

Physicians' responsibility for antibiotic use in infants from periurban Lima, Peru

Lucie Ecker,¹ Liset Olarte,² Gustavo Vilchez,¹ Theresa J. Ochoa,²
Isabel Amemiya,¹ Ana I. Gil,¹ and Claudio F. Lanata¹

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ABSTRACT

Objective. To describe the use of antibiotics in Peruvian children under 1 year in a setting where they are available without a prescription.

Methods. Data were analyzed from a cohort study between September 2006 and December 2007 of 1 023 children < 2 months old in periurban Lima, Peru, followed until they were 1 year old.

Results. Seven hundred seventy of 1 023 (75.3%) children took 2 085 courses of antibiotics. There were two courses per child per year (range 0–12). Higher rates of antibiotic use were found in children 3–6 months old (37.2%). Antibiotics were given to children for 8.2% of common colds, 58.6% of all pharyngitis, 66.0% of bronchitis, 40.7% of diarrhea, 22.8% of dermatitis, and 12.0% of bronchial obstructions. A physician's prescription was the most common reason for antibiotic use (90.8%). Medication use without a prescription was found in 6.9% of children, and in 63.9% of them it was preceded by a physician's prescription.

Conclusions. Infants are often exposed to antibiotics in this setting. Overuse of antibiotics is common for diagnoses such as pharyngitis, bronchitis, bronchial obstruction, and diarrhea but is typically inappropriate (83.1% of courses) based on the most common etiologies for this age group. Interventions to improve the use of antibiotics should focus on physicians, since a physician's prescription was the most common reason for antibiotic use.

Key words

Anti-bacterial agents; infant; drug resistance, microbial; inappropriate prescribing; Peru.

Antibiotics are important weapons for fighting infections. Since they were discovered, they have significantly reduced child mortality and increased life expectancy. Worldwide, they are the most commonly prescribed drugs for children, especially for acute respiratory illnesses and diarrhea (1–4). Increasing antibiotic resistance is usually attributed to overuse and misuse of antibiotics

(5–7); it has been estimated that use is unnecessary in 20%–50% of the courses (8–10). Unfortunately, misuse of antibiotics is causing the emergence of resistant pathogens early in life, especially in the developing world where antibiotics are available without prescriptions (3, 11–17). But misuse of antibiotics and the emergence of antibiotic resistance is not confined to developing countries; the increase in resistant pathogens is spreading worldwide (11, 17, 18).

Patterns of greater resistance to antibiotics necessitate the use of newer and

more expensive drugs in order to control infections; this pattern increases health care inequalities (11) and may contribute to higher risk of morbidity and mortality in small infants treated for serious infections in the developing world. In Peru, several studies have shown patterns of high resistance in respiratory bacteria and enteropathogens in children, probably due to abuse and misuse of antibiotics (12, 13, 15, 19–21). Since the pediatric population has the highest rates of antibiotic prescribing in primary care (1, 2), it is a recognized target group for inter-

¹ Instituto de Investigación Nutricional, Lima, Peru. Send correspondence to: Lucie Ecker, lecker@iin.sld.pe

² Universidad Peruana Cayetano Heredia, Lima, Peru.

ventions that aim to reduce unnecessary use of antibiotics.

In Peru, several drugs, including antibiotics, can be bought without a prescription in all pharmacies. It has been assumed that the availability of antibiotics without a prescription has been the main cause of antibiotic misuse in the developing world (22–26). However, several studies show high rates of inappropriate medical prescriptions as an important cause of misuse of antibiotics (16, 18, 27).

Few data are available on antibiotic use in children from the developing world; there is scant information on antibiotic use in infants in Peru. This study aims to describe the use of antibiotics in Peruvian infants, showing the dimensions and characteristics of the problem in order to identify possible targets for future interventions.

METHODS

Study design

This descriptive cohort study used prospectively recorded data from the clinical records of 1 066 children participating in a clinical trial that evaluated the safety of a new hexavalent vaccine³ and data from a passive diarrhea surveillance study of the same cohort in Lima, Peru (28). Secondary data were analyzed by reviewing 1 023 medical records of the 1 066 children who participated in the original study.

