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Risk Factors for Antibiotic-Resistant *Escherichia coli* Carriage in Young Children in Peru: Community-Based Cross-Sectional Prevalence Study

Henry D. Kalter,* Robert H. Gilman, Lawrence H. Moulton, Anna R. Cullotta, Lilia Cabrera, and Billie Velapatiño

Department of International Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland; Asociación Benéfica Proyectos en Informatica, Salud, Medicina y Agricultura (AB PRISMA), Lima, Peru; Infectious Disease Laboratory, Department of Pathology, Universidad Peruana Cayetano Heredia, Lima, Peru

Abstract. Few studies have examined the influence of individual-, household-, and community-scale risk factors on carriage of resistant commensal bacteria. We determined children's medical, agricultural, and environmental exposures by household, pharmacy, and health facility surveys and *Escherichia coli* cultures of children, mothers' hands, household animals, and market chickens in Peru. Among 522 children with a positive stool culture, by log-binomial regression, using "any antibiotic" and 1–14 (versus 0) sulfa doses in the past 3 months increased children's risk, respectively, for ampicillin- and sulfamethoxazole-resistant *E. coli* carriage ($P = 0.01$–0.02). Each household member taking "any antibiotic" increased children's risk for sulfamethoxazole- and multidrug-resistant *E. coli* carriage ($P < 0.0001$). Residence in a zone where a larger proportion of households served home-raised chicken (as contrasted with intensively antibiotic-raised market chicken) protected against carrying *E. coli* resistant to all drugs ($P = 0.0004$–0.04). Environmental contamination with drug-resistant bacteria appeared to significantly contribute to children's carriage of antibiotic-resistant *E. coli*.

INTRODUCTION

Antimicrobial resistance has emerged as a global public health problem in recent years,[1,2] and is a major impediment to the management of childhood diseases in developing countries such as Peru. Although resistance in pathogenic organisms poses a distinct clinical challenge, commensal bacteria may play a crucial role in the spread of resistance within a community[3] by acting as a major reservoir for resistance genes.[4] Exposure of commensals such as *Escherichia coli* and *Enterococcus faecium* to antibiotics increases the carriage levels of resistant organisms and, if plasmid-mediated, resistance might be transmitted to a more virulent acquired organism.[5]

The volume of antimicrobial use is the main factor in the development of resistance[6,7] both in individuals[8] and populations.[9,10] In populations with heavy use, the risk of carrying resistant organisms caused by household members' use of antibiotics,[11] intrafamilial transmission,[12,13] or proximity to an antibiotics source[14] often outweighs the risk of personal antibiotics use.

The quantity of antibiotics used in animal husbandry often exceeds their medical use.[15] Humans are exposed to animal microflora through meat consumption[16] and, in some settings, close contact.[17] The spread of resistance factors from animal to human flora, including interbacterial species transmission, has been documented or is highly suspected in *E. coli*, *Camphylobacter* spp.,[15] *Enterococcus* spp.,[18] and other bacteria. Exposure to drug resistant animal flora can lead to disease[19,20] and prevalent carriage of resistant bacteria in human populations.[18,21]

Low level antibiotics use also may contribute to resistance, by selecting low-level resistance strains.[22] Subtherapeutic treatment is common in developing countries where vendors often dispense an inadequate drug supply to lower treatment costs[23] or do not provide dosing instructions.[24] Maintenance dosing of farm animals to promote growth might also select low-level resistance strains.

Environmental contamination disseminates resistant organisms, particularly in developing countries because of crowding and inadequate excreta management.[25,26] Resistant bacteria have been detected in drinking water,[27] vegetables, fish,[28] and marine sediments.[29] Sources include human sewage, farm runoff, and integrated fish farming.[30] Moreover, plasmids carrying resistance factors can be transferred between bacteria within natural microenvironments.[31] Possible consequences include recycling and amplification of resistance genes within and between the environment, food animals, and the human population.

The relative importance of these factors in determining the risk of carrying resistant bacteria is unknown. Most studies of factors contributing to the carriage of resistant bacteria in the community[9–14,21] have focused on one or a few variables, and those that have examined community-level effects[9,12,14] have included no more than five study areas. This study aimed to assess the influence of various medical, agricultural, and environmental exposures at the individual, household, and community levels in determining the risk of young children in a developing country for carrying antibiotic-resistant *E. coli*. *Escherichia coli* was selected for study because they are common in humans and animals, can cause disease, have been used to gauge the spread of acquired resistance,[32,33] and might serve as markers of the transfer of resistance from animal to human intestinal microflora. Peru was chosen as the study site because of its high but variable levels of medical and agricultural antibiotics usage and generally weak but somewhat mixed sanitation and protection of water, thereby enabling simultaneous examination of several risk factors for carrying resistant organisms.

MATERIALS AND METHODS

Study site. To assure a range of values for potential risk factors, the study was conducted in 16 purposively selected zones in four regions of Peru, including peri-urban slums in Lima and towns and villages in Cajamarca in the Sierra Mountains, Iquitos in the Amazon rain forest, and Chincha on the coast. Zones were selected guided by the following observations.

*Address correspondence to Henry D. Kalter, Department of International Health, Johns Hopkins University Bloomberg School of Public Health, 615 North Wolfe Street, Rm E-8132, Baltimore, MD 21205. E-mail: hkalter@jhsph.edu

Antibiotics are available in Peru without a physician's prescription. Usage is thought to vary by economic status, urban or rural residence, and distance from a source. However, even rural villages may have a small store, a "bodega," where antibiotics can be purchased. School children 3–15 years of age are entitled to free antibiotics. In Iquitos, the known presence of *Plasmodium falciparum* malaria may lead to the presumptive use of sulfa drugs for febrile illnesses.

Most chickens are grown in commercial flocks that house 100 or more per pen on the ground with saw shavings for bedding. They are fed commercial feed, often containing antibiotics, from automatic dispensers. Chickens for eating are sold at around 7–8 weeks of age. Killing of chickens is often done individually and is not mechanized.

