Regional Review

Antibiotic resistance in Mexico: a brief overview of the current status and its causes

Carlos F. Amábile-Cuevas

Fundación Lusara, Mexico City, Mexico

Abstract

As in many other developing countries, conditions that may foster antibiotic resistance in Mexico differ from developed countries, as does resistance prevalence. Fecal pollution and other characteristics of overcrowded, poor cities might create ideal settings for selecting, exchanging and maintaining resistance traits. Medical abuse of antibiotics, along with low-quality drugs, is also present as in many other developing countries. Self-prescription, a common yet unmeasured practice among the Mexican population, may also contribute to increased resistance rates. Pneumococcal resistance towards penicillin and macrolides are the highest in Latin American countries, as is resistance of *Salmonella* and uropathogenic *Escherichia coli* towards ampicillin and sulfamethoxazole-trimethoprim; about one-tenth of isolates of these gram-negative pathogens seem to produce extended-spectrum beta-lactamases (ESBL). High rates of multiple-drug resistant *Mycobacterium tuberculosis* are also found in Mexico, although there is no report of extensively drug-resistant strains. As to hospital-acquired pathogens, about a third of *E. coli* and *Klebsiella* isolates are ESBL-producers, and half of *Staphylococcus aureus* isolates are resistant to oxacillin (MRSA). Approximately 40% of *Pseudomonas aeruginosa* isolates are resistant to ceftazidime, imipenem or levofloxacin. Although community-acquired MRSA, vancomycin-resistant enterococci, and other resistance problems found in developed countries are not as common in Mexico, local issues are no small concern, and are disturbingly moving towards outpatients.

Key words: antibiotic resistance, developing countries, MRSA, ESBL, self-prescription, prescription regulation

J Infect Dev Ctries 2010; 4(3):126-131.

(Received 10 August 2009 – Accepted 1 January 2010)

Introduction

Many articles on antibiotic resistance start with a statement about the threat it poses towards public health. This is, of course, true, but the threat differs among countries. First, the overall rate of resistance, which is often larger in developing than in developed countries, must be considered. Also, the kind of organisms in which resistance is dangerously growing is different: while rich countries are concerned with hospital-acquired pathogens such as the ESKAPE group including *Enterococcus*, *Staphylococcus*, *Klebsiella*, *Acinetobacter*, *Pseudomonas*, *Enterobacter*, (with the exception being community-acquired methicillin-resistant *Staphylococcus aureus*, CA-MRSA), poor countries are additionally challenged with multi-resistant pathogens in the community, such as *Mycobacterium tuberculosis*, pneumococci, uropathogenic *Escherichia coli* (UPEC) or *Salmonella*. As to the clinical impact, overcrowded, poorly staffed and poorly equipped hospitals allow for a rapid spread, slow detection and grim outcome of multi-resistant infections much more often in developing countries than in the US or most of Europe. With malnourished patients that have scarce access to medical services and drugs, such infections are crippling or fatal much more commonly. Finally, the financial burden that resistance imposes upon health services causes more hardship in poor countries. All these have been very recently reviewed [1], not only with regard to bacteria, but also to other microbial pathogens that are gaining resistance and that pose particular threats to the public health in developing countries. The current situation in Mexico is briefly reviewed here.

Causes for the rise of resistance, different from antibiotic usage

Despite some subtle differences, real or apparent, on the biology of the emergence and spread of resistance genes that will be discussed shortly, there is no reason to believe that there is a significant disparity on the molecular basis of antibiotic resistance between Mexico (or the whole of Latin America) and richer countries. Perhaps some drugs

that presumably promote the spread itself of resistance genes, such as quinolones [2] or tetracycline [3,4], are used more often in Latin America, hence enacting more than a mere selective pressure and increasing resistance rates when compared to low-usage countries. However, even if such a usage pattern difference exists, it is not likely to have a significant impact. Therefore, direct selective pressure is the most probable culprit of increased resistance in Mexico and other Latin American countries. Before going to the obvious selective pressure, *i.e.*, the abuse of antibiotics, some other peculiar characteristics of developing countries that might, albeit indirectly, influence bacterial resistance should be discussed.