During the original study 1 066 children < 2 months old were enrolled and followed until they were 12 months old. At enrollment, previous drug use of the child was recorded in the clinical record. They had scheduled visits and could attend the clinic when they were ill, and the study physician provided treatment advice. This arrangement provided better access to medical care than is available to the average child in Lima, since it was a cost-free service. However, parents of children participating in the trial had to buy the medications as opposed to what happens at health facilities where many receive them for free. The provision of any drug during the

trial was not considered a benefit for the original study.

Six physicians worked during the study; all of them were general physicians. A history of children’s previous illnesses and drug use from birth to enrollment were recorded in the medical record as well as a detailed history of illness, prescribed drug use, and treatment offered at home by the parents between scheduled visits.

Analysis

Diagnoses were grouped as upper respiratory tract infections (URTIs), including pharyngitis, common colds, and otitis, and lower respiratory tract infections (LRTIs), which included bronchitis and pneumonia. Analyses used data for antibiotic courses, even if more than one antibiotic was prescribed for some diagnoses. For the purpose of analysis and according to the most likely etiological agents in this age group (< 12 months old), use of antibiotics was considered inappropriate for the following diagnoses: pharyngitis, common colds, bronchitis, bronchial obstruction, diarrhea (excluding dysentery), and dermatitis (29). Antibiotic use data were analyzed with STATA 10 statistical packages.

Ethical considerations

The study was presented and approved by the Ethical Review Board of the Instituto de Investigación Nutricional (resolution number 281-2009). As this study was a secondary data analysis study, which used data from medical records, informed consent was not needed.

RESULTS

Between September 2006 and December 2007, 1 023 children were followed from 2 to 12 months of age. Fifty-five of the children were lost to follow-up and their use of antibiotics only during the period before they were lost to follow-up was analyzed. There were 15 344 medical visits during the study period at the clinic. Of those visits, 5 886 (38.4%) were scheduled and 8 636 (56.3%) were because the child was ill. Of the 8 636 diagnoses, 2 020 (23.4%) had a recorded use of antibiotics; 58.6% of all pharyngitis, 66.0% of bronchitis, and 40.7% of diarrheas were treated with antibiotics (Table 1). Seven hundred seventy chil-

TABLE 1. Diagnoses for which 2- to 12-month-old children received antibiotic treatment, periurban Lima, Peru, 2006–2007

Diagnosis	n	Received antibiotics	
		No.	%
Conjunctivitis	110	106	96.4
Skin infection	80	72	90.0
Otitis media	47	39	83.0
Pneumonia	36	24	66.7
Bronchitis	241	159	66.0
Urinary tract infection	36	22	61.1
Pharyngitis	1 042	611	58.6
Diarrhea	1 096	446	40.7
Dermatitis	574	131	22.8
Bronchial obstruction	1 386	166	12.0
Common cold	2 528	208	8.2
Other	1 460	35 ^a	2.4
Not specified	822	1	0.1
All diagnoses	8 636	2 020	23.4

^a Other diagnoses include other skin diseases (12 cases), allergic rhinitis (9 cases), meconium aspiration (1 historical case), viral pneumonia (2 cases), external otitis (2 cases), nonspecific symptoms (5 cases), meningitis (1 case), bronchiolitis (1 case), parasitosis (1 case), and sinusitis (1 case).

dren (75.3%) took at least one course of antibiotics during their first year of life: 243 children took only one course of antibiotics (31.6%), 194 took two courses (25.2%), 142 took three courses (18.4%), and 191 (24.8%) took more than four courses of antibiotics before they were 12 months old. The incidence of antibiotic use in the first year of life was two courses per child per year (range 0–12). Children took a total of 2 085 courses of antibiotics (Table 2). A physician’s prescription was the most common reason for antibiotic use (90.8%).

