

Trends in antibiotic utilization in eight Latin American countries, 1997–2007

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ABSTRACT

Objective. To describe the trends in antibiotic utilization in eight Latin American countries between 1997–2007.

Methods. We analyzed retail sales data of oral and injectable antibiotics (World Health Organization (WHO) Anatomic Therapeutic Chemical (ATC) code J01) between 1997 and 2007 for Argentina, Brazil, Chile, Colombia, Mexico, Peru, Uruguay, and Venezuela. Antibiotics were aggregated and utilization was calculated for all antibiotics (J01); for macrolides, lincosamides, and streptogramins (J01 F); and for quinolones (J01 M). The kilogram sales of each antibiotic were converted into defined daily dose per 1 000 inhabitants per day (DID) according to the WHO ATC classification system. We calculated the absolute change in DID and relative change expressed in percent of DID variation, using 1997 as a reference.

Results. Total antibiotic utilization has increased in Peru, Venezuela, Uruguay, and Brazil, with the largest relative increases observed in Peru (5.58 DID, +70.6%) and Venezuela (4.81 DID, +43.0%). For Mexico (–2.43 DID; –15.5%) and Colombia (–4.10; –33.7%), utilization decreased. Argentina and Chile showed major reductions in antibiotic utilization during the middle of this period. In all countries, quinolone use increased, particularly sharply in Venezuela (1.86 DID, +282%). The increase in macrolide, lincosaminde, and streptogramin use was greatest in Peru (0.76 DID, +82.1%), followed by Brazil, Argentina, and Chile.

Conclusions. Analyzing antibiotic utilization in Latin America presents a series of challenges. Creating policy-relevant evidence based on antimicrobial consumption patterns is needed in order to foster policies aimed at improving appropriate use of antibiotics in the region.

Key words

Pharmacoepidemiology; anti-bacterial agents; drug resistance, microbial; national drug policy; Latin America.

Resistance to antibiotics is an important public health problem as it leads to treatment failures (with incumbent morbidity and mortality) and the increased empirical use of more costly

broad-spectrum antibiotics. Over the last two decades, it has been clearly established that high levels of community antibiotic consumption correlate with high levels of community resistance to antibiotics (1–3). Consequently, learning about the patterns of community antibiotic consumption is fundamental in order to design regional and local interventions directed at optimizing the use of these important medicines.

In Europe, the European Surveillance on Antibiotic Consumption (ESAC),

among other initiatives funded by the European Union, is creating evidence to inform public health policies on use and surveillance of consumption (3). It has triggered an unprecedented wave of antibiotic consumption data all over Europe (4–6), national campaigns to improve antibiotic use (7), and many research studies to extend surveillance and other interventions to improve antibiotic use (8). In many other parts of the world, particularly developing countries, measuring consumption of antibi-

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otics presents a major challenge; it traditionally has received little attention and, consequently, modest funding (9). Information systems are scarce and unreliable; local studies are time and resource intensive, and extrapolating consumption from the local to the national level has major limitations (10).

In Latin America, the Pan American Conference on Antimicrobial Resistance held in 1998 concluded that among the main priorities for the region were measuring and reporting antibiotic consumption (11). Although notable advances have occurred in regional surveillance of resistance (12), the patterns and severity of antimicrobial consumption in Latin American countries have been monitored only sporadically (13, 14). The objective of this study was to describe the trends in antibiotic consumption in eight Latin American countries between 1997 and 2007.

MATERIALS AND METHODS

We used routinely collected retail sales data on antibiotics (World Health Organization (WHO) Anatomic Therapeutic Chemical (ATC) code J01) between 1997 and 2007 from eight Latin American countries: Argentina, Brazil, Chile, Colombia, Mexico, Peru, Uruguay, and Venezuela. Only antibiotic formulations with systemic absorption or delivery (oral or parenteral) were taken into account; excluded were products with topical and vaginal or rectal application. We chose countries with the largest pharmaceutical markets in Latin America.