Tetracycline and furazolidine are used by chicken and pig farms to varying degrees throughout the country and by one of two large fish farms in the Sierras. Several fluoroquinolone antibiotics are also used in chicken farming. In Iquitos, some small commercial fish ponds add droppings or entrails from local chicken farms to the water as a nutrient.

Like antibiotics, access to food markets is decreased by cost and distance. Villagers and some slum dwellers raise animals, mainly chickens, for their own use, usually without antibiotics. Home-grown meat is generally reserved for special occasions and may be supplemented with commercial meat according to the family's resources. Children do not eat meat until they are 1–2 years old, but consume eggs by 1 year of age.

Animals in the Sierras may drink river water tainted with antibiotics and stool from upstream fish farms. Children bathe in rivers and farmers irrigate their crops with this water. Villagers and animals in Iquitos drink from unprotected wells likely to contain human and animal feces from their own village and from nearby chicken farms. Although piped water from a municipal source in peri-urban Lima is microbiologically clean, it often becomes fecally contaminated before it is consumed.[34]

Variation in antibiotic exposures was sought in Cajamarca, Iquitos, and Chincha by purposively selecting zones and areas within zones along a rural–urban continuum, with allowance for proximity to a fish or chicken farm or health post. In Lima, newer and older slums were selected. Older areas are relatively well off, with increased access to municipal and health services. Table 1 shows some characteristics of the study zones.

Participants and data sources. A minimum of 25 households with one or more children 3 months to 3 years of age was sought in each of the 16 zones. A sweep census was conducted in the purposively selected villages and town areas until the desired minimum sample of 25 households was achieved. This entailed sampling all households in villages where the population was below the sample size but only one or two streets in some urban areas. Households where the youngest child had taken any antibiotic within 7 days of the original visit were revisited to take all cultures and conduct the interview at least 7 days after the child completed his/her antibiotics course. At each household, a rectal and hands-dip broth swab was obtained, respectively, from the youngest child and his or her mother and cultured for *E. coli*; and a rectal swab for *E. coli* culture was taken from a convenience sample of one of each animal type. Using a standardized questionnaire, the mother was asked about the child's age and breastfeeding; her own education; the household head's employment; home ownership, number of rooms, type of flooring, and cooking fuel; the child's individual- and household-level exposures listed in Table 2; the market where the family normally purchased chicken; and the source of any antibiotics used by family members in the last 3 months. All antibiotics use was ascertained whenever possible by examining the prescription, bottle label, or packaging of any used drugs. The study manager checked completed questionnaires and deleted any data for non-antibiotic drugs before computer entry.

Table 2 also lists community-level exposures that were evaluated. Freshly slaughtered chicken entrails were obtained at the most commonly used markets and cultured for *E. coli*. At each most frequently used health facility and pharmacy, respectively, two health providers and the pharmacist were interviewed about their prescribing practices; and the prior 6 months data on over-the-counter and prescription antibiotics

Table 1
Some characteristics of the study zones

Region	Zone	Number of sampled villages and towns	Population of sampled areas	Number of sampled households	Mean distance (km) of sampled areas to region center	Health care facilities
Iquitos	1	5	893	74	24.3	0
	2	2	1,205	73	14.75	1 health post in each village
	3	2	2,348	66	3.5	1 health center or post in each village
	4	1	2,573	112	2	1 health center
Subtotals			7,019	325		
Cajamarca	1	5	1,866	30	76.6	0
	2	2	1,456	28	32.5	1 health post
	3	8	5,976	26	20.5	1 health center
	4	1	1,585	27	0	1 hospital
Subtotals			10,883	111		
Chincha	1	11	2,698	25	6	0
	2	2	4,518	27	1.25	1 health post
	3	1	9,242	23	6	1 health center
	4	1	54,460	25	0	1 hospital
Subtotals			70,918	100		
Lima	1	5	8,226	25	0	1 health post
	2	4	9,157	25	0	1 polyclinic and 1 health center
	3	6	6,955	25	0	1 health post in each of 2 areas
	4	5	7,054	25	0	1 health post
Subtotals			31,392	100		
Totals			120,212	636		

TABLE 2
Study children's possible antibiotic and antibiotic-resistant bacteria exposures and measurement methods

Exposure	Measurement method
Child- and household-level exposures:	Household survey
Child's and other household members' prior 3-months any antibiotic use* and doses of particular antibiotics†	
Mother's prior 3-months any antibiotic use* while currently breastfeeding child	
Child's and other household children's day care use	
Child's and other household members' prior 3-months hospitalization	
Child's consumption of water, cow's milk, chicken, eggs, fish, and pig	
Household's use of safe drinking water‡	
Household's prior 1-year serving of home raised and market-purchased chicken and eggs	
Household presence of animals and their prior 3-months antibiotics doses†	
Household's protection of excreta§	
Community-level exposures:	
Zone's distance from its region's center	Measured
Household practices:	Household survey
All household members' prior 3-months any antibiotic use¶	
Prior 1-year serving of home-raised and market-purchased chicken and eggs¶	
Protection of excreta¶	
Antibiotics sales and prescribing practices:	Household survey and drug sales data of pharmacies and health facilities used by study households
Pharmacy and health facility prior 6-months sales**	
Over-prescribing of antibiotics	Survey of pharmacists and health practitioners at pharmacies and facilities used by study households
Other inappropriate prescribing practices	
Antibiotic-resistant *Escherichia coli*:	
Children	Culture stool of each child¶
Mothers of children	Culture hands of each child's mother¶
Household animals	Culture stool of one of each animal type in household††
Food (market chickens)	Culture chicken viscera from markets used by study households‡‡

* Reported use of "any antibiotic."
† Reported doses of ampicillin, amoxicillin, natural and semi-synthetic penicillins, cephalosporins, fluoroquinolones, sulfonamides, trimethoprim, tetracyclines, aminoglycosides, chloramphenicol, macrolides, lincosamides, metronidazole, and furazolidine.
‡ Boiled or chlorinated.
§ Bury, burn, latrine, excavated well, or septic tank vs. drain, river, irrigation ditch, stream, or open field.
¶ Proportion of zonal households with a practice or culture positive for antibiotic-resistant *E. coli*.
** Number of defined daily doses sold or dispensed to a zone per 100 persons, estimated from sales, household usage, and population data.
†† Proportion of zonal households with any animal with a culture positive for antibiotic-resistant *E. coli*.
‡‡ Proportion of regional samples with a culture positive for antibiotic-resistant *E. coli*.

dispensed and sold were abstracted. The number of defined daily doses of each antibiotic type distributed to each zone per 100 persons was estimated from the dispensing, sales, household usage, and population data. Antibiotic distributions were expressed with regard to users' residence, rather than facilities' location, because large pharmacies made many sales to residents from outside their zones.