Physicians were responsible for 1 894 courses (90.8%) of antibiotics. Medication provided by parents was documented in only 6.9% (Table 2), where no record of a prescription from a nurse or a pharmacist was found in the medical records. From 144 courses of parent-provided antibiotics, 92 (63.9%) were preceded by an antibiotic prescription from a physician; 44 of those children (30.6%) received the same antibiotic they had taken previously. Parents used antibiotics without a prescription mainly for diagnoses like common colds (32.6%) and diarrhea (20.8%), while physicians prescribed antibiotics mainly for children with pharyngitis (31.1%) and diarrhea (21.1%) (Table 2).

Children started antibiotic use as early as 9 days of age. The mean age of us-

³ Macias M, Lanata CF, Zambrano B, Gil AI, Ame-miya I, Mispireta M, et al. Safety and immunogenicity of an investigational fully liquid hexavalent DTaP-IPV-Hep B-PRP-T vaccine at 2, 4, 6 months of age compared to licensed vaccines in Latin America [unpublished work]. 2011.

TABLE 2. Number of antibiotic courses used due to physician's prescription and without medical advice in 2- to 12-month-old children from periurban Lima, Peru, 2006–2007

Diagnosis	n	Responsible for prescription					
		Physician		Parents		Unknown	
		No.	%	No.	%	No.	%
Common cold	214	159	74.3	47	22.0	8	3.7
Pharyngitis	616	589	95.6	22	3.6	5	0.8
Otitis media	39	37	94.9	2	5.1	0	0.0
Bronchitis	166	157	94.6	8	4.8	1	0.6
Bronchial obstruction	166	138	83.1	19	11.4	9	5.4
Pneumonia	33	32	97.0	1	3.0	0	0.0
Diarrhea	464	418	90.1	30	6.5	16	3.4
Urinary tract infection	24	23	95.8	0	0.0	1	4.2
Skin Infection	80	77	96.3	2	2.5	1	1.3
Dermatitis	132 ^a	126	95.5	5	3.8	1	0.8
Conjunctivitis	110 ^b	106	96.4	1	0.9	3	2.7
Other	40 ^c	32	80.0	6	15.0	2	5.0
Unknown	1	0	0.0	1	100.0	0	0.0
All diagnoses	2 085	1 894	90.8	144	6.9	47	2.3

^a Topical route of administration 86.6%.^b Topical route of administration 81.0%.^c Other antibiotic courses by diagnoses include other skin diseases (12 courses), allergic rhinitis (9 courses), viral pneumonia (3 courses), nonspecific symptoms (5 courses), external otitis (3 courses), meningitis (3 courses), meconium aspiration (2 historical courses), bronchiolitis (1 course), parasitosis (1 course), and sinusitis (1 course).

age was 6.5 months. Higher rates of antibiotic use were found in children 3–6 months old (776 courses, 37.2%) and 6–9 months old (645 courses, 30.9%). Lower rates of use were found in children younger than 3 months of age (215 courses, 10.3%) and older than 9 months of age (449 courses, 21.5%).

The leading diagnoses accounting for antibiotic use in children < 3 months of age were URTI (40.5%) and other diagnosis (34.0%) (with 39.7% of them for dermatitis and 34.2% for conjunctivitis). In children > 3 months of age, the most common diagnoses that received an antibiotic were URTI and diarrhea (3–6 months, 43.8% and 21.8%, respectively; 6–9 months, 39.7% and 27.3%, respectively; and older than 9 months, 41.4% and 20.9%, respectively).

The most frequently used antibiotics are shown in Table 3. Penicillins (687 courses, 33.0%) were most commonly used, followed by macrolides (488 courses, 23.4%), particularly erythromycin (64.5%) and azithromycin (31.4%); trimethoprim-sulfamethoxazole (TMP-SMX) was used in 15.1% of courses. Penicillins (38.6%) were used most commonly in children < 3 months old, and macrolides (30.5%) were used most commonly in children > 9 months old (Figure 1).

URT and LRTI were treated preferentially with penicillins (56.4% and 48.7%, re-

spectively), macrolides (19.2% and 21.6%, respectively), and TMP-SMX (19.8% and 14.6%, respectively). Diarrhea was treated mainly with macrolides (49.6%), nitrofurans (24.8%), and TMP-SMX (17.2%) (Figure 2).

