Antibiotic Use and Stewardship Practices in a Pediatric Community-Based Cohort Study in Peru: Shorter Would be Sweeter

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Short Title: Antibiotic stewardship in a pediatric cohort
Abstract

Background: There is a need to evaluate antibiotic use, duration of therapy and stewardship in low- and middle-income countries to guide the development of appropriate stewardship programs that are global in scope and effectively decrease unnecessary antibiotic use.

Methods: We prospectively collected information on illness occurrence and antibiotic use from a cohort of 303 children. We evaluated the incidence, duration of therapy and appropriateness of antibiotic prescriptions by five main antibiotic prescribers (physicians and nurses, pharmacists, nursing assistants, self-prescriptions and neighbors or family members).

Results: Ninety percent of children received an antibiotic during follow-up time, and on average, by the end of follow-up a child had spent 4.3% of their first five years of life on antibiotics. The most frequent prescribers were physicians/nurses (79.4%), followed by pharmacists (8.1%), self-prescriptions (6.8%), nursing assistants (3.7%) and family or neighbors (1.9%). Of the 3702 courses of antibiotics prescribed, 30.9% were done so for the occurrence of fever, 25.3% for diarrhea, 2.8% for acute lower respiratory disease, 2.7% for dysentery and 38.2% for an undetermined illness. Courses exceeding the recommended duration were common for the principal diseases for which treatment was initiated, with 27.3% of courses exceeding the recommended length duration, representing a potential reduction in 13.2% of days on which this cohort spent on antibiotics.

Conclusion: Stewardship programs should target medical personnel for a primary care stewardship program even in a context where antibiotics are available to the public with little or no restrictions and appropriate duration should be emphasized in this training.

Key words: antimicrobial stewardship, primary healthcare, outpatient, antibiotic resistance, Iquitos
Background

Antibiotic resistant infections are among the greatest global threats to public health [1, 2]. They are a complex problem that occur due to the misuse of antibiotics in human and veterinary medicine, as well as in the production of livestock. The World Health Organization (WHO) Global Action Plan identifies a need to use an integrative approach to counter the improper use of antibiotics, including the implementation of effective stewardship programs in inpatient and outpatient settings [1, 3]. Human antibiotic prescription predominantly occurs in the outpatient setting, where estimates from the United States show that up to 30% are prescribed erroneously [4], but that appropriate stewardship in this setting can effectively reduce prescriptions [5-7].

However, despite the global misuse of antibiotics, the epidemiology of antibiotic use in most global contexts is poorly studied.

The extension of antimicrobial stewardship to low and middle income countries (LMICs), where the majority of the world’s population resides, is both an obvious necessity and a nascent concern already recognized by the International Disease Society of America [8]. Antibiotics are available without prescription in most of the world and stewardship programs, if they are to be effective globally, must understand usage patterns in diverse contexts [9]. Yet, patterns of prescription have not been well characterized in low-resource settings. Among Latin American countries, by 2007 Peru was situated among the top four countries with highest antibiotic utilization, with 13.50 daily doses per 1000 inhabitants per day (only surpassed by Argentina and Venezuela), representing a 70.6% increase since 1997 [10]. Studies have characterized antibiotic prescriptions at tertiary level hospitals in Peru, showing a reduction of prescriptions as a result of stewardship programs [11]. However, antimicrobial stewardship at the primary health care level remains poorly described, even though that majority of antibiotic exposure occurs in the outpatient setting.
The objective of this study is to characterize antibiotic use to treat dysentery, diarrhea, acute lower respiratory infections (ALRIs), and fever within a community-based birth cohort study in a population living in extreme poverty with access to universal health care. Because individual children were followed over their early life course, the study comprehensively measured antibiotic exposure from both formal and informal health sectors in an unbiased manner. We aimed to delineate who the prescribers of antibiotics were for this cohort of children with the aim of guiding future context specific antimicrobial stewardship interventions.