All positive cultures were tested for resistance to four drugs representing antibiotic classes that are commonly used against gram negatives, including ampicillin, sulfamethoxazole, ceftriaxone, and ciprofloxacin. Some community-level exposures, such as the zonal proportion of children carrying antibiotic-resistant *E. coli*, were derived from household data. For such variables each household's data were excluded from the calculation of its own value so that the variable would reflect the environment beyond the household. Other community-level data, such as market chickens' drug-resistant *E. coli* carriage, were gathered from common source exposure sites.

Microbiology materials and methods. The clinical microbiology laboratories of the Universidad Peruana Cayetano Heredia Hospital in Lima conducted or guided all laboratory tests. All specimens were placed in a sterile screw cap tube containing a transport medium and held at 4°C for up to 24 hours before culture. Rectal swabs were directly inoculated onto MacConkey agar plates. After aerobic incubation at 37°C for 24 hours, two lactose fermenting colonies typical of *E. coli* were subcultured onto sheep blood agar for each subject and confirmed by a spot indole test the following day. After confirmation, 0.5 MacFarland suspensions were made from the pure subcultures and inoculated onto Mueller Hinton agar. Susceptibility to ampicillin, sulfamethoxazole, ceftriaxone, and ciprofloxacin were determined using the Kirby-Bauer disk diffusion test. After aerobic incubation at 37°C for 24 hours, the zone diameters were measured and interpreted according to Clinical and Laboratory Standards Institute (CLSI) standards. Confirmed *E. coli* isolates were suspended in trypticase soy broth with 20% glycerol and stored frozen at −80°C.

Statistical analyses. The study examined the null hypothesis that there is no relationship between various types of antibiotic exposures and the carriage of antibiotic-resistant *E. coli*. The sample size of 400 children was selected to achieve 80% power with a type 1 error of 5% of detecting any particular exposure with a risk ratio of two for carriage of a resistant organism, assuming 100% carriage of enteric *E. coli* in the sampled children and a resistance level of at least 20% in the population. Studies in South America have found high carriage rates of resistant *E. coli*,[32,33] suggesting that this was an adequate sample size to achieve the study's objectives. To assure an adequate range of values of risk factors, in particular of community-level variables such as resistant *E. coli* carriage levels and antibiotic sales, the study was conducted in 16 zones throughout the country, with at least 25 households in each zone.

Although the children's *E. coli* carriage rate was determined in each zone, only children with known age 3 months to 3 years and a positive culture were included in the analyses. Separate analyses of risk factors for carriage of *E. coli* resistant to ampicillin and sulfamethoxazole—each with high levels in the children—and for *E. coli* multiply resistant to both

these substances were conducted. We examined ampicillin, sulfonamide, tetracycline, and ciprofloxacin exposures in all three models because of possible genetically linked resistance caused by plasmid[35,36] and transposon[37] transmission of multiple resistance factors, and to account for possible collinearity of antibiotic exposures.

Log-binomial regression models that accounted for positive within-zone correlation (SAS Proc Genmod[38]) were used to identify exposures that were present in at least 5% of the observations with an unadjusted risk ratio greater than 1.50 (or less than 0.67) or a *P* value less than 0.20, which qualified to enter into multivariable modeling. Multivariable logistic regression with forward and stepwise selection procedures was used to select the variables from among those that qualified to enter into the final multivariable modeling procedure, which again used a log-binomial model with estimated scale parameter that accounted for within-zone correlation to identify adjusted variables with a *P* value less than 0.05.

Ethical approval. The study was approved by the Johns Hopkins Committee for Human Research and by PRISMA's institutional review board. Each respondent provided informed consent, and each mother consented to a rectal swab being taken of her child.

RESULTS

***E.coli* cultures and antibiotic-resistant carriage levels.** The study included 636 households, with at least 25 households each in 15 zones; one zone had 23 households (Table 1). Regional ampicillin- and sulfamethoxazole-resistant *E. coli* carriage levels of the 523/636 (82.2%) children with a positive culture ranged, respectively, from 42.7% to 58.1% and 43.9% to 66.1%, with wide inter-zone variation. Like these two drugs, ciprofloxacin resistance in children was highest in Chincha, though the levels were comparatively low. All child cultures were sensitive to ceftriaxone (Table 3).

Escherichia coli cultured from mothers' hands also were most frequently resistant to ampicillin, sulfamethoxazole, and ciprofloxacin in Chincha. Household animal carriage levels of ampicillin- and sulfamethoxazole-resistant *E. coli*, generally one-quarter to one-half of which was contributed by household chickens, were far lower than in humans; whereas *E. coli* from

TABLE 3

Escherichia coli culture positivity and antibiotic-resistant *E. coli* carriage levels in four regions of Peru