Antibiotic usage rates were significantly higher in males (56.4%, $P = 0.001$). Events associated with antibiotic use were mostly mild (89.2%); events of moderate and severe intensity were rare (8.8% and 1.8%, respectively), and

three events had no registered intensity. Route of administration was mainly oral (84.4%); less frequently used routes were topical (12.2%) and intravenous or intramuscular (3.4%). Topical routes included dermal (59.2%), ophthalmic (40.4%), and otic (0.4%). In 477 courses of antibiotic use, data were available for total days of use. Mean duration of antibiotic use was 5.7 days (standard deviation 2.1 days).

According to the diagnoses present and the most common etiologies for this age group (< 12 months old), 83.1% of the antibiotics prescribed were inappropriate. Antibiotics are inexpensive in this setting. The average total cost was about \$1 798 (U.S. dollars), or \$1.80 per child per year during the first year of life.

DISCUSSION

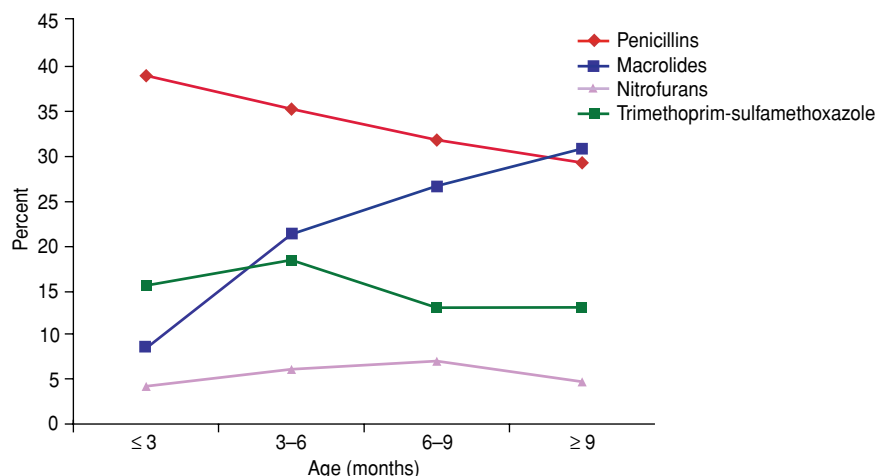
This study offers strong evidence of antibiotic overuse in small children, showing that infants from periurban Lima are commonly exposed to antibiotics. Among children < 12 months old, 75.3% received at least one antibiotic course, which is much higher than the proportion of children < 5 years old making ambulatory care visits in the United States of America, Canada, North-Central Europe, and Italy, where preschool children had a reported prevalence of antibiotic therapy of 72% (18). The antibiotic prescription rate reached two courses per child per year in children < 1 year old; this rate appears to be higher than that reported in the United States (0.9 course per child per year in

TABLE 3. Percentage of antibiotics used, by diagnosis, in 2- to 12-month-old children from periurban Lima, Peru, 2006–2007

Antibiotic	URT (n = 869)	LRT (n = 199)	Diarrhea (n = 464)	Bronchial obstruction (n = 166)	Other ^a (n = 387)	All diagnoses (n = 2 085)
Penicillins	56.4	48.7	1.9	44.6	4.4	33.0
Cephalosporins	3.7	10.1	0.7	11.5	5.7	4.6
Macrolides	19.2	21.6	49.6	25.3	1.6	23.4
Aminoglycosides	0.1	3.0	2.6	0.0	58.9 ^b	11.9
Quinolones	0.1	0.0	2.6	0.6	2.8	1.2
Nitrofurans	0.4	0.0	24.8	0.0	1.0	5.9
TMP-SMX	19.8	14.6	17.2	17.5	1.3	15.1
Other antibiotics ^c	0.4	2.0	0.7	0.6	24.3	5.0

