caribbean.[117–123]

Treatment failures in gonococcal infection can lead to pelvic inflammatory disease and infertility in women, and can increase the probability of HIV transmission.[124,125] Therefore, resistance has greater consequences than for the epidemiology of gonorrhoea alone. It is generally accepted that antimicrobials used for empirical treatment of gonorrhoea should be effective against more than 95% of isolates from the geographic area where infection took place.[117] In vitro

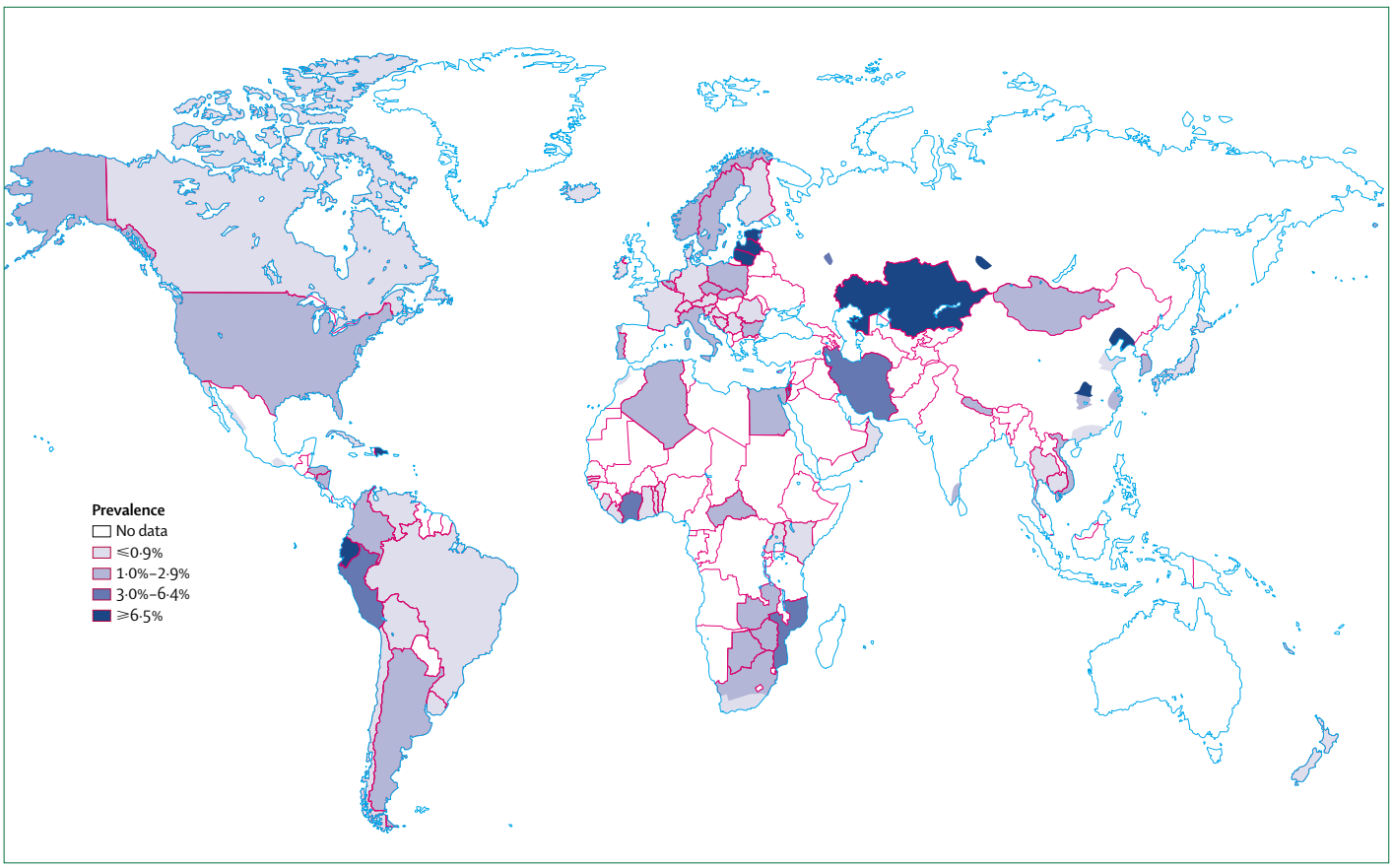

Figure 2: **Prevalence of multidrug-resistant tuberculosis among new tuberculosis cases, 1994–2000**
Source: WHO