Region and zone	Children rectal swabs % (n/*N*)	Mothers' hand swabs % (n/*N*)	All household animal† rectal swabs % (n/*N*)	Household chicken rectal swabs % (n/*N*)	Market chicken viscera % (n/*N*)
			Culture positivity		
All regions:	82.2 (523/636)	25.9 (164/632)	78.5 (768/978)	89.6 (242/270)	75.5 (252/334)
Cajamarca	73.9 (82/111)	7.3 (8/110)	63.3 (229/362)	81.5 (53/65)	57.5 (84/146)
Chincha	62.0 (62/100)	15.0 (15/100)	80.9 (157/194)	85.7 (24/28)	93.8 (90/96)
Iquitos	87.4 (284/325)	38.8 (125/322)	89.1 (228/256)	91.4 (127/139)	69.1 (29/42)
Lima	95.0 (95/100)	16.0 (16/100)	92.8 (154/166)	100.0 (38/38)	98.0 (49/50)
			Ampicillin resistance		
All regions:	53.7 (281/523)	37.2 (61/164)	13.5 (104/768)	12.4 (30/242)	46.0 (116/252)
Cajamarca:	42.7 (35/82)	37.5 (3/8)	17.0 (39/229)	18.9 (10/53)	48.8 (41/84)
Zones 1–4	30.8, 41.7, 50.0, 56.3	0.0, 42.9, 0.0, 0.0	12.5, 13.8, 24.4, 20.0	15.8, 20.0, 17.7, 50.0	–*
Chincha:	58.1 (36/62)	66.7 (10/15)	11.5 (18/157)	8.3 (2/24)	44.4 (40/90)
Zones 1–4	36.4, 53.9, 80.0, 75.0	71.4, 66.7, 75.0, 0.0	9.2, 20.0, 20.0, 20.0	9.5, 0.0,–,–	–*
Iquitos:	56.3 (160/284)	32.8 (41/125)	9.7 (22/228)	9.5 (12/127)	24.1 (7/29)
Zones 1–4	51.5, 46.4, 67.2, 60.2	60.0, 25.7, 27.9, 29.4	6.3, 7.5, 5.0, 19.0	3.0, 7.7, 8.3, 19.4	–*
Lima:	52.6 (50/95)	31.3 (5/16)	16.2 (25/154)	15.8 (6/38)	57.1 (28/49)
Zones 1–4	72.7, 44.0, 44.0, 52.2	50.0, 40.0, 0.0, 0.0	20.0, 17.6, 17.4, 8.8	12.5, 0.0, 21.4, 33.3	–*
			Ceftriaxone resistance		
All regions:	0.0 (0/523)	0.6 (1/164)	0.9 (7/768)	0.8 (2/242)	0.8 (2/252)
Cajamarca	0.0 (0/82)	0.0 (0/8)	1.3 (3/229)	1.9 (1/53)	1.2 (1/4)
Chincha	0.0 (0/62)	0.0 (0/15)	0.6 (1/157)	0.0 (0/24)	1.1 (1/90)
Iquitos	0.0 (0/284)	0.8 (1/125)	0.4 (1/228)	0.0 (0/127)	0.0 (0/29)
Lima	0.0 (0/95)	0.0 (0/6)	1.3 (2/154)	2.6 (1/38)	0.0 (0/49)
			Ciprofloxacin resistance		
All regions:	1.5 (8/523)	1.8 (3/164)	1.7 (13/768)	2.5 (6/242)	20.6 (52/252)
Cajamarca	1.2 (1/82)	0.0 (0/8)	1.3 (3/229)	3.8 (2/53)	9.5 (8/84)
Chincha	4.8 (3/62)	6.7 (1/15)	0.6 (1/157)	0.0 (0/24)	23.3 (21/90)
Iquitos	0.7 (2/284)	1.6 (2/125)	1.8 (4/228)	2.4 (3/127)	24.1 (7/29)
Lima	2.1 (2/95)	0.0 (0/16)	3.3 (5/154)	2.6 (1/38)	32.7 (16/49)
			Sulfamethoxazole resistance		
All regions:	51.8 (271/523)	21.3 (35/164)	9.1 (70/768)	12.8 (31/242)	53.2 (134/252)
Cajamarca:	43.9 (36/82)	25.0 (2/8)	7.9 (18/229)	17.0 (9/53)	42.9 (36/84)
Zones 1–4	42.3, 41.7, 37.4, 50.0	0.0, 28.6, 0.0, 0.0	10.2, 10.3, 3.8, 0.0	26.3, 20.0, 5.9, 0.0	–*
Chincha:	66.1 (41/62)	46.7 (7/15)	5.7 (9/157)	8.3 (2/24)	57.8 (52/90)
Zones 1–4	54.6, 61.5, 86.7, 66.7	57.1, 66.7, 25.0, 0.0	5.1, 6.7, 0.0, 20.0	9.5, 0.0,–,–	–*
Iquitos:	52.5 (149/284)	19.2 (24/125)	10.1 (23/228)	11.0 (14/127)	79.3 (23/29)
Zones 1–4	45.5, 47.8, 59.0, 56.8	28.0, 11.4, 18.2, 20.6	7.9, 7.5, 10.0 15.5	0.0, 10.3, 12.5 22.6	–*
Lima:	47.4 (45/95)	12.5 (2/16)	13.0 (20/154)	5.3 (6/38)	46.9 (23/49)
Zones 1–4	68.2, 44.0, 36.0, 43.5	33.3, 0.0, 0.0, 0.0	22.5, 14.7, 13.0, 0.0	25.0, 20.0, 14.3, 0.0	–*

* Markets in one or more zones served the entire region.

† 270 chickens, 224 dogs, 95cats, 77 guinea pigs, 72 pigs, 64 ducks, 34 cows, 30 rabbits, 27 sheep, 23 turkeys, 15 donkeys, 12 doves, 12 goats, 8 horses, 8 canaries/parrots, 2 geese, 2 monkeys, 1 quail, 1 squirrel, 1 unknown.

market chickens was similarly resistant to ampicillin and sulfamethoxazole, and much more so to ciprofloxacin (Table 3). Market chicken carriage of *E. coli* resistant to these drugs was significantly higher than in live household chickens in all regions (Pearson's χ^2 test or two-tailed Fisher's exact test, $P < 0.0001$–0.05) except Cajamarca ($P = 0.32$).