Cities in developing countries are interesting playgrounds for a variety of humans' and animals' pathogenic and commensal bacteria. The lack of adequate urban infrastructure—along with overcrowding, stray animals, and improper management of garbage and wastewater—makes for increased levels of fecal pollution of urban dust. Aside from the direct health effects of chronic exposure to these contaminants, the chances for horizontal transfer of resistance and even virulence genes are increased by merely putting together bacteria that do not often interact [5]. Furthermore, chemical pollution, another feature of developing countries due to under-regulation, under-enforcement, or plain corruption, can play a role in the selection of resistant bacteria. Ozone, for instance, is a common air pollutant in large Mexican cities, derived from photochemical reactions of automobile exhaust fumes and household propane gas, and has been shown to select for bacteria with oxidant-response mechanisms that also confer a multi-resistant phenotype [6]. This and other agents might be at play in selecting resistance to multiple antibiotics among *E. coli* isolates in urban dust in Mexico City, as well as low-level quinolone resistance in urban water bodies [7]. It is even possible that such selective pressures are enough to keep class 1 integrons in *E. coli*, despite being a rather unstable mobile element in this species in the absence of antibiotics [8]. Further research is needed in this mostly ignored area.

Antibiotic usage in Mexico

The use and abuse of antibiotics is regarded, however, as the most important cause of increasing resistance. Perhaps the first problem we have in Mexico is the lack of information about the amount of antibiotics used for both clinical and non-clinical purposes. A recent review published in the journal of the National Institute of Public Health of Mexico relied mostly on some few papers on prescription practices and antibiotic usage that are 10 to 20 years old [9]. Furthermore, there is no mention of the agricultural use of antibiotics that amounts, worldwide, to more than half of the total antibiotics produced. Furthermore, documented information on the use of antibiotics in Mexico cannot be provided, but there is no reason to suppose that the agricultural use of antibiotics is less intense and reckless here than in any developed country, but rather the opposite. It is also commonly presumed that medical training is of lower quality in Mexico than in the USA or Europe. It is likely that Mexican physicians use antibiotics as badly as most of their colleagues abroad, *i.e.*, wrongly in about half of the cases [10]. Nonetheless, there is not sufficient local information on this matter.

The quality of antibiotics used clinically might have some bearing in promoting resistance. Generic drugs have been reported as having significantly less active antibiotic than the "original" counterpart [11,12]. Again, this has been tested elsewhere, but there is no reason to think that generic drugs available in Mexico (most of which are manufactured abroad) are any better. Furthermore, for many years a third, rather odd, category of drugs existed in Mexico: "similar" drugs. Similar drugs are manufactured by a single company, owned by a "well-connected" individual, the brother of the "owner" of a mid-size national political party. This category of drugs was not tested, even in the minimal and obscure way that is requisite for generics, escaping external quality controls of any kind [13]. It is easy to imagine that less potent drugs that fail to keep inhibitory concentrations in blood and tissues for as long as they are supposed to can potentially engender resistance easily, but that would also need to be tested.

Falsified drugs are not, apparently, as big a problem here as they are in other developing countries [14]. A peculiar issue, however, is the mostly un-quantified black market of stolen drugs. These come from illegally sold samples that physicians are supposed to receive free of charge as well as from the two large public hospital networks in the country, from which a continuous flow of stolen drugs is allowed. Many of these drugs are improperly stored, possibly leading to partial or total inactivation, and are often sold past their expiration

Table1. Antibiotic resistance in Mexico at a glance.

Organism	Antibiotic	Resistance (%)	Additional Information
Community-Acquired			
S. pneumoniae	penicillin	70	non-susceptible (resistant+intermediate)
	clarithromycin	49	
Salmonella spp.	ampicillin	66	from 14% in 1994-1995
	co-trimoxazole	66	from 27% in 1994-1995
	chloramphenicol	20	from 20% in 1994-1995
	ceftriaxone	12	
Shigella spp.	ampicillin	81	from 63% in 1994-1995
	co-trimoxazole	81	from 59% in 1994-1995
	chloramphenicol	11	from 37% in 1994-1995
E. coli (uropathogenic)	ampicillin	74	
	co-trimoxazole	60	
	ciprofloxacin	33	
	ceftazidime	8	
M. tuberculosis		17	MDR
Nosocomial Pathogens			
Klebsiella spp.		28	ESBL-producers
S. aureus	methicillin	48	
E. faecium	vancomycin	33	
P. aeruginosa	amikacin	20	
	ceftazidime	39	
	imipenem	43	
	levofloxacin	40	
	piperacillin/ tazobactam	28	
Acinetobacter spp.	amikacin	40	
	ceftazidime	72	
	levofloxacin	51	
	piperacillin/ tazobactam	51	

dates. Most of the drugs made available this way are costly, such as anti-neoplastic agents, but some intravenous antibiotics also make their way to the neighborhoods and towns well-known as cheap drugstores. How many of these drugs are sold and used, and what is the impact of this upon bacterial resistance, we might never know.

