Protective Effect of Antibiotics on Mortality Risk from Acute Respiratory Infections in Mexican Children¹

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A case-control study of mortality from acute respiratory infections (ARI) among children under five years of age was conducted in Naucalpan, an urban-suburban area of Mexico City, and in rural localities of Tlaxcala, Mexico. The study found that ARI deaths tended to occur in the poorest neighborhoods; 78% of the deceased study subjects were infants under six months old; and 68% of the deaths occurred at home.

Comparison of the data for cases (fatalities) and control children who had severe ARI but recovered showed that failure to receive antibiotics was associated with death (odds ratio 28.5, 95% confidence interval 2.1–393.4). This antibiotic effect was controlled for numerous potentially confounding factors. It is evident that antibiotics had a much greater effect in the early days of the illness than later on. In general, the findings strongly support PAHO/WHO primary health care strategies—including such strategies as standardized management of severe ARI cases—that seek to reduce childhood ARI mortality.

A cute respiratory infections (ARI) are a leading cause of illness, disability, and death. They cause an estimated four million deaths among children under the age of five annually and about 2.5 million deaths among infants (1). Most of these

deaths occur in developing countries. The World Health Organization (WHO) and Pan American Health Organization (PAHO) have devised an ARI control program designed to reduce these mortality levels (2); one of this program's mainstays is provision of appropriate therapy with antibiotics.

Since antibiotics were first introduced in the treatment of pneumonias in the 1940s, they have produced dramatic improvement in patient survival, reducing both the duration of ARI episodes and the rate of complications; however, only a few studies have sought to assess antibiotics' potential for influencing life-threatening events such as infant pneumonia from a population-based perspective.

The study reported here was motivated by an earlier pilot study in an urbansuburban area that showed an association between ARI deaths and lack of

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antibiotic therapy (3). The study being reported included a rural area as well as the same urban-suburban area included in the pilot study.

METHODS

Subjects

The urban-suburban study area consisted of the municipality of Naucalpan, which has a population of about one million people and is part of the northern metropolitan area of Mexico City. The rural area consisted of four districts with a total population of about 100,000 in the state of Tlaxcala that are located about 200 kilometers east of Mexico City.

These areas were chosen because an ARI control program had been activated there. Cases were identified through regional municipalities' death registries. (Registered infant mortality was 24 deaths per thousand live births in the urban area and 35 per thousand in the rural area in 1987.) Measles transmission was not occurring during the study period. All the recorded deaths among children under five years old were classified twice a week in accordance with the 9th Revision of the International Classification of Diseases (ICD) (4).

From 15 November 1986 to 31 May 1987 an attempt was made to visit the families of all children under five in the study areas who had died of ARI with ICD codes 460–66, 470–74, and 480–90 (including acute respiratory infections such as laryngitis, ARI of multiple localization or without localization, acute bronchitis and bronchiolitis, influenza, pneumonia, and bronchitis without specification).

Controls who had suffered an episode of acute respiratory illness were sought through a clockwise house-to-house search in the case's neighborhood (Photo 1). They were matched to the fatal cases with regard to the time of case onset (within a

one-month period) and the subject's age at the time of onset (within one month if the subject had been under three months old and within two months if the subject had been older).

Both clinical and timing criteria were used to decide if a case or control should be enrolled in the study. The clinical criteria were the same for cases and controls. Only cases and controls who had suffered an episode with cough, hoarseness, or wheezing, and also with chest retractions, nasal flaring, or cyanosis were enrolled. These criteria are similar to those recommended by WHO (5). The informants, who were the children's caretakers and in most instances (85%) their mothers, were shown slides of children with and without malnutrition who had labored respiration (i.e., retraction of intercostal spaces) in order to help with the histories (Photo 2). Free and informed consent was obtained to interview these caretakers.

Regarding timing, only fatal cases whose caretakers were interviewed within 15 days of the child's death were enrolled in the study. Controls who had completely recovered one month before the date of the interview were excluded, as were those who were not free of respiratory signs or symptoms during the two days before the interview.

Data Collection

Collected data included the mother's age, whether the mother was employed outside the home, whether or not the child was breast-fed, the breast-fed child's age at last breast-feeding, the duration and physical signs of the acute severe respiratory illness episode, whether a physician was consulted for the illness, and the medications used.

The caretakers were shown samples of available medicines used for treating respiratory illness that could have been pre-





Photo 1 (top). Two of the interviewers (nurses Patricia González and Alejandro Rosales) with a mother and child who were interviewed in connection with this study. The boxes carried by the interviewers hold samples of labels and containers for medical products commonly used to treat ARI cases. Photo 2 (bottom). One of the clinical slides used in the study as a visual aid during both case and control interviews. (Photo by Imagen Lima.)

scribed or purchased without a prescription. When possible, leftover medicine was examined to improve the history regarding the subject's medication with antibiotics, and such leftovers were added to the samples shown.