N gonorrhoeae resistance, according to official breakpoints, correlates strongly with clinical failure.[117] Knowledge of susceptibility patterns is therefore directly applicable to chemotherapy and essential for antimicrobial selection. The propensity of newly drug-resistant strains of gonococci to spread rapidly, due to their peculiar epidemiology and a common lack of control programmes, creates a special but rarely met need for surveillance to detect microepidemics of such strains promptly. The introduction of tetracyclines and then spectinomycin for the management of gonorrhoea was quickly followed by the emergence of strains resistant to single and multiple drugs.[117] Tetracycline resistance is especially common in sub-Saharan Africa, where the low cost and wide distribution of these drugs has contributed to their use and abuse in the management of actual, presumed, or expected infectious disease.[117,119,126] Studies from various locations south of the Sahara have observed increases or stable highs in pencillin-resistant *N gonorrhoeae* of about 70% and concomitant increases in tetracycline resistance from 20% to 40–65% in the early 1990s.[119,127,128]

Widespread resistance has necessitated the replacement of penicillin and tetracycline with more expensive first-line drugs, to which resistance quickly emerged. In the Caribbean and South America, azithromycin resistance was found in 16–72% of isolates in different locations, resulting in the recommendation that this drug in turn be replaced by ceftriaxone, spectinomycin, or the quinolones.[122,129,130] Studies in Rwanda and Benin have documented rapid emergence of resistance to multiple agents, although all isolates were sensitive to ceftriaxone, ciprofloxacin, spectinomycin, and kanamycin at the time of the last report.[127,128] In other parts of the world, selective pressure due to chemotherapy of other infections and drug misuse may have contributed to the emergence and rapid spread of quinolone-resistant *N gonorrhoeae*. Quinolone resistance is most commonly reported from Asia,[117,121,123,131] with the prevalence of ciprofloxacin resistance in *N gonorrhoeae* in Hong Kong rising from 18% to 73% in a 6-year period.[116] Although quinolone resistance has emerged in Africa, Latin America, the Caribbean, and the middle east, it appears less common than in Asia.[117,122,132]

The emergence of quinolone resistance increasingly leaves only less available parenteral drugs—eg, spectinomycin or ceftriaxone—as fully reliable therapy. The high cost of third-generation cephalosporins in

particular makes their use prohibitive in many developing countries. More comprehensive surveillance might attempt to map expedient exploitation pockets of still-persisting susceptibility to one or another of the older drugs. This mapping could potentially be accomplished by the WHO's Global Gonococcal Antimicrobial Susceptibility Programme (GASP), which aims to monitor *N gonorrhoeae* susceptibility from laboratory networks and ultimately disseminate this information to prescribers and public-health policymakers.[133] The programme operates from regional offices in Latin America, the Caribbean, and parts of Asia and the western Pacific. GASP has been instrumental in documenting penicillin and tetracycline resistance trends as well as detecting the emergence of resistance to newer therapies, including azithromycin, cephalosporins, and the fluoroquinolones. In some areas, notably sub-Saharan Africa, GASP has been limited by poor infrastructure.

Nosocomial infections

Nosocomial infections continue to compromise the ability of hospitals to prevent deaths and effect cures worldwide. Organisms of current concern in developed countries—meticillin-resistant *Staphylococcus aureus,* glycopeptide-intermediate and resistant *S aureus,* vancomycin-resistant enterococci, and multidrug-resistant Gram-negative bacteria—are also important nosocomial pathogens in the developing world.[134] However, over the past 25 years, nosocomial transmission of commonly encountered, community-acquired, multidrug-resistant organisms—eg, the pneumococcus,[88] *M tuberculosis,*[135–137] *Salmonella* spp,[138] *Shigella* spp,[139] and *V cholerae*[140]—has been increasingly documented in developing countries.

Assuming a conservative nosocomial infection rate of 15% for a developing country, based on estimates from South Africa, and an associated attributable mortality rate of 5%, it could be that hospital-acquired infections rank—either directly or indirectly—among the most important causes of death in the developing world.[141] Antimicrobial resistance is a major factor undermining empirical therapy of infections and, therefore, patient mortality.[134] When initial empirical therapy for nosocomial bloodstream infections is inappropriate, there is a substantial chance that the patient will die.[134] Resistant nosocomial infections adversely affect patient prognosis, increase the cost of patient management, and lengthen the duration of hospital stay.[142] In addition to the selection pressure provided in hospitals, these establishments also house vulnerable hosts, and therefore the spread of a resistant clone can be rapid and have severe consequences. Horizontal transfer of resistance genes from one strain to another can also exacerbate the possibility of resistant nosocomial infections.[143]