Unadjusted risk factors for antibiotic-resistant *E. coli* carriage. Variables of all three types—child, household, and community—met the statistical threshold for inclusion in the multivariable analyses (Table 4). Several community factors were strongest, particularly the zonal proportion of households that served home-raised chicken. Antibiotics use was among the most powerful child and household variables, although use in household animals, including chickens, did not qualify for entry into the multivariable analyses. This was likely because of the low rates of use in household animals, with 0.81 and 0.77 mean doses of all antibiotics given, respectively, to all animals and chickens in the 522/523 households with a child 3 months to 3 years of age in the prior 3 months.

Adjusted risk factors for antibiotic-resistant *E. coli* carriage. Table 5 shows the three final models. All included home non-ownership and mother's education as socioeconomic status adjustors.

Children's use of "any antibiotic" in the prior 3 months increased their risk of carrying ampicillin-resistant *E. coli*, and their use of sulfa drugs showed a dose-response relationship to sulfamethoxazole resistance. Household members' antibiotics use increased children's risk of carrying sulfamethoxazole- and multidrug-resistant bacteria. There was no association between children's and household members' antibiotics use (unadjusted prevalence risk ratio [UPRR] 1.20, 95% confidence interval [CI] 0.94–1.51); and household members' use was a risk factor for sulfamethoxazole resistance even in children with no usage (UPRR 1.17, 95% CI 1.11–1.23).

Residing in a zone where a larger proportion of households served home-raised chicken in the past year protected against carriage of *E. coli* resistant to all three antibiotic categories.

TABLE 4

Potential risk and preventive factors associated with antibiotic-resistant *Escherichia coli* carriage in Peruvian children, which qualified for entry into the multivariable analysis*

	Not resistant	Resistant		
	n (%) or mean (SD)†‡	n (%) or mean (SD)†‡		
	Model 1: Ampicillin resistance			
Potential factor	*N* = 242	*N* = 280	PRR	*P* value
Child factors:				
Age (years)	1.72 (0.75)†	1.53 (0.76)†	0.86	0.13
Took any antibiotic§¶	76 (32.07)	123 (44.89)	1.28	0.10
Household factors:**				
Served any home-produced eggs	56 (23.1)	37 (13.20)	0.70	0.08
Number of times served home-produced eggs	41.53 (96.69)†	22.15 (70.92)†	0.99	0.13
Served any home-raised chicken	96 (39.7)	73 (26.1)	0.74	0.02
Community factors:**††‡‡				
HHs: any person taking any antibiotic§¶	0.59 (0.13)‡	0.61 (0.12)‡	2.05	0.17
HHs child: ampicillin-resistant *E. coli*	0.52 (0.11)‡	0.55 (0.12)‡	2.28	0.02
HHs child: sulfamethoxazole-resistant *E. coli*	0.51 (0.09)‡	0.53 (0.11)‡	2.76	0.02
HHs mother: sulfamethoxazole-resistant *E. coli*	0.05 (0.04)‡	0.06 (0.04)‡	2.41	0.65
HHs any animal: ampicillin-resistant *E. coli*	0.16 (0.12)‡	0.14 (0.10)‡	0.39	0.14
HHs any animal: sulfamethoxazole-resistant *E. coli*	0.12 (0.08)‡	0.11 (0.09)‡	0.45	0.35
HHs: served any home-raised chicken	0.38 (0.27)‡	0.28 (0.23)‡	0.48	< 0.01
HHs: served any market-purchased chicken	0.86 (0.15)‡	0.89 (0.13)‡	2.20	0.15
FM chickens: sulfamethoxozole-resistant *E. coli*	0.64 (0.16)‡	0.66 (0.15)‡	1.52	0.39
FM chickens: ciprofloxacin-resistant *E. coli*	0.23 (0.07)‡	0.24 (0.06)‡	2.39	0.44
	Model 2: Sulfamethoxazole resistance			
	N = 252	*N* = 270	PRR	*P* value
Child factors:				
Age (years)	1.69 (0.75)†	1.55 (0.76)†	0.89	0.16
Currently breastfed and mother took any antibiotic§¶	13 (5.24)	27 (10.15)	1.34	0.10
Took any antibiotic§¶	83 (33.60)	116 (43.94)	1.23	0.10
Number of sulfa§§§ doses taken	1.06 (3.71)†	2.10 (5.56)†	1.02	< 0.01
Household factors (persons other than the child):**				
Family does not own their home	38 (15.08)	63 (23.33)	1.27	0.08
Number of members who took any antibiotic§¶	0.41 (0.71)†	0.68 (0.89)†	1.16	< 0.01
Served any home-raised chicken	92 (36.51)	77 (28.52)	0.83	0.18
Community factors:**††‡‡				
HHs: any person took any antibiotic§¶	0.59 (0.12)‡	0.61 (0.13)‡	2.16	0.04
HHs child: sulfamethoxazole-resistant *E. coli*	0.51 (0.09)‡	0.52 (0.11)‡	1.81	0.12
HHs child: ampicillin-resistant *E. coli*	0.53 (0.11)‡	0.55 (0.13)‡	2.36	0.02
HHs mother: sulfamethoxazole-resistant *E. coli*	0.05 (0.04)‡	0.06 (0.04)‡	4.69	0.35
HHs mother: ampicillin-resistant *E. coli*	0.09 (0.07)‡	0.10 (0.06)‡	2.07	0.49
HHs any animal: ampicillin-resistant *E. coli*	0.16 (0.12)‡	0.14 (0.11)‡	0.63	0.46
HHs: served any home-raised chicken	0.36 (0.25)‡	0.30 (0.25)‡	0.60	0.05
HHs: served any market-purchased chicken	0.87 (0.14)‡	0.89 (0.13)‡	1.92	0.13

(*continued*)