The data were derived from a health care consultancy organization, which relies on reports of a sample of retail wholesalers and, in addition, on information provided by a sample of pharmacies in some countries (15). All data provided by the health care consultancy organization were national antibiotic sales to retail sectors (direct sales in private pharmacies and indirect sales in private clinics and hospitals) and do not include antibiotics purchased by the public sector (government providers). Given the Latin American context in which restrictions to sell antibiotics only with a medical prescription are not enforced, the data include sales both with and without prescriptions. These data represent the industry standard for estimating national retail sales volume of medications and have been widely used in stud-

ies of antibiotic utilization patterns (16), among them the ESAC project (3). For analysis, we used the WHO ATC classification and the defined daily dose (DDD) system of WHO for 2008 (17).

The unit of analysis provided was kilogram of sales per year aggregated by country, which we converted to defined daily dose per 1 000 inhabitants per day (DID). We obtained population information from the Pan American Health Organization database (18). For the eight countries studied, we analyzed the trend of antibiotic consumption measured as DID between 1997 and 2007 and carried out a cross-sectional analysis of the main therapeutic groups of antibiotics consumed in 2007. We also conducted focused analyses on the use of two therapeutic classes of antibiotics: macrolide, lincosamides, and streptogramins (J01 F) and quinolone (J01 M). They were selected because of recent observations that macrolide resistance among *Streptococcus pneumoniae* and group A streptococcus is associated with azithromycin consumption (because of its long half-life) (19, 20) and that new patterns of fluoroquinolone resistance are emerging among *S. pneumoniae* as well as among enteric and genitourinary pathogens (21).

In order to calculate national rates of antibiotic utilization based on national population estimates, we adjusted the numerator for antibiotic sales volume

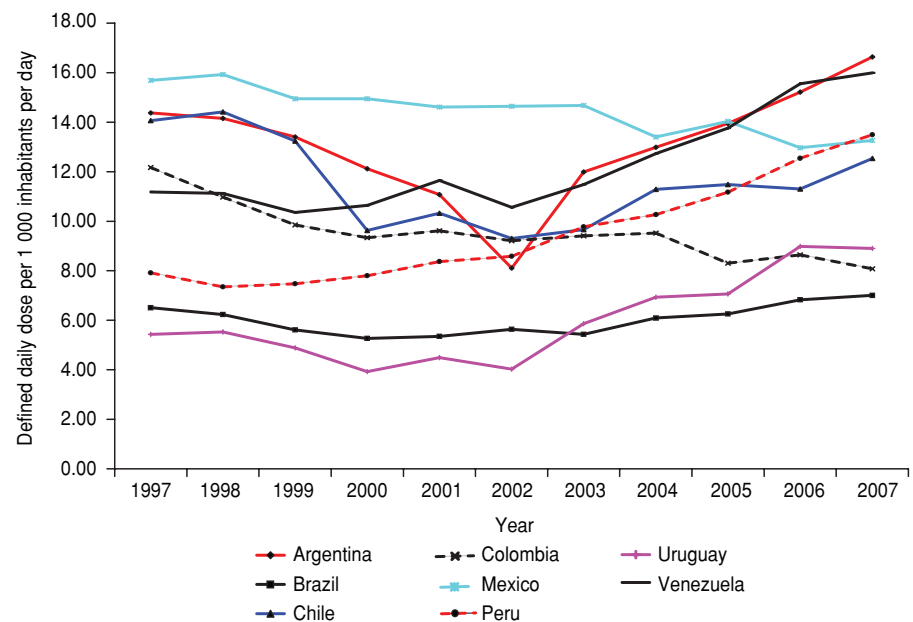
based on the proportion of a given country's total medication market volume that was distributed via retail sector versus government (15). These data were available for specific years for each country: 2008 data for Colombia and Uruguay; 2007 data for Argentina, Brazil, and Peru; 2004 data for Mexico; 2001 data for Venezuela; and 2000 data for Chile.

The funding source of this study did not play a role in study design; in collection, analysis, and interpretation of data; in writing the report; and in the decision to submit the paper for publication.

RESULTS

Figure 1 presents national antibiotic utilization rates in eight Latin American countries between 1997 and 2007. In 1997, Mexico (15.69 DID) had the highest antibiotic utilization followed by Argentina (14.37 DID) and Chile (14.07 DID). The three countries with the lowest utilization in 1997 were Peru (7.91 DID), Brazil (6.51 DID), and Uruguay (5.43 DID). By 2007, Argentina (16.64 DID) and Venezuela (15.99 DID) headed the list of countries in antibiotic use followed by Peru (13.50 DID), Mexico (12.53 DID), and Chile (12.53 DID). Significantly lower was antibiotic use in Uruguay (8.90 DID), Colombia (8.09 DID), and Brazil (7.01 DID), with the lowest utilization rates of the eight countries studied.