In one of few studies from developing countries, Hsueh and colleagues[144] assessed resistance trends in isolates from a Taiwanese hospital between 1981 and 1999. Although the number of infections caused by enterococci did not change appreciably during the period, they saw the incidence of vancomycin-resistant enterococci increase from 3% to 50% between 1995 and 1999, and the data they present show a close fit to an exponential trend. Data on resistance in neonatal infections from Pakistan suggest a steady and alarming increase in resistance among common pathogens in hospitals.[145] Bello and co-workers[146] examined isolates of the *Acinetobacter calcoaceticus–Acinetobacter baumannii* complex from hospitalised patients in Chile between 1990 and 1998. They observed a decline in ampicillin and sulbactam activity during the study period associated with use of this combination for management of nosocomial infections.

Severe financial constraints, inadequate staffing, overcrowding in hospitals, inadequate medical and medicinal resources, and lack of recognition of the cost-effectiveness of infection control create difficulties for implementing basic infection control programmes in health-care facilities. A case in point is a report from Trinidad describing the bacterial contamination of disinfectants and antiseptics in hospitals by multidrug-resistant bacteria.[147] It follows that where infection control practices are lacking, the containment of the spread of multidrug-resistant organisms becomes extremely difficult.

On a positive note, the introduction of infection control programmes in developing countries has increased substantially during the past decade, particularly in Latin America, Asia, and South Africa. Experience in many high-income countries suggests that where sound infection control programmes are in place, the incidence of hospital-acquired infections can be substantially reduced.

Resistance reservoirs

Resistant commensals are likely to be selected and maintained without detection, providing ample opportunity for them to serve as reservoirs of resistance genes.[148] An early study demonstrated that resistant non-pathogenic *E coli* were more commonly carried by children residing in Caracas, Venezuela, and Qin Pu, China, than by those in Boston, USA.[149] Other studies have shown that faecal carriage of resistant *E coli* is very common in people in developing countries.[150–153] The trends seen in these organisms and the agents affected have paralleled temporal trends in enteric pathogens and in pathogens that could come in contact with these organisms in other niches.[154]

Studies with commensals have been instrumental in identifying factors that may contribute to the selection and spread of resistant bacteria. Studies with *E coli* throughout the developing world[155,156] and with *S pneumoniae* in Lesotho and Asia[72,81,157] reveal that resistant organisms are more likely to be encountered in

urban than rural settings. One explanation for these findings is the greater use and abuse of antimicrobials in urban settings, permitting selection of resistant strains.[81,155,157]

Food animal husbandry account for an enormous proportion of antimicrobial agents consumed. Although some antimicrobials are used for the prevention and treatment of animal infections, non-therapeutic application—eg, growth promotion and prophylactic use—accounts for a substantial fraction of consumption. Estimates for non-therapeutic use from the USA alone range from between 12 million and 70 million kg a year.[158,159] The use of antimicrobial agents in agriculture can contribute to the spread of antimicrobial resistance in farm animals and subsequent transmission to human beings.[160,161]

In developing countries, household subsistence farming is common, which means that a large proportion of the population has close contact with food animals.[162] Therefore, if resistant organisms are common in animals, the chance that they will be transmitted to human beings is likely greater. Kolawole and colleagues[163] found that resistant staphylococci conventionally associated with animals were a predominant cause of wound infections in Nigerian outpatients. In China, an outbreak caused by a multidrug-resistant strain of *Enterococcus faecium* occurred in pigs, was transferred to human beings, and led to fatalities.[164]

WHO has recommended that antimicrobials normally prescribed for human beings should no longer be used for growth promotion in animals.[165] In developing countries, there are rarely guidelines for antimicrobial use in animals, particularly the restriction of use of agents used for human therapy. A Kenyan report suggested that resistance is uncommon in *E coli* among farmed chickens, even though it is common in farm personnel, suggesting that the animal isolates were naive to selective pressure.[166] In Africa and many other developing countries it is often, anecdotally, deemed unlikely that most subsistence farmers use antimicrobials for animal husbandry, particularly growth promotion, even though this has not been an area of much study. In one rare study, Ogeniyi and colleagues[167] found that resistance was more common in *E coli* isolates from poultry produced in a large modern farm than from free-range subsistence chickens in Nigeria. Other reports have highlighted the existence of unacceptably high antibiotic residues in meat in Kenya and Nigeria,[168,169] suggesting that the use of antimicrobials for animal husbandry in Africa is not a rare occurrence.[170]