Self-prescription is another problem. As in many other Latin American countries (the exceptions being Cuba, Chile, Costa Rica and Venezuela), antibiotics of any kind, from ophthalmic chloramphenicol to intravenous linezolid, can be bought in Mexico without medical prescription. Self-prescription causes antibiotic abuse in a number of ways, not restricted to the use against non-infectious or non-bacterial diseases: self-prescribed antibiotic treatments are shorter and/or improperly dosified and also rely upon expired remnants of past, medically prescribed treatments. The easiest way to stop self-prescription is to make mandatory the presentation of a medical prescription (although in countries where such restrictions exist, as in the USA, antibiotics can be purchased from friendly pharmacists, immigrants, the internet, and even pet stores). That has been the path chosen by the few Latin American countries where antibiotics are no longer over-the-counter drugs. However, in countries such as Mexico, where many people do not have access to health care services, it is possible that self-prescription actually saves many lives. Before restricting the free-sale of antibiotics, it would be necessary to assess the cost of such a measure (denying access to life-saving drugs to low- and very-low-income people) against its benefits (decreased resistance and adverse drug effects). One can only hope that surveillance of resistance in those countries where restrictions have recently been put in

place would answer the latter question. In any case, one of the very few published reports quantifying self-prescription in Mexico [15,16], indicates that it might amount for up to 28-43% of antibiotics sold at drugstores, still leaving medical prescription as the main source of antibiotic requests, and as the main risk of getting unnecessary antibiotics.

Consequences: more antibiotic resistance

From the brief overview above, where antibiotic abuse and other conditions seem like an ideal setting for the emergence and spread of resistance determinants, we can surmise that antibiotic resistance in Mexico is high, more so than in other comparable countries. Indeed, the prevalence of resistance seems higher than that of developed countries, and even than that seen in other Latin American countries. Therefore, some recent, representative results of susceptibility surveys from both, community- and hospital-acquired pathogens will be discussed next. Most relevant data are summarized in Table 1.

Respiratory diseases are the main cause of medical consult; the most common bacterial pathogen is *Streptococcus pneumoniae*, followed by *Haemophilus influenzae*, *Moraxella catarrhalis* and those causing "atypical" pneumonia (*Legionella pneumophila*, *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*). In a recent survey that included isolates from outpatients, mainly in Mexico City, up to 70% of pneumococci were not susceptible to penicillin (13% resistant, 57% intermediate), 71% were resistant to sulfamethoxazole-trimetoprim (co-trimoxazole), and 49% to clarithromycin (70% of them also resistant to clindamycin). Forty-five percent of *H. influenzae* isolates were resistant to co-trimoxazole, 33% to ampicillin (all of them producing beta-lactamases), and 21% to clarithromycin (Amábile-Cuevas and Arredondo-García, unpublished results). None of the strains (150 of each species) were resistant to fluoroquinolones, but there is a report of a 6.5% resistance to ofloxacin in Mexican pneumococci, the highest in the region [17]. An older survey, reporting only MIC values for respiratory pathogens in Latin America, shows that Mexico, Venezuela and Chile have the highest MIC_{90} of penicillin for pneumococci (2-4 µg/mL), and Mexico has the highest MIC_{90} of clarithromycin (16 µg/mL) and of co-trimoxazole (8 µg/mL) for pneumococci [18]. With different rates, Mexico is often cited as the Latin American country with the highest prevalence of penicillin-nonsusceptible penumococci: 51.6% (22.2% resistant) in year 2000 [19], and 57% in year 2007 [17].