FIGURE 1. Trends of national antibiotic utilization in eight Latin American countries, 1997–2007



In terms of relative change using 1997 as a baseline, antibiotic utilization has increased in Peru (5.58 DID, +70.6%), Uruguay (3.48 DID, 64.0%), and Venezuela (4.81 DID, +43.0%), whereas in Mexico (−2.43 DID, −15.5%) and Colombia (−4.10 DID, −33.7%) it has declined (Table 1). Two countries, Argentina and Chile, showed major drops in antibiotic use in the middle of this period. However, Argentina has increased antibiotic use during the last few years to exceed its baseline rate (2.26 DID, +15.7%), whereas in Chile utilization is slightly lower than

its baseline rate (−1.53 DID, −10.9%). With respect to the average change (1.07 DID) in all eight countries between 1997 and 2007, Colombia showed the largest percentage decrease (−483.2%) and Peru showed the largest percentage increase (+421.5%) (Table 1).

We analyzed the distribution of antibiotic classes being consumed in each country based on 2007 (Figure 2). Penicillins were the most common therapeutic group of antibiotics consumed in all Latin American countries in our study, followed by the group composed of

macrolides, lincosamides, and streptogramins and the group of quinolones.

Examining 10-year trends for macrolide, lincosamide, and streptogramin antibiotics showed large increases in Peru (0.76 DID, +82.1%), Brazil (+0.41 DID, +61.5%), and Argentina (0.74 DID, +42.0%) but relatively little change or even decreases in Uruguay, Mexico, and Colombia (Figure 3). We examined the distribution of specific macrolide antibiotics within this therapeutic class in 2007. In all countries except Argentina and Chile, azithromycin consumption was higher than that of clarithromycin (Figure 4).

Quinolone utilization increased in all eight countries studied. The decrease in overall antibiotic utilization for Chile during the middle of the period studied does not apply to quinolone antibiotics, for which sales have increased evenly over the last 11 years. Whereas quinolone utilization in Chile and Uruguay doubled (0.87 DID, +157%; 0.32 DID, +152%, respectively), in Venezuela it tripled (1.86 DID, +282%) between 1997 and 2007 (Figure 5). Quinolone use varied 5-fold among Latin American countries in 2007. Again, Venezuela was leading (2.49 DID) and Uruguay (0.53 DID) had the lowest utilization (Figure 5). The use of newer quinolones such as levofloxacin was highest in Venezuela (0.651 DID) and moxifloxacin saw the most use in Mexico (0.104 DID) (Figure 6).

DISCUSSION

There is substantial variation in the total antibiotic utilization rate and trends among Latin American countries between 1997 and 2007, with a ratio of 2.4 between the highest and the lowest consumption in 2007. Although this study cannot provide evidence on the determinants of this variation, evidence from intracountry studies (22, 23) indicates that socioeconomic factors play a role. For example, our results suggest that the economic crisis in Argentina—and the subsequent collapse of public health services (24)—between 2001 and 2003 was associated with substantial decreases in antibiotic utilization. Policy changes are also forces whose effects can be examined with these data. In Chile in 1999, the implementation of regulatory enforcement prohibiting sales of all antibiotics without a prescription in retail pharmacies, along with a mass media campaign, ap-

TABLE 1. Changes in antibiotic utilization in eight Latin American countries, 1997–2007

Country	Antibiotic utilization, 1997 (DID) ^a	Antibiotic utilization, 2007 (DID)	Change in utilization 1997–2007 (DID)	Percent change with respect to average change ^b	Minimum annual utilization 1997–2007 (DID)	Maximum annual utilization 1997–2007 (DID)
Argentina	14.37	16.64	+2.26	+111.2	8.11	16.64
Brazil	6.51	7.01	+0.50	−53.3	5.27	7.01
Chile	14.07	12.53	−1.53	−243.0	9.30	14.42
Colombia	12.17	8.07	−4.10	−483.2	8.07	12.17
Mexico	15.69	13.26	−2.43	−327.1	12.97	15.93
Peru	7.91	13.50	+5.58	+421.5	7.35	13.50
Uruguay	5.43	8.90	+3.48	+225.2	3.93	8.99
Venezuela	11.18	15.99	+4.81	+349.5	10.36	15.99
Latin American average	10.92	11.99	+1.07			

^a DID, defined daily dose per 1 000 inhabitants per day.