Methods

Setting, Study Design and Definition of Illnesses

The MAL-ED study was a prospective community-based cohort study conducted in a peri-urban community of Iquitos, Loreto, Peru, between 2012 and 2018. Specific details of the study design, enrollment and surveillance have been described previously [12-14]. Briefly, a total of 303 healthy newborns were enrolled within the first 17 days of life and followed until 5 years of age. Surveillance was conducted two times a week generating a continuous daily history of symptoms and antibiotic usage. Illness episodes were reported by caretakers, observed and recorded by trained health care workers. An illness episode was identified as being separated by at least two symptom-free days. ALRI was identified if the child presented cough or had difficulty breathing and if measured breathing rate was ≥60 breaths/min in children ≤2 months, ≥50 breaths/min in children 2–11 months, and ≥40 breaths/min in children 1–5 years as measured by an average of duplicate measures or lower chest wall indrawing as recommended by the WHO [15, 16]. Diarrhea was defined as more than three loose stools in a 24-hour period, and dysentery was defined as diarrhea in which the mother reported seeing blood [17]. Fever was ascertained by caregiver report. Antibiotic courses were assigned to illness syndromes.
based on the symptoms reported on the day of or immediately prior to the date of course
initiation. Assignment of syndromes to courses were mutually exclusive. The assignment of a
course to ALRI, took precedent to that of fever, dysentery, and diarrhea as per WHO guidelines
regarding attributions for child mortality. The assignment of a course to dysentery, took
precedent to that of diarrhea and undifferentiated fever. Finally, the assignment of a course to
diarrhea took precedent to that of fever. If none of the four syndromes were reported during that
window, courses were assigned to a separate category, undetermined illness. These
predominantly represent less common diagnoses (ear infection, tonsillitis, skin infection, urinary
tract infection), which were annotated as noted by physician and nurses. Mothers reported daily
injectable or oral antibiotics prescribed to the infant, the length of the antibiotic course and who
prescribed it. Fieldworkers asked to visually verify the use of the antibiotic by observing the
antibiotic package or the prescription [18]. Validation of maternal reports has been described
previously [18].

Antibiotic Use Categorization and Definitions

Endpoint definitions are the same as those presented previously [18]. Specifically, the length of
the antibiotic course was defined as the total number of days on which a child received an
antibiotic. A distinct antibiotic course was identified by being separated by two antibiotic-free
days. An antibiotic course taken for an episode of dysentery, fever, diarrhea or an undetermined
illness was considered of standard duration if it lasted between 3 and 5 days (>3 - <=5)
according to national therapeutic guidelines, short if it lasted 3 days or less (<=3) and extended
if it lasted for more than 5 days (>5). An antibiotic courses taken for an episode of ALRI were
considered of standard duration if it lasted between 5 and 7 days (>5 - <=7) according to
national therapeutic guidelines, short if it lasted 5 days or less (<=5) and extended if it lasted
more than 7 days (>7) [19, 20]. Antibiotics were recorded with their specific names and
analyzed as individual variables. Antibiotic prescribers were identified as either 1) medical
doctor or nurse 2) pharmacists, 3) nursing assistant 4) neighbor, family, or friend, and 5) self-prescribed. Additional covariates analyzed included age and sex of the child, maternal primary education completion, and monthly household income (U.S. dollars) recorded at baseline.

Statistical Analysis

Follow-up days are defined as the number of days each child was enrolled and observed within the cohort study. The percent of days a child spent on antibiotics within their first month, more than one month to 6 months, more than 6 months to 12 months and more than 12 months to 60 months was calculated as the number of days receiving an antibiotic as a proportion of the total number of follow-up days. The average percent of follow-up days spent on any antibiotic and the average and total number of courses of antibiotics were calculated for the entire cohort and as prescribed by each specific prescriber. The incidence of antibiotic use was calculated as the number of antibiotic courses per child-year as prescribed by each specific prescriber.