Enteropathogens *Salmonella* and *Shigella* are common causes of disease in developing countries. In a small survey conducted in 2001-2002, Mexican *Salmonella* isolates were mainly resistant to tetracycline (82%), co-trimoxazole (66%) and ampicillin (66%) (Amábile-Cuevas, unpublished results), contrasting with a 14% resistance to co-trimoxazole and 27% resistance to ampicillin in 1994-1995 [16], and with a very low prevalence of resistance (2-3%) towards the two latter drugs in the whole of Latin America. Mexico, along with Colombia and Argentina, had the highest resistance prevalence in the region [20]. *Shigella* strains had similar trends in 2001-2002, with 100% resistance to tetracycline and 81% to co-trimoxazole and ampicillin, up from 59% resistance to co-trimoxazole and 63% to ampicillin in 1994-1995. However, resistance to chloramphenicol remained steady, approximately 20% in *Salmonella*, and decreased from 37% to 11% in *Shigella*. A surprising 12% of *Salmonella* isolates were resistant to ceftriaxone; perhaps the worrisome presence of extended-spectrum beta-lactamases (ESBLs) in community-acquired pathogens, mostly reported in enteropathogens in Latin America [21], are already in Mexico.

Community-acquired, uropathogenic *E. coli* is a cause of growing concern as all three "first choice" drugs are facing high resistance prevalence. In a recent survey, 74% of isolates were resistant to ampicillin, 60.1% to co-trimoxazole, and 32.6% to ciprofloxacin. Furthermore, nearly two-thirds of ciprofloxacin-resistant strains had minimal inhibitory concentrations (MICs) of 128 µg/ml or higher, making them able to withstand concentrations attained in urine; also, 8.1% of isolates were resistant to ceftazidime, and three-fourths of them produced ESBLs [22]. Resistance prevalences in other Latin American countries (Argentina, Ecuador, Guatemala, Paraguay, Uruguay and Venezuela) are similar: 53-79% resistant to ampicillin, 33-68% to co-trimoxazole, and 7-32% to ciprofloxacin. Interestingly, Mexico's neighbor, Guatemala, had strikingly similar resistance rates: 79%, 68% and 32%, respectively; the highest in the region [23].

Tuberculosis is a "disease of the poor"; hence it is endemic in Mexico, with 12.8 cases per 100,000 inhabitants, and about 10 deaths per day, according to official records. A recent review places multi-drug resistance (MDR, to at least isoniazid and rifampin)

at a median of 17% (ranging from 6.2 to 64%) in all cases, 4.5% in new cases and 35% in treated cases [24]. No report of extensively drug-resistant (XDR, *i.e.*, MDR that is also resistant to second-line drugs, such as kanamycin, amikacin or capreomycin plus a fluoroquinolone) strains was mentioned. Other reports place MDR at 2.4% in new cases, and 22.4% in treated cases, contrasting with 1.2% and 5.6%, respectively, in the USA, and 0.0% and 7.1%, respectively, in Cuba [25].

Nosocomial pathogens included in the Tigecycline Evaluation and Surveillance Trial (TEST; www.testsurveillance.com) show a partial picture of the resistance trends inside Mexican hospitals. Nearly 70% of *E. coli* isolates are resistant to levofloxacin, and 36% produced ESBLs, while 28% were resistant to amoxicillin-clavulanate; 32% *Klebsiella pneumoniae* isolates were resistant to levofloxacin and 28% produced ESBLs; 48% of *S. aureus* isolates were resistant to oxacillin (MRSA), and 49% were resistant to levofloxacin; 33% of *Enterococcus faecium* isolates were resistant to vancomycin; 20% of *Pseudomonas aeruginosa* were resistant to amikacin, 39% to ceftazidime, 43% to imipenem, 40% to levofloxacin and 28% to piperacillin-tazobactam; 40% of *Acinetobacter baumannii* were resistant to amikacin, 72% to ceftazidime, 51% to levofloxacin and 51% to piperacillin-tazobactam. Fortunately, there was no detectable carbapenem resistance among Enterobacteriaceae, vancomycin resistance among *S. aureus* or *Enterococcus faecalis*, nor linezolid resistance among gram-positive cocci; only one *K. pneumoniae* isolate, among 1,001 isolates tested, was resistant to tigecycline (Ponce de León A, Amábile-Cuevas CF and Benítez A,18th European Congress of Clinical Microbiology and Infectious Diseases, Barcelona, 2008). A comparison between regional trends within the TEST data show that, overall, antibiotic susceptibility is lower in Latin American and Asian countries, than it is in the USA and EU.