^b Average change in utilization, 1.07 DID.

FIGURE 2. Antibiotic utilization in eight Latin American countries, by therapeutic class, 2007

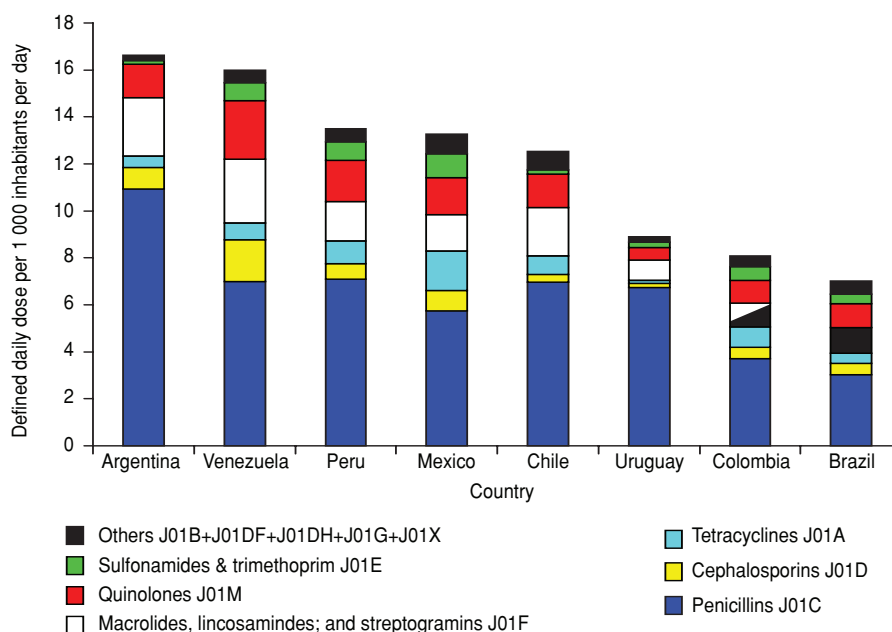


FIGURE 3. Utilization of macrolides, lincosamides, and streptogramins in eight Latin American countries, 1997–2007