Note: URTI: upper respiratory tract infection, LRTI: lower respiratory tract infection, TMP-SMX: trimethoprim-sulfamethoxazole.^a Other diagnoses included urinary tract infection (n = 24), skin infection (n = 80), dermatitis (n = 132), conjunctivitis (n = 110), other skin diseases (n = 12), allergic rhinitis (n = 9), viral pneumonia (n = 3), nonspecific symptoms (n = 5), external otitis (n = 3), meningitis (n = 3), meconium aspiration (n = 2, historical courses), bronchiolitis (n = 1), parasitosis (n = 1), sinusitis (n = 1), and not specified diagnosis (n = 1).^b 94.7% used topically to treat skin diseases and conjunctivitis.^c Other antibiotics include oxacillin and dicloxacillin (62 courses), neomycin (23 courses), oxytetracycline (5 courses), metronidazole (4 courses), chloramphenicol (4 courses), clindamycin (2 courses), sulfacetamide (2 courses), sulfadiazine (1 course), lincomycin (1 course), and vancomycin (1 course).

FIGURE 1. Percentage of antibiotics used in 2- to 12-month-old children, periurban Lima, Peru, 2006–2007 (≤ 3 months, $n = 215$ courses; 3–6 months, $n = 776$ courses; 6–9 months, $n = 645$ courses; and ≥ 9 months, $n = 449$ courses)



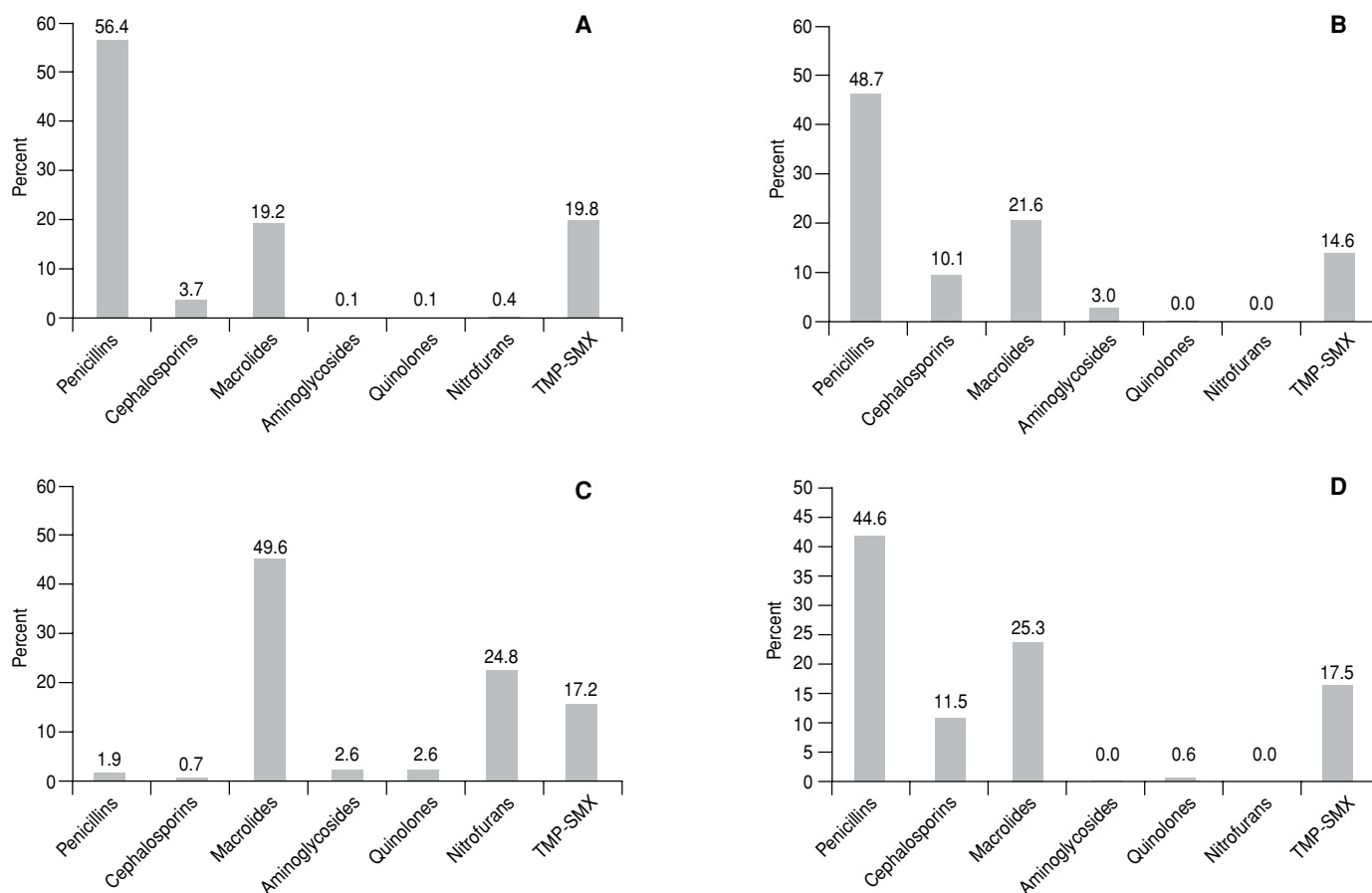
children 3–18 months old) and in Sweden and Germany (0.8 course per child per year in children < 6 years old) (18).