The percent of days a child received antibiotics while experiencing ALRI, diarrhea, dysentery, and fever was calculated. Additionally, the number of antibiotic courses taken, and the number of days spent on an antibiotic for each specific illness were calculated for each specific prescriber. The duration of the length of each antibiotic course was classified as short, standard or extended. The percent of extended number of courses as well as the corresponding percent of additional days on antibiotics as fraction of total follow-up days were calculated for the entire cohort and by each specific prescriber.

Antibiotic use was analyzed as a time-varying repeated binary outcome and occurrences of each illness type as binary time-varying exposures. Odds ratios for the association between the prescription and intake of an antibiotic and the occurrence of illness (ALRI, dysentery, diarrhea, and fever) were modelled using log-binomial model regressions fitted with generalized linear models and robust variance estimation. Final models for each type of illness were adjusted for
age (months), sex, maternal primary education completion (yes/no), and monthly household income, which are factors hypothesized could impact antibiotic purchasing capacity and decision to give them to their children. Statistical analysis was performed in Stata 17.0 (Stata Corp., College Station, TX).

**Ethics Statement**

Formal paternal informed consent was obtained for all children participating in the study. The study was approved by the Ethics committee of Asociación Benéfica Prima, Lima, Peru and the Institutional Review Board of the Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA.

**Results**

A total of 303 children were enrolled and followed for up for 372,199 child-days (median 1501 child-days or 4.1 child-years per child). Overall, the entire cohort of children received 3702 courses of antibiotics representing 16,870 days. A total of 9,109 illness episodes were recorded for the entire cohort. Of these, 29.7% (105/353) of ALRI episodes, 63.5% (99/156) of dysentery episodes, 31.0% (938/3027) of diarrhea episodes and 20.5% (1144/5573) of fever episodes received an antibiotic course. An extra 1416 course of antibiotics were prescribed for undetermined illness.

Out of all children, 273 subjects (90.1%) received at least one antibiotic during follow-up. Overall, by the end of follow-up on average a child had spent cumulatively 4.3% of their first five years of life on antibiotics. Amoxicillin was the most commonly prescribed antibiotic (2.08% of days of follow-up time), followed by erythromycin and trimethoprim-sulfamethoxazole (Table 1).
On average, subjects received a cumulative 3.63 antibiotic courses per year. Physicians and nurses prescribed 79.4% (2941/3702) of the courses received by all children in this cohort, equating to 2.88 antibiotic courses per child-year. The second most common antibiotic prescriber were pharmacies, who prescribed 8.1% (301/3702) of antibiotic courses or 0.3 antibiotic course per child-year, followed by self-prescriptions representing 6.8% (251/3702) of antibiotic courses (0.25 antibiotic courses per child-year), nurse technicians with 3.7% (136/3702) of antibiotic courses (0.13 antibiotic courses per child-year) and neighbors or family members with 1.9% (71/3702) of antibiotic courses (0.07 antibiotic courses per child-year) (Table 2).

Physicians and nurses were the principal prescribers for antibiotic courses prescribed for ALRI (102/105 courses) and dysentery (95/99 courses). For episodes of uncomplicated diarrhea, undifferentiated fever and undetermined illnesses, physicians and nurses prescribed 76.2% (715/938), 83.9% (960/1144) and 75.5% (1069/1416) of the antibiotic courses, respectively (Table 3). Taken together, courses prescribed for uncomplicated diarrhea and undifferentiated fever constituted 56% (2082/3702) of the total number of courses prescribed. Table 4 translates antibiotic courses into days on antibiotics associated for each specific illness and antibiotic prescriber. Specifically, 16,870 days on antibiotics were recorded for the entire cohort, representing 4.5% of total follow-up time.