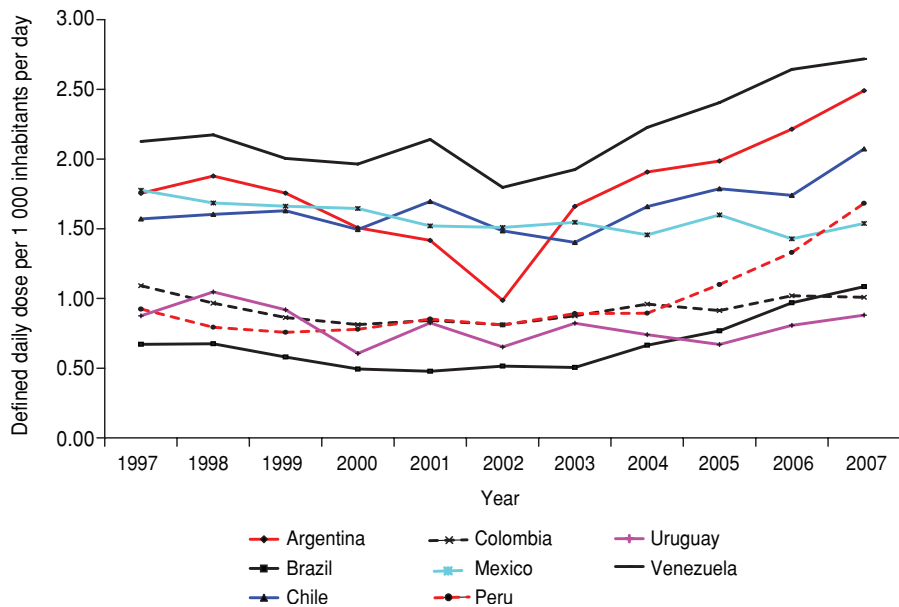
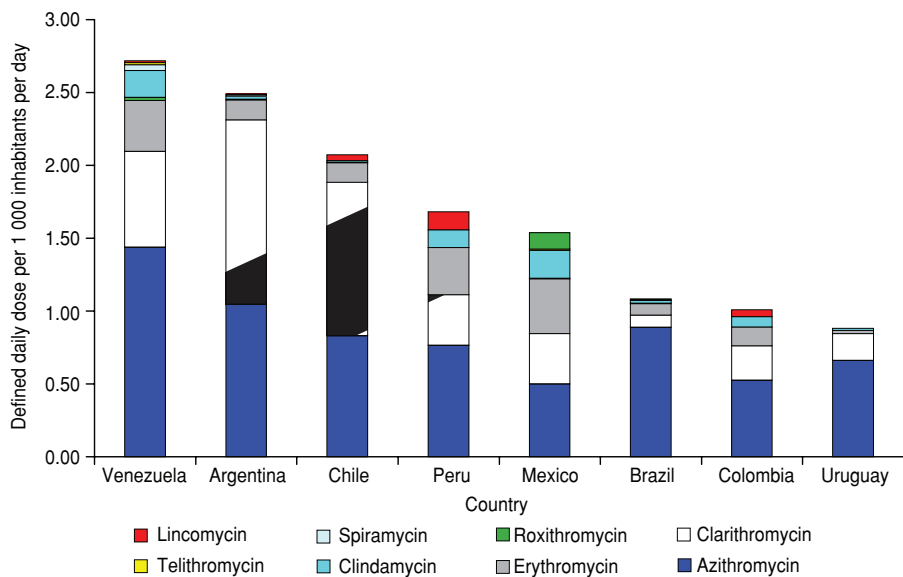


FIGURE 4. Utilization of macrolides, lincosamides, and streptogramins in eight Latin American countries, 2007



peared to have major effects (25). Although the initial success of this policy change on antibiotic use has been previously reported, our results show that these improvements appear to have been short-lived and that the greatest impact of this policy occurred shortly after its introduction and during the next two years. Unfortunately, antibiotic utilization rates have increased steadily since 2002—returning to levels close to the baseline in 1997. In contrast to Chile, reg-