TABLE 4
Continued

Potential factor	Not resistant n (%) or mean (SD)†‡ Model 3: Multidrug¶¶ resistance *N* = 299	Resistant n (%) or mean (SD)†‡ Model 3: Multidrug¶¶ resistance *N* = 223	PRR	*P* value
Child factors:				
Age (years)	1.69 (0.76)†	1.53 (0.75)†	0.85	0.14
Took any antibiotic§¶	101 (34.35)	98 (45.16)	1.29	0.12
Number of sulfa§§§ doses taken	1.18 (3.94)†	2.16 (5.68)†	1.02	0.07
Household factors (persons other than the child):**				
Number of members who took any antibiotic§¶	0.45 (0.76)†	0.68 (0.89)†	1.17	0.02
Served any home-produced eggs	64 (21.40)	29 (13.00)	0.69	0.09
Served any home-raised chicken	113 (37.79)	56 (25.11)	0.70	0.01
Community factors:**††‡‡				
HHs: any person taking any antibiotic§¶	0.59 (0.13)‡	0.61 (0.13)‡	2.17	0.16
HHs child: ampicillin-resistant *E. coli*	0.53 (0.11)‡	0.55 (0.12)‡	2.24	0.06
HHs child: sulfamethoxazole-resistant *E. coli*	0.51 (0.10)‡	0.52 (0.11)‡	1.89	0.27
HHs mother: ampicillin-resistant *E. coli*	0.10 (0.07)‡	0.10 (0.06)‡	1.59	0.74
HHs mother: sulfamethoxazole-resistant *E. coli*	0.05 (0.04)‡	0.06 (0.04)‡	3.76	0.55
HHs any animal: ampicillin-resistant *E. coli*	0.16 (0.12)‡	0.14 (0.10)‡	0.41	0.22
HHs any animal: sulfamethoxazole-resistant *E. coli*	0.12 (0.08)‡	0.11 (0.08)‡	0.47	0.42
HHs: served any home-raised chicken	0.36 (0.26)‡	0.28 (0.24)‡	0.46	< 0.01
HHs: served any market-purchased chicken	0.87 (0.14)‡	0.89 (0.13)‡	2.14	0.18
FM chickens: ampicillin-resistant *E. coli*	0.37 (0.14)‡	0.35 (0.13)‡	0.60	0.43
FM chickens: sulfamethoxazole-resistant *E. coli*	0.64 (0.16)‡	0.66 (0.15)‡	1.60	0.39

PRR = prevalence risk ratio; HH = household; FM = food market.
* Potential factors qualified for entry into the multivariable analysis with ≥ 5% positive observations, and 0.67 > PRR > 1.50 or Score χ^2 *P* value < 0.20 determined by unadjusted log-binomial regression models that accounted for within-zone correlation (SAS Proc Genmod[38]).
† Mean and standard deviation for the zone.
‡ Mean and standard deviation of the zone (HH) or region (FM) proportions.
§ All antibiotics consumption in prior 3 months.
¶ Reported use of "any antibiotic."
** All foods served in prior 1 year.
†† All community factors are the proportion of zonal (HHs) or regional (FM chickens) units with the factor. The proportion for each household excludes its own value from the calculation.
‡‡ *E. coli* cultures were rectal (child and HH animal), hands (mothers), and viscera (FM chickens).
§§ Trimethoprim/sulfamethoxazole and sulfadoxine.
¶¶ Ampicillin and sulfamethoxazole.

There was an inverse relationship (Spearman rank correlation, –0.55, $P < 0.0001$) between the zonal household serving levels of home-raised and market-purchased chicken, and while living in a zone with increased serving of market-purchased chicken was an unadjusted risk factor for resistance to all three antibiotic types, this variable was not strong enough to enter the adjusted models.

Although the models included two socioeconomic status adjustors, we were concerned that the zonal serving levels of home-raised and market-purchased chicken might be confounded by socioeconomic status and the related level of antibiotics use. Stratified analyses showed that there was no confounding of these variables' relationship to children's carriage of drug-resistant *E. coli* by geographical region, antibiotics use, or home ownership (Table 6).

Resistant *E. coli* carriage levels significantly decreased as age increased for all drug types (Table 7), and older age protected against ampicillin and multidrug resistance (Table 5). This was not because of differences in antibiotics usage by age (UPRR 0.97, 95% CI 0.65–1.47), nor was age confounded by the zonal proportion of households that served home-raised chicken (UPRRs for 0% to 12%, 14% to 33%, and 42% to 92% serving levels: ampicillin: 0.85, 0.86, 0.95, and multidrug: 0.95, 0.80, 0.89).

A socioeconomic adjustor, home non-ownership, was found to increase the risk for sulfamethoxazole- and multidrug-resistant *E. coli* carriage. This was not because of differences in children's (UPRR 1.06, 95% CI 0.31–3.66) or household members' (UPRR 1.01, 95% CI 0.49–2.07) antibiotics use by home ownership; nor to home owners serving more or less home-raised (UPRR 0.83, 95% CI 0.12–5.77) or market-purchased (UPRR 1.07, 95% CI 0.95–1.21) chicken. Maternal education was higher in households that did not own their home (UPRR 1.35, 95% CI 1.08–1.68).

DISCUSSION

The study setting of 16 zones in four widely dispersed regions of Peru, purposively selected to include a mix of medical, agricultural, and environmental exposures, and with high and variable levels of ampicillin- and sulfamethoxazole-resistant *E. coli* carriage, enabled the assessment of the relative importance of a broad range of exposures to the risk for antibiotic-resistant *E. coli* carriage in young children. The two main risk factors identified were the children's and their household members' recent antibiotics use. Family home non-ownership also was a risk factor. Residing in a community where a greater proportion of households served home-raised chicken protected against resistance. Being older also protected against resistance.