Figure 1 shows density plots for the duration of antibiotic courses for each illness and prescriber. Out of the 105 antibiotic courses prescribed for ALRI, 59.0% (62/105) were short courses, and 34.4% (36/105) were of standard length. Out of the 99 courses prescribed for episodes of dysentery, 76.8% (76/99) were of short length and 19.2% (19/99) were of standard length. Among courses associated with uncomplicated diarrhea 59.6% (559/938) were short courses and 25.6% (240/938) were of standard length. Among courses associated with undifferentiated fever and undetermined illnesses, 25.0% (286/1144) and 26.6% (377/1416)
were classified as short courses, and 39.9% (456/1144) and 40.9% (579/1416) were classified as standard courses, respectively.

The number of extended courses of antibiotics in comparison to standard and short courses of antibiotics (27.3% (1012/3702)), translated into 2223 extra days on antibiotics, or 13.2% (2223/16870) of the total number of days on which a child received an antibiotic. The number of extended and standard courses of antibiotics in comparison to short courses of antibiotics (63.3% (2342/3702), translated into 6530 extra days on antibiotics, or 38.7% of the total number on which a child received an antibiotic (STable 1 and STable 2.)

Additionally, among the antibiotic courses of extended length for ALRI, dysentery, diarrhea and fever, physicians prescribed 85.7% (6/7), 100% (4/4), 89.9% (125/139) and 92.0% (370/402) of these. These represented 5.9% (6/102) of the ALRI associated courses, 4.2% (4/95) of the dysentery associated courses, 17.0% (125/715) of the diarrhea associated courses and 38.5% (370/960) of the fever associated courses prescribed by physicians or nurses.

Finally, the odds of being prescribed an antibiotic were strongly associated with the occurrence of an episode of ALRI (OR: 15.11 (95% CI: 11.82 - 19.32); p-value <0.001) and dysentery (OR: 26.47 (95% CI: 19.83 - 35.34); p-value <0.001), after adjusting for age, sex, maternal education, and average household income. The equivalent associations with the occurrence of episodes of fever, without diarrhea, ALRI or dysentery ((OR: 6.04 (95% CI: 5.59 – 6.54); p-value <0.001), as well as diarrhea without fever, ALRI dysentery (OR: 5.89 (95% CI: 5.31 – 6.53); p-value <0.001), were observed (Table 5).

Discussion

Most studies in low-resource areas address antibiotic prescriptions at the outpatient setting where physicians and physician assistants are the predominant prescribers [21]. This study is
one of the few that captures data that includes the prescribers that expose children to antimicrobials and the overall diagnosed syndrome, providing highly granular data that has the potential to drive interventions that reduce antibiotic use at the community level. Within a cohort of children in a low-resource community of peri-urban Iquitos, Peru, on average a child had spent 4.3% of their first five years of life on antibiotics. This demonstrates that antibiotic use is intense when measured at the population level, with likely consequences being not only evolutionary pressure towards the development of resistant pathogens but ecologic restriction of the host microbiome.

Although it is often assumed that increased availability of antibiotics to the public creates a situation of unfettered use, little objective data supports this assumption as universal [22]. In this cohort early life antibiotic use was common, with medical personnel as the main prescribers. Other prescribers had limited participation, similarly to previous findings in the Peruvian capital [23, 24]. This is likely a result of universal primary care in Peru and may not reflect the reality in other countries where access to primary care is less available. That said, this study was carried out in one of the most impoverished areas of Latin America and so does provide a valid representation of vulnerable populations in such contexts.

These results provide evidence that interventions that aim to reduce antibiotic prescriptions at the community level should be tailored towards doctors and nurses, who constitute an easier, accessible, and cost-effective target than the non-medical population given that they already have some level of medical training and are easy to reach through professional networks. Additionally, at least 13% of days in which children were on antibiotics could have been prevented if the duration of courses were within the length recommended by national and international standards. Duration of antibiotic therapy is an attractive and feasible target for intervention that has the potential to decrease a considerable burden of antibiotic utilization [25] in settings where rapid diagnostics are likely inaccessible. Prolonged courses of antibiotics, are
at times given with the poorly evidenced rationale that therapy of insufficient duration to
completely clear the infection will result in clinical relapse with a resistant pathogen. The
application of this thinking has entrenched courses of therapy without critical evaluation over
time. Recent evidence suggests that shorter courses for most common syndromes are equally
effective [26, 27].