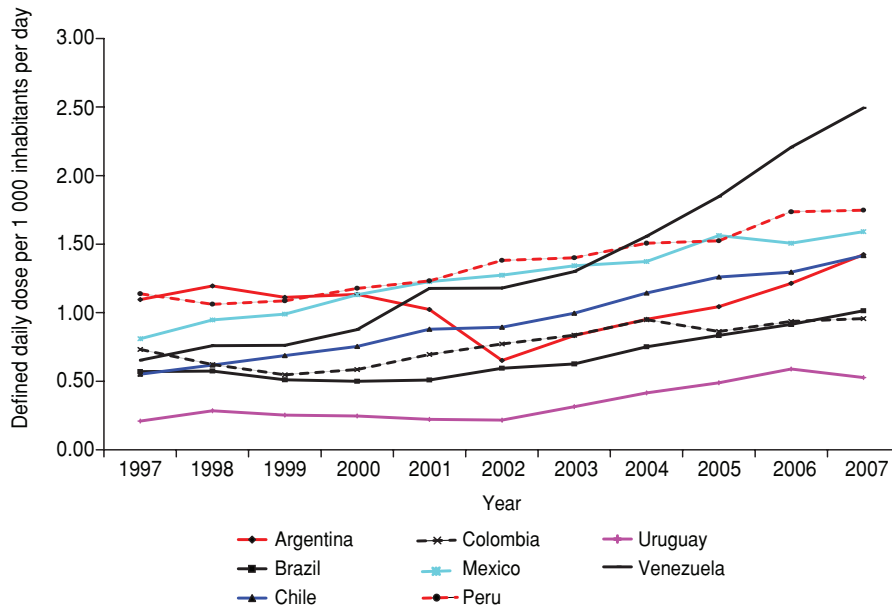
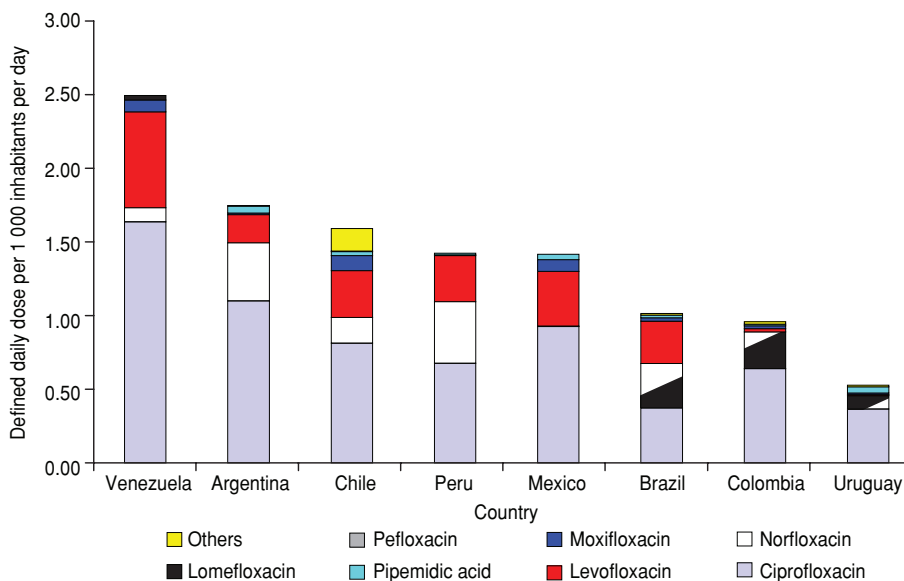
ulatory enforcement prohibiting the sales of certain antibiotics without a prescription in Venezuela in early 2006 (26) does not appear to have had any short-term impact on overall antibiotic utilization.

What these data cannot tell us, however, is how much of a given country's rate of antibiotic use reflects overuse, underuse, and appropriate use. For instance, in the case of large increases in antibiotic utilization that have occurred in Peru, Venezuela, and Uruguay, have

health care reforms contributed to the change in utilization by improving access to medicines via the public sector—that is, increases in antibiotic utilization that might be totally appropriate? Nonetheless, understanding the utilization pattern and its trends can allow for more focused interventions or policy changes on improving antibiotic use and containing antibiotic resistance to be developed, as well as for assessing the impact of such interventions or policy changes. For example, evidence about increasing community antibiotic use was among the main forces to trigger the development of nationwide interventions in France and in Chile (7, 25). The large increase in Uruguay and the large decrease in Colombia observed in our study warrant further scrutiny. The data also underline the need to be observant of the antibiotic-resistance patterns that could arise after the increasing consumption of some therapeutic classes, particularly macrolides and quinolones.

Although we have based this report on data that represent the industry standard, there are significant limitations that one should consider. For each Latin American country in this study, there are no regularly collected, reliable data on the percentage of the population that obtains medicines through the retail (or government) sector. People with government-sponsored insurance may purchase retail antibiotics because of convenience and lack of supply in their government-sponsored program (27, 28). Conversely, some people without insurance obtain their medication from government institutions (which run their own pharmacies) that provide medication access to the poor. To address this limitation, we extrapolated utilization rates for the retail sector to the entire population for each country based on the proportion of a given country's total medication market volume that was distributed via retail sector with data provided by the health care consultancy organization. This adjustment was most relevant for three countries (Mexico, Peru, and Colombia); for the other five countries in our study, the pharmaceutical retail volume covers more than 80% of the total sales volume in the country.

Although the WHO ATC/DDD system is the leading consensus method to assess and compare antibiotic use, having been used widely for benchmarking and evaluating the impact of interven-

FIGURE 5. Quinolone utilization in eight Latin American countries, 1997–2007**FIGURE 6. Quinolone utilization in eight Latin American countries, 2007**

tion studies (18), there are several limitations one must consider. The DDD as a technical unit does not reflect actual treatment dose or length of therapy prescribed (19). In addition, the DDD system cannot be applied to children, because it relates to an average adult weight (17). Consequently, in many studies, liquid oral antibiotic preparations (intended for children) are excluded from the numerator. When children's preparations are considered (as

in our study), it has been inferred that consumption is greater than what was estimated (15). In addition to oral preparations, we included injectable preparations because they make up a considerable amount of total consumption. It is known that sales data are not equivalent to consumption as products purchased by pharmacies or by consumers might expire without having been taken; however, the information has been widely used as a proxy measure

for medicine utilization at the population level.