Concluding remarks

Antibiotics are the main selective and maintenance pressure for antibiotic resistance determinants amongst bacterial populations. Antibiotic abuse, once a worldwide trend, is slowly receding, but developing countries have, as with many other issues, a significant lag. Other features included in the euphemistic "developing" qualifier, might also increase the prevalence of antibiotic resistance. All these conditions are present in Mexico, along with a dramatic lack of information and of epidemiological surveillance.

Although rational use and sales restrictions are strongly recommended, it must be clear that resistance is in itself a trait that is resistant to elimination [26, 27]. In other words, the high prevalence of resistance is here to stay, and strategies designed to curtail antibiotic abuse will result in the stabilization of resistance at best. It is therefore imperative that such measures be taken immediately to prevent the growing loss of antimicrobial efficacy of our current drug arsenal. It is also important to realize that this is not a local, internal problem in Mexico: microorganisms do travel, and Mexico is both the main exporter of migrants worldwide and the obligated pathway for migrants from other Latin American countries. International pressure is needed to drive the regulatory changes regarding antibiotic usage that are long overdue in Mexico.

References

1. Sosa AJ, Byarugada DK, Amábile-Cuevas CF, Hsueh PR, Kariuki S and Okeke I, editors (2010) Antimicrobial resistance in developing countries. New York: Springer 554 p.
2. Beaber JW, Hochhut B, Waldor MK (2003) SOS response promotes horizontal dissemination of antibiotic resistance genes. Nature 427: 72-74.
3. Shoemaker NB, Salyers AA (1988) Tetracycline-dependent appearance of plasmidlike forms in *Bacteroides uniformis* 0061 mediated by conjugal *Bacteroides* tetracycline resistance elements. J Bacteriol 170: 1651-1657.
4. Torres OR, Korman RZ, Zahler SA, Dunny GM (1991) The conjugative transposon Tn*925*: enhancement of conjugal transfer by tetracycline in *Enterococcus faecalis* and mobilization of chromosomal genes in *Bacillus subtilis* and *E. faecalis*. Mol Gen Genet 225: 395-400.
5. Rosas I, Amábile-Cuevas CF, Calva E, Osornio-Vargas A (2011) Health implications of animal and human waste as components of urban dust pollution. In Nriagu JO, editor. Encyclopedia of environmental health. Amsterdam: Elsevier, accepted.
6. Jiménez-Arribas G, Léautaud V, Amábile-Cuevas CF (2001) Regulatory locus *soxRS* partially protects *Escherichia coli* against ozone. FEMS Microbiol Letters 195: 175-177.
7. Amábile-Cuevas CF, Arredondo-García JL, Cruz A, Rosas I (2010) Fluoroquinolone resistance in clinical and environmental isolates of *Escherichia coli* in Mexico CIty. J Appl Microbiol 108: 158-162.
8. Díaz-Mejía JJ, Amábile-Cuevas CF, Rosas I, Souza V (2008) An analysis of the evolutionary relationships of integron integrases, with emphasis on the prevalence of class 1 integron in *Escherichia coli* isolates from clinical and environmental origins. Microbiol 154: 94-102.
9. Dreser A, Wirtz VJ, Corbett KK, Echániz G (2008) Uso de antibióticos en México. Salud Publica Mex 50 Suppl 4: S480-S487.