A survey performed in Lima including 1,200 caregivers of children under the age of 5 concluded
that caregivers tended to respect a decision not to prescribe an antibiotic when it came from a
physician, a decision that in combination with robust stewardship programs can reduce
unnecessary antibiotic use [24]. That said, antibiotic prescriptions by non-medical providers are
still prevalent in this community where over-the-counter antibiotics are attainable [28, 29]. As a
result, including pharmacists in antibiotic stewardship programs should also be evaluated [30].

At least half of the antibiotic courses taken by children were attributed to a case of fever or
uncomplicated diarrhea, showing that a considerable percent of courses could have been
potentially prevented, given that these episodes are likely viral in nature and the intake of
antibiotics is unlikely to have an impact on case resolution [31, 32]. Antibiotic prescriptions for
cases of diarrhea are common in comparable settings, with up to 40% of diarrhea cases treated
with an antibiotic [23]. However, this dataset is limited by the resolution regarding undetermined
illnesses, and as a result appropriateness cannot be evaluated for this category. Additionally,
we are not able to determine the fraction of those illness episodes that sought care but were not
prescribed an antibiotic, unable to discern them from episodes that did not seek any type of
care. Similarly, in previous studies, amoxicillin was the most commonly prescribed antibiotic,
followed by trimethoprim-sulfamethoxazole, erythromycin and ciprofloxacin [29, 33]. These are
all listed by the World Health Organization as essential medicines and their successful use for
the treatment of severe cases of bacterial gastroenteritis is threatened by the emergence of
antimicrobial resistance [2].
Establishing antibiotic stewardship at a global level is a critical requirement to control the emergence of highly resistant pathogens [34]. Appropriate auditing of prescriptions by medical personnel, as well as effective point of care practices such as rapid diagnostic tests, clinical decision support tools and delayed prescriptions are possible and appropriate especially in countries that provide universal health care to large portions of the population [34]. Although it is frequently presumed that antibiotic therapy is initiated by untrained personnel in situations where these drugs are directly available to the public, empiric studies in this and similar contexts suggest that stewardship strategies may not need to differ in strategy as much as has been presumed. The meaningful inclusion of LMICs into stewardship practice has the potential to add the majority of the world’s population to improved practices to contain the emergence of AMR.

**Conclusion**

Physicians are the main antibiotic prescribers within a pediatric community-based cohort in Iquitos, Peru. Antibiotic use was common among the cohort, and highly associated with moderate to severe illness including acute respiratory disease and dysentery. However, during episodes of uncomplicated diarrhea and fever it was also common for children to receive antibiotics. Antibiotic stewardship programs should be implemented at the primary care level and tailored towards the requirements of the community in need based on a baseline evaluation of main providers and use.

**NOTES**

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Potential Conflicts

FS reports payment or honoraria from Universidad Peruana Cayetano Heredia for lecture at undergraduate and graduate level and Universidad Científica del Sur for lecture at undergraduate level. JMC reports grants or contracts outside of the submitted work paid to the university from CDC-U01GH002270 Conducting Integrated Infectious Disease and Public Health Research in Peru, NIH-R03AI158576 Genomic Epidemiology of Campylobacter to Improve Disease Control in Low- and Middle-Income Countries, NIH- R03AI151564-01 Global Geospatial Mapping and Modeling of Household-level Covariates of Infectious Disease Transmission and Child Health, NASA/JHU 16-GEO16-0047 Environmental Determinants of Enteric Infectious Disease: a GEOSS platform for analysis and risk assessment with COVID-19 supplement, BMGF SL12449 Enterics for Global Health (EFGH): Multisite Shigella surveillance
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Tables and Figures

Table 1. Average percent of follow-up days children spent on antibiotics by age category.