These rates may be higher because of the younger age selection compared with the cited studies. If this trend continues,

the development of resistant pathogens at early ages is a serious risk.

In many countries in the developing world, like Peru, antibiotics are sold in pharmacies without need for a medical prescription (26). Generally, it has been assumed that the availability of antibiotics without a medical prescription leads to higher rates of self-medication (23–26). However, physicians were responsible for almost all the antibiotic use in this setting (90.8% of antibiotic use), as in the developed world (1, 6, 7, 18), and data show that antibiotic use without a prescription was preceded by an antibiotic prescription from a physician in 63.9% of the cases. This rate is higher than that found in the urban community of Yurimaguas in the Amazonian area of Peru, where antibiotics used were prescribed by physicians in 70% of the cases (16). In other developing countries of South America, physicians recommended 54% of these antibiotics (24). The authors strongly believe

FIGURE 2. Percentage of antibiotic classes^a used to treat 2- to 12-month-old children from periurban Lima, Peru, 2006–2007, for upper respiratory tract infection (A) ($n = 869$), lower respiratory tract infection ($n = 199$) (B), diarrhea ($n = 464$) (C), and bronchial obstruction ($n = 166$) (D)



^a TMP-SMX = trimethoprim-sulfamethoxazole.

that physicians have the responsibility to explain why antibiotics are not needed, and this study shows that parents follow a physician's recommendation for antibiotic use; however, they are also learning how to reuse antibiotic prescriptions for their children at very early ages. This fact gives responsibility for antibiotic use to physicians, probably due to a deficient explanation of antibiotic usage.

As in other studies, the most frequently used antibiotics were penicillins (32.9%) (2, 18, 27). The second most commonly used antibiotics were macrolides (23.4%). TMP-SMX (15.1%) was next most common, in contrast to data from other studies in the developing world but following the trend of antibiotic use in developing countries (18). Macrolides were used more frequently in children > 9 months old and in children with diarrhea, which is probably due to higher diarrheal rates among older children.

Proper use of antibiotics was found in diagnoses like skin infections, pneumonias, otitis media, and urinary tract infections. Only 8.5% of all common cold diagnoses received antibiotic treatment. According to diagnoses and usual etiologies in this age group, 83.1% of the antibiotics prescribed were inappropriate (29), leading to unnecessary early exposure of children to drugs. The fact that physicians made diagnoses that are rare among infants, like bronchitis and pharyngitis, speaks to their inexperience with children. Statistics of the Ministry of Health confirm that > 93% of pediatric primary care units have only general physicians in these settings (30, 31).

Antimicrobial resistance is a great challenge, and it is related to the high intake of antibiotics, to the use of inappropriate doses, and to the inappropriate choice of an antibiotic for a given infection. Several studies show that recent an-

tibiotic use raises the risk for developing infection or colonization with resistant bacterial pathogens (7, 32, 33). This study shows excessive and inappropriate use of antimicrobials for infections that have mainly viral etiologies, which probably was part of the cause of the high antibiotic resistance found in diarrheagenic *Escherichia coli* from stool samples in this study (19); the diarrheagenic *E. coli* as a group showed resistance to ampicillin, cotrimoxazole, tetracycline, and gentamicin. Thirteen percent of strains showed intermediate resistance to nitrofurantoin among diarrheal samples. Multidrug resistance (resistance to three or more antibiotics) was common in diarrheal (63%) and control samples (51%).