Many so-called cost-effective agricultural technologies are being suggested as solutions to food shortages in developing countries. For example, spraying fruit trees with antimicrobials—a practice that emerged in the USA—is now employed in Central and South America, and integrated fish farming, which uses farm animal waste as fodder for cultivated fish and is practised extensively in southeast Asia. Petersen and colleagues found that although the latter practice is economically viable, it encourages the shedding of antibiotic-resistant organisms into the environment.[171] The survival of these organisms and their impact are likely to be greater in the tropics than in temperate climates, where integrated fish-farming protocols were developed.[171]

Search strategy and selection criteria

References for this review were identified by searches of Medline, ISI Webofscience, and references from relevant articles; additional articles were identified through searches of the extensive files of the authors. Search terms used in combination were "antimicrobial resistance", "antibiotic resistance", "developing countries", "Africa", "Asia", "Latin America", "South America", "*Salmonella*", "*Shigella*", "*Vibrio cholerae*", "*Escherichia coli*", "*Streptococcus pneumoniae*", "*Mycobacterium tuberculosis*", "*Neisseria gonorrhoeae*", and "nosocomial infection".

The economic burden of resistance in developing countries

Costs associated with antimicrobial resistance among outpatients in the USA have been estimated to lie between US$400 million and US$18·6 billion,[172] and corresponding inpatient costs are likely to be several times higher. For example, Abramson and Sexton[173] demonstrated that the attributable financial cost and time to cure were trebled in cases of meticillin-resistant *S aureus* infections compared with infections caused by susceptible strains. Although there is little published evidence on the economic burden of resistance in developing countries, the absence of evidence is not evidence of absence. Hensher[174] reports that the cost of a full course of drug treatment for multidrug-resistant tuberculosis in the northwest province of South Africa was Rand 26 354 (roughly US$4300) compared with Rand 215 for susceptible tuberculosis (roughly US$35). Data from Peru support the hypothesis that multidrug-resistant tuberculosis is much more expensive to treat than susceptible tuberculosis strains that are resistant only to one or two drugs—costs were estimated at US$8000 and US$267, respectively.[175]

At the very least, chemotherapeutic failure due to resistance results in an equivalent burden of one new case of the disease, since the infection must be retreated. In actuality, second-line treatments are often more costly. Also, second-line therapies require more complicated dosing, have more side-effects, and may need a greater degree of medical attention. Therefore, the true cost of curing one resistant infection is likely to greatly exceed that for two non-resistant ones, with less than half the assurance of success. Patients with resistant infections are more likely to experience

prolonged illness or to die.[176–178] They also remain infectious for longer and are therefore more likely to transmit the pathogens they carry. Thus, there are costs associated with loss of productivity as well as those directly related to health care.

When resistance is known to exist, even when it is not widespread, susceptible infections are also treated with more expensive, less safe second-line therapies, further increasing the consequences imposed by resistant infections. Expensive clinical trials are needed to assess new treatments when resistance emerges. Health-care workers must be retrained, drug production processes changed, and health-care facilities stocked in response to policy changes made necessary by resistance. By contrast with developed countries, where a large section of the population can afford more effective and expensive alternatives—eg, vancomycin and imipenem—drug resistance in developing countries could substantially increase mortality from common infectious diseases. Exacerbating factors—eg, poor sanitation, lack of reliable water supply, and an increase in the number of immunocompromised patients attributable to the ongoing HIV epidemic—are likely to further increase the cost of antimicrobial resistance.[179] As incomes increase and insurance plans take hold, drug use in developing countries is likely to rise. Already, interventions to promote rational drug use and infection control, and financial incentives to conserve antimicrobials have become more essential than ever before.

Conclusions

Available data suggest that resistance has reached unacceptable levels in the pathogens most common in developing countries and that trends show further increases. Resistance appears to have emerged and spread rapidly in many areas, with important consequences for individual patients and public health. The agents most affected are inexpensive, older antimicrobials, which in many cases are all that are available or affordable. Widespread selective pressure and efficient dissemination channels for multidrug-resistant organisms are major factors that may have contributed to the rapid emergence and spread of resistant organisms. A pressing and unmet need exists to alter these factors in areas where susceptibility has been recorded and to identify other contributors to these alarming trends. The role of antimicrobial pressure from agricultural use remains to be evaluated, but there is no evidence to suggest that errors committed in developed countries will not be replicated. Inadequate surveillance means that resistance prevalence and trends are largely understudied and that baseline data for evaluating potential interventions are unlikely to be sufficient. National and international policy decisions backed by political and social will are necessary to provide a more accurate assessment of the problem and interrupt the unacceptable trends.

Conflicts of interest

We declare that we have no conflicts of interest.

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