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<thead>
<tr>
<th>Any Antibiotic</th>
<th>0-1 month</th>
<th>1-6 months</th>
<th>6-12 months</th>
<th>12-60 months</th>
<th>0-60 months</th>
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<td>Betalactams</td>
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<tr>
<td>Amoxicillin</td>
<td>0.07 (0-0)</td>
<td>0.45 (0-0.5)</td>
<td>0.50 (0-0.71)</td>
<td>1.34 (0.54-1.96)</td>
<td>2.08 (0.82-3.00)</td>
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<td>0.01 (0-0)</td>
<td>0.01 (0-0)</td>
<td>0.02 (0-0)</td>
<td>0.05 (0.0-0.0)</td>
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<tr>
<td>Ceftriaxone</td>
<td>0.01 (0-0)</td>
<td>0 (0-0)</td>
<td>0.01 (0-0)</td>
<td>0.02 (0-0)</td>
<td>0.05 (0.0-0.0)</td>
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<tr>
<td>Dicloxacillin</td>
<td>0.01 (0-0)</td>
<td>0.02 (0-0)</td>
<td>0.03 (0-0)</td>
<td>0.2 (0-0.29)</td>
<td>0.20 (0.0-0.32)</td>
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<td>Penicillin</td>
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<td>0.08 (0-0)</td>
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<td>0.3 (0-0.41)</td>
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<td>-</td>
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<td>0.59 (0.0-0.72)</td>
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<td>-</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
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<td>-</td>
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<tr>
<td>Nitrofurans</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furoxazolide</td>
<td>-</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0.08 (0-0)</td>
<td>0.07 (0.0-0.0)</td>
</tr>
<tr>
<td>Nitroimidazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>-</td>
<td>0 (0-0)</td>
<td>0.01(0-0)</td>
<td>0.29 (0-0.41)</td>
<td>0.25 (0.0-0.34)</td>
</tr>
</tbody>
</table>

IQR = Interquartile Range; (-) = no antibiotics received for the specific age category
Table 2. Incidence of antibiotic courses taken per child year, average number of antibiotic courses and average percent of follow-up days a child spent on antibiotics by antibiotic prescriber.

<table>
<thead>
<tr>
<th>Source of Prescription</th>
<th>Incidence (courses/child-year)</th>
<th>Average Number of Courses</th>
<th>Total Number of Courses</th>
<th>Average Percent of Follow-up Days on Antibiotics</th>
<th>Total Number of Days on Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Sources</td>
<td>3.63</td>
<td>12.22</td>
<td>3702</td>
<td>4.32</td>
<td>16870</td>
</tr>
<tr>
<td>MD/Nurse</td>
<td>2.88</td>
<td>9.71</td>
<td>2941</td>
<td>3.60</td>
<td>14079</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>0.30</td>
<td>0.99</td>
<td>301</td>
<td>0.30</td>
<td>1268</td>
</tr>
<tr>
<td>Self-Prescribed</td>
<td>0.25</td>
<td>0.83</td>
<td>251</td>
<td>0.22</td>
<td>761</td>
</tr>
<tr>
<td>Nurse Assistant</td>
<td>0.13</td>
<td>0.45</td>
<td>136</td>
<td>0.13</td>
<td>544</td>
</tr>
<tr>
<td>Neighbor/Family</td>
<td>0.07</td>
<td>0.23</td>
<td>71</td>
<td>0.06</td>
<td>212</td>
</tr>
<tr>
<td>Undetermined</td>
<td>0.002</td>
<td>0.006</td>
<td>2</td>
<td>&lt;0.01</td>
<td>6</td>
</tr>
</tbody>
</table>

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Table 3. Percent (Number) of Antibiotic Courses Prescribed According to the Associated Illness Episode.