Many studies have addressed antibiotic use, but few studies have recorded antibiotic use data within a cohort (24). This cohort study assembled detailed data on antibiotic use during the first year of life of a large number of participants. However, this study is limited because findings cannot be generalized to all children in this periurban community. Even though data were gathered on antibiotic prescriptions outside the study, most treatments were at the study clinic, limiting the study to one clinic with a few physicians. One can only infer that physicians at the study clinic acted similarly to others in the study area. Since the study children clearly had better access to medical care than the average child in this poor setting around Lima, it is impossible to assess how many parents would have purchased an antibiotic if they had to pay for the visit. However, around 50% of the children had free access to state health facilities because of their financial condition and around 13% had free access to insurance health facilities. Medical visits in these settings can cost around \$2.00, which is affordable

for most residents. Parents may have underreported antibiotic use without a prescription, since no active surveillance at home was performed. Physicians may have reported diagnoses in a biased manner, which would likely lead to a wrong estimation of antibiotic prescribing diagnoses. Moreover, no data were recorded on the advice of pharmacists or relatives for antibiotic use in the medical records of the children studied. Specific information about prescriptions by non-doctors (medical students, pharmacists, and relatives or friends) is also lacking. A complementary investigation in community and primary health facilities is needed to add to this assessment.

In summary, children in this setting receive early and frequent antibiotics. Inappropriate use of antibiotics in children < 12 months old is very common, especially for respiratory infections and diarrhea, with a risk for the development of resistant pathogens. The type of antibiotics used follows the trend of antibiotic use in developing countries. It seems that parents seek medical advice before using antibiotics without a prescription and physicians were responsible for antibiotic use in these children more often than in other studies from the developing world. This study offers strong evidence that parents follow physicians' recommendations for antibiotic use in their children, and this finding suggests that interventions need to focus on physician education in order to reduce inappropriate antibiotic use.

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RESUMEN

Responsabilidad del médico en el uso de antibióticos en niños menores de 1 año de zonas periurbanas de Lima, Perú

Objetivo. Describir el uso de antibióticos en niños de 2 a 12 meses de edad en entornos donde estos medicamentos se pueden obtener sin prescripción.

Métodos. Se analizaron los datos de un estudio de cohorte efectuado entre septiembre del 2006 y diciembre del 2007 en 1 023 niños menores de 2 meses de la zona periurbana de Lima, Perú, cuyo seguimiento se realizó hasta el año de edad.

Resultados. De los 1 023 niños, 770 (75,3%) tomaron 2 085 tandas de tratamiento antibiótico. Se registraron dos tandas por niño por año (rango 0–12). Las tasas más elevadas de uso de antibióticos se encontraron en los niños de 3 a 6 meses (37,2%). Los niños recibieron antibióticos para 8,2% de los resfriados comunes, 58,6% de las faringitis, 66,0% de las bronquitis, 40,7% de las diarreas, 22,8% de las dermatitis y 12,0% de las obstrucciones bronquiales. La prescripción de un médico fue la razón más frecuente para el uso de antibióticos (90,8%). Se comprobó el uso de medicamentos sin prescripción en 6,9% de los niños, y en 63,9% de ellos este fue precedido por una prescripción médica.

Conclusiones. En el entorno estudiado, los niños menores de 1 año a menudo están expuestos a los antibióticos. El abuso de los antibióticos es frecuente ante enfermedades como faringitis, bronquitis, obstrucción bronquial y diarrea, pero por lo general es inadecuado (83,1% de las tandas de tratamiento antibiótico) según las etiologías más comunes en este grupo etario. Las intervenciones dirigidas a mejorar el uso de los antibióticos deben concentrarse en los médicos, ya que la prescripción médica fue la razón más común para el uso de antibióticos.

Palabras clave

Agentes antibacterianos; lactante; resistencia a medicamentos; prescripción inadecuada; Perú.