We assessed antibiotics use in the prior 3 months; a 1–4 months interval being shown by many investigators to contribute to current resistance.[9,12,21,39–41] Most of these studies were conducted in health care settings and ascertained antibiotics use mainly from medical records, whereas ours and another community-based study[12] relied more on caregivers' recall. We took similar measures as described by other investigators to increase the accuracy of these reports.[42] In the current study, asking about "any antibiotic use" was the most sensitive way to detect usage. However, the dose-response relationship

TABLE 5
Risk and preventive factors associated with antibiotic-resistant *Escherichia coli* carriage in Peruvian children*

Factor	PRR	95% CI	*P* value
		Model 1: Ampicillin resistance ($N = 510$)	
Child's age (years)	0.89	0.80–0.98	0.0223
Child took any antibiotic† in prior 3 months	1.21	1.04–1.41	0.0137
Zonal serving level of home-raised chicken‡	0.52§	0.36–0.75	0.0005
Family does not own their home	1.15	0.96–1.38	0.1174
Mother's years of schooling	0.98	0.93–1.04	0.5214
		Model 2: Sulfamethoxazole resistance ($N = 510$)	
Child took 1–14 sulfa¶ doses in prior 3 months	1.24	1.03–1.49	0.0244
Child took ≥15 sulfa¶ doses in prior 3 months	1.43	1.14–1.79	0.0021
Each additional household member (other than the child) who took any antibiotic† in prior 3 months	1.16	1.13–1.19	< 0.0001
Zonal serving level of home-raised chicken‡	0.71§	0.52–0.98	0.0390
Family does not own their home	1.23	1.06–1.43	0.0073
Mother's years of schooling	1.01	0.96–1.06	0.7391
		Model 3: Multidrug** resistance ($N = 521$)	
Child's age (years)	0.86	0.78–0.96	0.0044
Each additional household member (other than the child) who took any antibiotic† in prior 3 months	1.16	1.13–1.20	< 0.0001
Zonal serving level of home-raised chicken‡	0.52§	0.36–0.75	0.0004
Family does not own their home	1.27	1.07–1.52	0.0078
Mother's years of schooling	0.99	0.93–1.04	0.6244

PRR = prevalence risk ratio.
* PRRs for risk and preventive factors determined by multivariable log-binomial regression models that accounted for within-zone correlation (SAS Proc Genmod[38]).
† Reported use of "any antibiotic."
‡ The proportion of zonal households that served any home-raised chicken in the last year. The proportion for each household excludes its own value from the calculation.
§ PRRs for zones with 100% vs. zones with 0% serving. For each 25% points increase in households, this equals a 15% risk reduction for ampicillin (PRR 0.85, 0.77–0.93), 8% for sulfamethoxazole (PRR 0.92, 0.85–0.998), and 15% for multidrug (PRR 0.85, 0.78–0.95) resistance.
¶ Trimethoprim/sulfamethoxazole and sulfadoxine.
** Ampicillin and sulfamethoxazole.

found for sulfa use to sulfamethoxazole resistance strengthens the plausibility of the caregivers' reports.

The risk to children from household members' antibiotics use was likely caused by contamination of household surfaces, persons, or consumables with drug-resistant bacteria (i.e., fecal-oral exposure). Studies documenting intrafamilial transmission of resistance[12,13] support this conclusion, but few studies[11] before ours have shown an increased risk caused by household members' antibiotics use. It is unlikely that familial usage was simply an indicator of children's access to antibiotics; because there was no association between children's and household members' recent use, and family use was a risk factor even in children with no recent antibiotics use.

The protective effect of a greater proportion of community households serving home-raised chicken is especially plausible given the significantly lower levels of antibiotic-resistant *E. coli* found in live household chickens than in market chicken.

TABLE 6
Effects of community serving levels of home-raised and market-purchased chicken on antibiotic-resistant *Escherichia coli* carriage in Peruvian children, for all children and stratified by potential confounders*

	Proportion† of zonal households serving any home-raised chicken in last year			Proportion† of zonal households serving any market-purchased chicken in last year		
	Antibiotic-resistant *E. coli* carriage			Antibiotic-resistant *E. coli* carriage		
Potential confounder	Sulfa‡	Ampicillin	Multidrug§	Sulfa‡	Ampicillin	Multidrug§
	PRR	PRR	PRR	PRR	PRR	PRR
			All children			
	0.60	0.48	0.46	1.92	2.20	2.14
			Stratified by potential confounders			
Region:						
Chincha ($N = 62$)	0.71	0.44	0.46	> 100	> 100	> 100
Cajamarca ($N = 82$)	0.78	0.58	0.69	1.26	3.51	2.06
Iquitos ($N = 283$)	0.52	0.51	0.34	2.43	2.28	3.82
Lima ($N = 95$)	0.29	0.52	0.49	All served	All served	All served
Child took any antibiotic:¶						
No ($N = 312$)	0.43	0.39	0.36	2.16	3.61	2.64
Yes ($N = 199$)	0.92	0.65	0.61	1.54	1.02	1.53
Home ownership:						
Yes ($N = 421$)	0.67	0.51	0.46	1.85	2.05	2.16
No ($N = 101$)	0.47	0.43	0.48	1.51	2.34	1.55

PRR = prevalence risk ratio.
* PRRs for potential confounders determined by unadjusted log-binomial regression models that accounted for within-zone correlation (SAS Proc Genmod[38]).
† The proportion for each household excludes its own value from the calculation.
‡ Sulfamethoxazole.
§ Ampicillin and sulfamethoxazole.
¶ Reported use of "any antibiotic" in the last 3 months.

Table 7
Antibiotic-resistant *Escherichia coli* carriage levels in Peruvian children, by age

Antibiotic	3–12 months (N = 145)	13–24 months (N = 197)	25–36 months (N = 180)	1 DF X^2 for trend (P value)
Ampicillin	60.0%	54.3%	47.8%	4.86 (0.027)
Sulfamethoxazole	57.9%	51.8%	46.7%	4.06 (0.044)
Multidrug*	49.0%	43.2%	37.2%	4.54 (0.033)

*Ampicillin and sulfamethoxazole.

Regarding why serving home-raised chicken appeared to protect against resistance, rather than the inversely related serving level of market-purchased chicken being a risk: this may be a substitution effect, wherein an innocuous product is used instead of a harmful one, thereby producing the impression that the former is protective in and of itself.