<table>
<thead>
<tr>
<th>Illness Associated with Antibiotic Intake</th>
<th>MD/Nurse</th>
<th>Pharmacy</th>
<th>Self-Prescribed</th>
<th>Nurse Assistant</th>
<th>Neighbor/ Family</th>
<th>Undetermined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antibiotic Courses (% (n/N))</td>
<td>Antibiotic Courses (% (n/N))</td>
<td>Antibiotic Courses (% (n/N))</td>
<td>Antibiotic Courses (% (n/N))</td>
<td>Antibiotic Courses (% (n/N))</td>
<td>Antibiotic Courses (% (n/N))</td>
</tr>
<tr>
<td>All Causes</td>
<td>79.4% (2941/3702)</td>
<td>8.1% (301/3702)</td>
<td>6.8% (251/3702)</td>
<td>3.7% (136/3702)</td>
<td>1.9% (71/3702)</td>
<td>0.1% (2/3702)</td>
</tr>
<tr>
<td>Acute Lower Respiratory Infection (ALRI)</td>
<td>97.1% (102/105)</td>
<td>2.9% (3/105)</td>
<td>0% (0/105)</td>
<td>0% (0/105)</td>
<td>0% (0/105)</td>
<td>0% (0/105)</td>
</tr>
<tr>
<td>Dysentery</td>
<td>96.0% (95/99)</td>
<td>1.0% (1/99)</td>
<td>3.0% (3/99)</td>
<td>0% (0/99)</td>
<td>0% (0/99)</td>
<td>0% (0/99)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>76.2% (715/938)</td>
<td>6.8% (64/938)</td>
<td>8.1% (76/938)</td>
<td>5.2% (49/938)</td>
<td>3.4% (32/938)</td>
<td>0% (2/938)</td>
</tr>
<tr>
<td>Fever</td>
<td>83.9% (960/1144)</td>
<td>8.1% (93/1144)</td>
<td>3.5% (40/1144)</td>
<td>3.6% (41/1144)</td>
<td>0.9% (10/1144)</td>
<td>0% (0/1144)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>75.5% (1069/1416)</td>
<td>9.9% (140/1416)</td>
<td>9.3% (132/1416)</td>
<td>3.2% (46/1416)</td>
<td>2.0% (29/1416)</td>
<td>0% (0/1416)</td>
</tr>
</tbody>
</table>

Table 4. Percent (Number) of Antibiotic Days Children Spent of Antibiotics According to the Prescriber and Associated Illness Episode.

<table>
<thead>
<tr>
<th>Illness Associated with Antibiotic Intake</th>
<th>MD/Nurse</th>
<th>Pharmacy</th>
<th>Self-Prescribed</th>
<th>Nurse Assistant</th>
<th>Neighbor/ Family</th>
<th>Undetermined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Days on Antibiotics (% (n/N))</td>
<td>Days on Antibiotics (% (n/N))</td>
<td>Days on Antibiotics (% (n/N))</td>
<td>Days on Antibiotics (% (n/N))</td>
<td>Days on Antibiotics (% (n/N))</td>
<td>Days on Antibiotics (% (n/N))</td>
</tr>
<tr>
<td>All Causes</td>
<td>83.5% (14079/16870)</td>
<td>7.5% (1268/16870)</td>
<td>4.5% (761/16870)</td>
<td>3.2% (544/16870)</td>
<td>1.3% (212/16870)</td>
<td>0% (6/16870)</td>
</tr>
<tr>
<td>Acute Lower Respiratory Infection (ALRI)</td>
<td>97.0% (516/532)</td>
<td>7.5% (16/532)</td>
<td>0% (0/532)</td>
<td>0% (0/532)</td>
<td>0% (0/532)</td>
<td>0% (0/532)</td>
</tr>
<tr>
<td>Dysentery</td>
<td>97.5% (310/318)</td>
<td>3.0% (2/318)</td>
<td>1.9% (6/318)</td>
<td>0% (0/318)</td>
<td>0% (0/318)</td>
<td>0% (0/318)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>81.4% (2827/3473)</td>
<td>0.6% (222/3472)</td>
<td>5.0% (174/3473)</td>
<td>4.7% (163/3473)</td>
<td>2.3% (81/3473)</td>
<td>0.2% (6/3473)</td>
</tr>
<tr>
<td>Fever</td>
<td>87.7% (4972/5669)</td>
<td>6.4% (368/5669)</td>
<td>2.4% (135/5669)</td>
<td>2.9 (165/5669)</td>
<td>0.5% (29/5669)</td>
<td>0% (0/5669)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>79.3 (5454/6878)</td>
<td>6.5% (660/6878)</td>
<td>6.5% (446/6878)</td>
<td>3.1% (216/6878)</td>
<td>1.5% (102/6876)</td>
<td>0% (0/6878)</td>
</tr>
</tbody>
</table>
Table 5. Associations between antibiotic prescriptions and the occurrence of diarrhea, fever, acute lower respiratory infections, and dysentery among children followed, adjusted for covariates.