Our study analyzes utilization at the population level but did not account for differences in income or insurance coverage, which have been identified as factors influencing utilization in European countries (9, 10). We found no clear association between country income level or insurance coverage and antibiotic consumption, except that the reduced income during the economic crisis in Argentina seems a very likely explanation for the reduced utilization between 1999 and 2003. More research is necessary to determine factors that can explain variations in antibiotic use in Latin America. Finally, in this study we do not present any correlation between antibiotic utilization and resistance patterns, which will be the subject of a separate analysis.

Conclusion

The substantial intercountry variation and increase in antibiotic consumption between 1997 and 2007 tie well into findings of escalating antibiotic resistance in Latin America (29), which are being fueled by a combination of forces acting in concert: physicians who frequently prescribe antibiotics when they are not necessary, the public that demands antibiotics from doctors when they are not necessary or purchases antibiotics without a prescription, pharmacy staff inadequately trained to give sound advice for over-the-counter antibiotic purchases, and governments that have no political will or economic resources for enforcing policies prohibiting antibiotic sales without a prescription and implementing interventions to improve antibiotic use (11, 30–32). The European Union is funding ESAC, which aims to create policy-relevant evidence by analyzing and comparing antimicrobial consumption patterns across Europe (33). A similar agency in Latin America would be important to foster policies aimed at improving appropriate use of antibiotics.

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RESUMEN**Tendencias en el consumo de antibióticos en ocho países latinoamericanos entre 1997 y 2007**

Objetivo. Describir las tendencias en el consumo de antibióticos en ocho países latinoamericanos entre 1997 y el 2007.

Métodos. Se analizaron los datos de las ventas al por menor de antibióticos orales e inyectables (Código J01 de la clasificación anatómica, terapéutica y química [ATC] de la Organización Mundial de la Salud [OMS]), entre 1997 y el 2007, en Argentina, Brasil, Chile, Colombia, México, Perú, Uruguay y Venezuela. Se consolidaron los datos correspondientes a todos los antibióticos y se calculó el consumo de todos los antibióticos (J01); los macrólidos, lincosamidas y estreptograminas (J01 F); y las quinolonas (J01 M). Las ventas de cada antibiótico expresadas en kilogramos se convirtieron en dosis diarias definidas por 1 000 habitantes por día (DHD), según el sistema de clasificación anatómica, terapéutica y química de la OMS. Calculamos la variación absoluta de los valores de las DHD y la variación relativa, expresada en porcentaje de variación de las DHD, adoptando como referencia los datos correspondientes a 1997.

Resultados. El consumo total de antibióticos ha aumentado en Perú, Venezuela, Uruguay y Brasil, observándose los mayores incrementos relativos en Perú (5,58 DHD, +70,6%) y Venezuela (4,81 DHD, +43,0%). En México (-2,43 DHD; -15,5%) y Colombia (-4,10 DHD; -33,7%), el consumo ha disminuido. En Argentina y Chile se observaron grandes reducciones en el consumo de antibióticos a mediados de este período. En todos los países, aumentó el consumo de quinolonas, de forma particularmente pronunciada en Venezuela (1,86 DHD, +282%). El mayor aumento del consumo de macrólidos, lincosamidas y estreptograminas se observó en Perú (0,76 DHD, +82,1%), seguido de Brasil, Argentina y Chile.

Conclusiones. El análisis del consumo de antibióticos en América Latina plantea una serie de retos. Es preciso obtener datos probatorios sobre las pautas de consumo de fármacos antimicrobianos que sean pertinentes para la formulación de políticas con objeto de fomentar las que estén orientadas hacia un uso más apropiado de los antibióticos en la Región.

Palabras clave

Farmacoepidemiología; agentes antibacterianos; farmacorresistencia microbiana; política nacional de medicamentos; América Latina.