That the community serving level of home-raised chicken was stronger than the same household attribute can be explained by two factors. First, children in Peru are unlikely to eat chicken before they are 1–2 years of age, therefore many children would not have been directly exposed at home. Second, the strength of a community effect does not depend on each individual's contact with the primary source. Increased circulation of drug-resistant bacteria is likely to boost exposure even of those who never eat chicken. This is especially true in poor communities in a developing country with inadequate sanitation. Protection of excreta was examined as a community variable, but was too weak to enter the multivariable analysis. This suggests that the study zones were uniformly characterized by poor sanitation and that the significant factor distinguishing communities in this setting was the level of the offending agent, that is, market chicken feces. We also examined household antibiotics use as a community variable, but this too failed to enter any of the final models, strengthening the suggestion that market chicken was the source of the community level risk for antibiotic-resistant *E. coli* carriage.

Exposure to commercial-scale farm raised chickens[17] and consumption of retail meat[19] have been shown to increase individuals' risk for carriage of and infection by antibiotic-resistant *E. coli*, and the causal link between the carriage of resistant fecal flora in human populations and the use of antibiotics in farm animals has been amply demonstrated.[15,18,21] Conditions of poor sanitation are thought to play an important role in the widespread dissemination of resistant fecal bacteria in developing countries,[25,26] but the degree of risk in such settings caused by medical versus agricultural use of antibiotics is unclear. Ours is the only study we know of that examines the contribution of the community level exposure to agriculturally introduced resistance together with a host of other potentially important risk factors for young children's carriage of antibiotic-resistant *E. coli* in a developing country setting with poor sanitation. In this site, personal antibiotics use and exposure to other household users were important factors, but the community level exposure to agriculturally introduced antibiotics appeared to contribute as much or more to children's risk for carrying resistant *E. coli*.

Younger children had higher carriage levels of *E. coli* resistant to all three drug types, and older age protected against ampicillin and multidrug resistance. To our knowledge, the current study represents the youngest age group in which this phenomenon has ever been described. Increased *E. coli*[43–46] and *Streptococcus pneumoniae*[9,47–49] resistance in younger children generally have been attributed to greater antibiotics use by these children,[43–47] although one study cautioned that this could not be true for quinolone resistance because this drug was not used in their youngest age group.[46] Many investigators lacked data on their subjects' antibiotics use, and only two[9,45] examined use and age together in a multivariable analysis. Although both found that younger age and greater use were independent risk factors for resistance, they hypothesized that younger age increased risk through elevated use. The current study showed conclusively that older age protected against resistance independent of its association with antibiotics use or the community serving level of home-raised chicken. One possible explanation is the increased likelihood for "oral investigation" among younger children,[50] which in the context of our study could be responsible for increased fecal-oral exposure. However, the fact that the youngest, least mobile, children were at highest risk suggests that this does not fully explain the finding.

Home non-ownership, included in the statistical models as a socioeconomic adjustor, increased the risk for resistant *E. coli* carriage. This was not caused by its association with antibiotics use or the type of chicken served in the home. We hypothesized that home non-ownership would be associated with reduced access to resources and antibiotics, and decreased resistance. The association we found could be caused by less access to health care and consequent inappropriate antibiotics use, which also can cause resistance.[22] However, the inverse relationship we found between home ownership and maternal education counters this reasoning, because more educated mothers should limit inappropriate antibiotics use.

The study did not find an association between antibiotic resistance and antibiotics sales or inappropriate dispensing practices. Arason and others[9] found that the community sales level was a risk factor, despite the fact that we included 16 study zones compared with their five areas, and we included over-the-counter sales, which constitute most antibiotics sold in Peru. Cross-zone sales might have weakened this variable in our study, because this required us to estimate to where antibiotics were sold from our population's purchasing practices. We also could not assess day care attendance, which is a known risk for pediatric antibiotic resistance,[51] because none of our study children were in day care. Similarly, only six children had been hospitalized in the prior 3 months.

Possible study limitations included inaccurate recall of antibiotics usage, chicken serving, and other variables, which might have weakened the findings. However, there is no reason to believe mothers' reports were biased, because neither the interviewers nor respondents knew which children were carrying drug-resistant bacteria. Despite the plausibility of its protective effect, an unidentified factor may have confounded the community serving level of home-raised chicken. Ideally, a study designed to assess community risk factors should include many study areas, to optimize the detectable risk ratio in the presence of within-area correlation. We did, however, include more than three times the number of study areas of any prior assay of community risk factors for antibiotic-resistant bacterial carriage.

In conclusion, the study identified four main factors affecting antibiotic-resistant *E. coli* carriage in young children in Peru. Children's own, and their household members' recent antibiotics use increased the risk for resistance; the latter likely

acting by household contamination with resistant bacteria. Residing in a zone where a greater proportion of households served home-raised chicken protected against resistance, presumably by reducing the environmental load of drug-resistant bacteria resulting from more frequent serving of intensively antibiotic-raised market-purchased chicken. In these poor communities in a developing country, with inadequate protection of excreta and water, contamination of the environment with antibiotic-resistant bacteria appeared to play at least as great a role in children's carriage of resistant *E. coli* as did the children's own antibiotics use. Further study is warranted to determine whether this finding generalizes to other similar settings with heavy agricultural use of antibiotics and limited protection of sewage and water. Nevertheless, it adds weight to the evidence supporting decreased use of antibiotics in farming. Decreasing household members' and children's own antibiotics use also could be important protective measures. Finally, older age protected children against resistance, independent of their exposure to antibiotics or chicken. Further study is needed to determine whether this is caused by an unidentified exposure or a host factor.

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Authors' addresses: Henry D. Kalter, Robert H. Gilman, and Lawrence H. Moulton, Department of International Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, E-mails: hkalter@jhsph.edu, gilmanbob@gmail.com, and lmoulton@jhsph.edu. Anna R. Cullotta, Creticos ID Associates, Chicago, IL, E-mail: annacullotta@msn.com. Lilia Cabrera, Asociación Benéfica PRISMA, San Miguel, Lima, Perú, E-mail: lcabrera@peruresearch.com. Billie Velapatiño, Department of Pathology and Laboratory Medicine, University of British Columbia, Child and Family Research Institute, Vancouver, BC, Canada, E-mail: bvelap@interchange.ubc.ca.

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