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALRI</strong></td>
<td>15.11 (11.82 - 19.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (Female)</td>
<td>1.01 (0.90 - 1.15)</td>
<td>0.848</td>
</tr>
<tr>
<td>Age</td>
<td>0.99 (0.98 - 0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maternal Education (primary completed)</td>
<td>1.10 (0.96 - 1.24)</td>
<td>0.164</td>
</tr>
<tr>
<td>Household Income (USD)</td>
<td>0.99 (0.99 - 1.00)</td>
<td>0.845</td>
</tr>
<tr>
<td><strong>Dysentery</strong></td>
<td>26.47 (19.83 - 35.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (Female)</td>
<td>1.01 (0.89 - 1.15)</td>
<td>0.849</td>
</tr>
<tr>
<td>Age</td>
<td>0.99 (0.98 - 0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maternal Education (primary completed)</td>
<td>1.09 (0.96 - 1.24)</td>
<td>0.170</td>
</tr>
<tr>
<td>Household Income (USD)</td>
<td>0.99 (0.99 - 1.00)</td>
<td>0.856</td>
</tr>
<tr>
<td><strong>Diarrhea</strong>**</td>
<td>5.89 (5.31 - 6.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (Female)</td>
<td>1.02 (0.90 - 1.16)</td>
<td>0.712</td>
</tr>
<tr>
<td>Age</td>
<td>0.99 (0.98 - 0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maternal Education (primary completed)</td>
<td>1.09 (0.96 - 1.24)</td>
<td>0.152</td>
</tr>
<tr>
<td>Household Income (USD)</td>
<td>0.99 (0.99 - 1.00)</td>
<td>0.519</td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td>6.04 (5.59 - 6.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (Female)</td>
<td>1.02 (0.90 - 1.15)</td>
<td>0.731</td>
</tr>
<tr>
<td>Age</td>
<td>0.99 (0.98 - 0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maternal Education (primary completed)</td>
<td>1.10 (0.97 - 1.25)</td>
<td>0.099</td>
</tr>
<tr>
<td>Household Income (USD)</td>
<td>0.99 (0.99 - 1.00)</td>
<td>0.676</td>
</tr>
</tbody>
</table>

*Fever without diarrhea, ALRI or dysentery
**Diarrhea without fever, ALRI or dysentery
**Figure 1.** Probability Distribution of the Length of Antibiotic Courses (Days) by Illness and Prescriber.

<table>
<thead>
<tr>
<th>Illness</th>
<th>MD/Nurse</th>
<th>Pharmacy</th>
<th>Nurse Assistant</th>
<th>Self-Prescribed</th>
<th>Family/Neighbor</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysentery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Length of Antibiotic Courses (Days)

**Figure 1**

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