10. Kumarasamy Y, Cadwgan T, Gillanders IA, Jappy B, Laing R, Gould IM (2003) Optimizing antibiotic therapy -the Aberdeen experience. Clin Microbiol Infect 9: 406-411.
11. Jones RN, Fritsche TR, Moet GJ (2008) In vitro potency evaluations of various piperacillin/tazobactam generic products compared with the contemporary brand (Zosyn, Wyeth) formulation. Diagn Microbiol Infect Dis 61: 76-79.
12. Lambert PA, Conway BR (2003) Pharmaceutical quality of ceftriaxone generic drug products compared with Rocephin. J Chemother 15: 357-368.
13. Amábile-Cuevas CF (2010) Global perspectives of the resistance problem. In Sosa AJ, Byarugada DK, Amábile-Cuevas CF, Okeke I, Kariuki S, Hsueh PR, editors. Antimicrobial resistance in developing countries. New York: Springer. 3-13.
14. Newton PN, Fernández FM, Green MD, Primo-Carpenter J and White NJ (2010) Counterfeit and substandard anti-infectives in developing countries. In Sosa AJ, Byarugada DK, Amábile-Cuevas CF, Okeke I, Kariuki S, Hsueh PR, editors. Antimicrobial resistance in developing countries. New York: Springer. 413-443.
15. Amábile-Cuevas CF, Cabrera R, Fuchs LY and Valenzuela F (1998) Antibiotic resistance and prescription practices in developing countries. Meth Microbiol 27: 587-594.
16. Calva JJ, Niebla-Pérez A, Rodríguez-Lemoine V, Santos JI and Amábile-Cuevas CF (1996) Antibiotic usage and antibiotic resistance in Latin America. In Amábile-Cuevas CF, editor. Antibiotic resistance: from molecular basics to therapeutic options. Austin/New York: R.G. Landes/Chapman & Hall. 73-97.
17. Bartoloni A and Gotuzzo E (2010) Bacterial resistant infections in resource-limited countries. In Sosa AJ, Byarugada DK, Amábile-Cuevas CF, Okeke I, Kariuki S, Hsueh PR, editors. Antimicrobial resistance in developing countries. New York: Springer. 199-231.
18. López H, Sader H, Amábile-Cuevas CF, Pedreira W, Muñoz-Bellido JL, García-Rodríguez JA, Grupo MSP-LA (2002) Actividad *in vitro* de moxifloxacino frente a patógenos respiratorios en Iberoamérica. Rev Esp Quimioterap 15: 325-334.
19. Ruvinsky R (2006) Resistencia a los antibióticos de los principales patógenos respiratorios. In Levy-Hara G, Sosa A, editors. Uso y abuso de los antibióticos ¿dónde estamos y adónde queremos llegar? Montevideo: Arena. 53-69.
20. Hernández Escobar M and Prado Jiménez V (2006) Situación actual de la resistencia a los antibióticos en los enteropatógenos. In Levy-Hara G, Sosa A, editors. Uso y abuso de los antibióticos. Montevideo: Arena. 81-88.
21. Casellas JM and Quinteros MG (2007) A Latin American "point de vue" on the epidemiology, control, and treatment options of infections caused by extended-spectrum beta-lactamase producers. In Amábile-Cuevas CF, editor. Antimicrobial resistance in bacteria. Wymondham: Horizon Bioscience. 99-122.
22. Arredondo-García JL, Amábile-Cuevas CF (2008) High resistance prevalence towards ampicillin, co-trimoxazole and ciprofloxacin, among uropathogenic *Escherichia coli* isolates in Mexico City. J Infect Develop Ctries 2: 350-353.
23. Guzmán-Blanco M and Istúriz RE (2010) Antimicrobial drug resistance in Latin America and the Caribbean. In Sosa AJ, Byarugada DK, Amábile-Cuevas CF, Okeke I, Kariuki S, Hsueh PR, editors. Antimicrobial resistance in developing countries. New York: Springer. 331-345.
24. Zazueta-Beltran J, León-Sicarios C and Canizalez-Roman A (2009) Drug resistant *Mycobacterium tuberculosis* in Mexico. J Infect Develop Ctries 3: 162-168.
25. Joloba M and Bwanga F (2009) Drug resistance in *Mycobacterium tuberculosis*. In Sosa AJ, Byarugada DK, Amábile-Cuevas CF, Okeke I, Kariuki S, Hsueh PR, editors. Antimicrobial resistance in developing countries. New York: Springer. 117-135.
26. Heinemann JA, Ankenbauer RG, Amábile-Cuevas CF (2000) Do antibiotics maintain antibiotic resistance? Drug Discov Today 5: 195-204.
27. Salyers AA, Amábile-Cuevas CF (1997) Why are antibiotic resistance genes so resistant to elimination? Antimicrob Agents Chemother 41: 2321-2325.

Corresponding author

Carlos F. Amábile-Cuevas
Fundación Lusara
Apartado Postal 8-895
Mexico City, 08231
Mexico
Phone/Fax: (52-55)52195855
Email: carlos.amabile@lusara.org

Conflict of interest: No conflicts of interest are declared.