An attempt was also made to ascertain the subject's birth weight and weight at the time of disease onset from the caretaker. The subject's weight-for-age was then calculated according to the National Center for Health Statistics reference population, and the subject was classified as underweight if his or her weight fell more than two standard deviations below the mean weight-for-age ($<-2\ z$ score), otherwise being placed in the reference category. The former group corresponded to those with second or third degree malnutrition according to the Gómez weight-for-age classification (6).

The number of lifetime physician visits for routine care, immunization, and illness care were ascertained from the caretaker.

Several indicators were used to assess social and economic conditions in the household. These included the nature of household furniture, monthly household income, parents' occupation, parents' educational level, home construction, and basic sanitation.

Close field supervision was maintained, and the reliability of the interview data was judged by assessing the degree of agreement between the original interview and a second interview conducted by a different interviewer in a random sample of 5.4% of the interviews.

Data Analysis

Paired odds ratios (OR) and 95% confidence intervals (CI) were calculated as described by Schlesselman (7). The attributable risk among the exposed was calculated as described by Cole and MacMahon (8). The etiologic fraction and

corresponding confidence interval were calculated using the formula of Kuritz and Landis (9). Continuous variables were tested by t-tests, analysis of variance, and log-rank tests. Unpaired dichotomous variable associations were collapsed across strata of additional variables using the Mantel-Haenszel method (10). Tests for homogeneity of the odds ratio across strata using the Breslow and Day chi square statistic were performed (11). Conditional multiple logistic regression analysis was used to control for confounding in the analysis of independent factors and to test the hypothesis of deviation from multiplicative joint effects (12).

All variables that maintained an independent relationship to case-control status (p < 0.10) or that had a reasonable potential for changing the estimate of antibiotic use were entered into the model. They were also entered to check for joint confounding of the relationship between antibiotic use and case-control status. We checked the aptness of the logistic model, particularly whether or not there was a monotonically increasing and sigmoidal risk function, using an informal goodness of fit examination as described by Neter, Wasserman, and Kutner (13), and then using a formal Hosmer and Lemeshow goodness of fit test (14) with two degrees of freedom by collapsing the groups in quartiles of the fitted values.

RESULTS

One hundred thirty-four apparent ARI deaths among children under five years of age were identified in the study period. Sixty-nine of these deaths were excluded because the caretaker interview could not be conducted within 15 days of death, aspiration (as opposed to ARI) could not be ruled out as the cause of death, or an appropriate control could not be found. These excluded cases had approximately the same age and geo-

graphic distribution as the 65 accepted cases. Of the latter, 46 were in the urban-suburban area and 19 were in the rural area. The 46 cases in the urban-suburban area were clustered geographically in a pattern similar to the clustering of poverty within that area.

Forty-nine of the fatalities studied (75%) occurred in the first six months of life, 11 (17%) occurred in the second six months, and 5 (8%) occurred in later childhood. The average time from the onset of illness to death was 6.8 days, with 16 (25%) of the subjects dying during the first reported day of illness and 23 (35%) during the second through fourth days of illness.

Forty-four of the 65 deaths (68%) occurred at home. Only 7 (11%) took place in a hospital, the remaining 14 (21%) having happened outside the home (in an ambulance, emergency room, or doctor's office) while medical care for the victim was being sought. Thirty-five (80%) of the 44 children dying at home had seen a physician during the course of their fatal illness.

Antibiotic Use

Information on antibiotic use was available for all but two of the fatal cases

and one control. The difference between cases and controls regarding receipt of antibiotics was remarkable. Fifty-five percent of the cases but only 12% of the controls failed to receive any antibiotics. There were 29 case-control pairs where the control received antibiotics and the case did not-but only one case-control pair where the reverse was true. The matched pair odds ratio was thus 29 with a 95% confidence interval of 3.9-213; and the attributable risk among the exposed was 97% (95% CI = 90%-100%), meaning that if the association were causal, approximately 97% of the fatalities that did not receive antibiotics could have been prevented with antibiotics. The etiologic fraction was 54% (95% CI = 41%-68%), indicating that approximately 54% of all the study group fatalities due to ARI could have been prevented if all the study group children had received antibiotics.

Table 1 lists specific antibiotics used to treat study cases and controls and shows the numbers of children known to have received each type. These data indicate that penicillin was not frequently prescribed but that ampicillin was the drug of choice, being received by the largest numbers of both study children and controls. When caretakers said they had given antibiotics or any other medication to

Table 1. Antibiotics given to fatal ARI cases and matched controls in the 1986–1987 Naucalpan-Tlaxcala study, by type of antibiotic.

	Cases		Controls	
	No.	(%)	No.	(%)
Type of antibiotic known	19	(68)	45	(8)
Type not known	9	(32)	11	(20)
Total receiving antibiotics	28	(100)	56	(100)
Types received where known:				
Ampicillin	12	(63)	20	(44)
Penicillin	5	(26)	3	(7)
Erythromycin	1	(5)	7	(16)
Sulfamethoxazole	0	(O)	4	(9)
Others	1	(5)	11	(24)
Subtotal	19	(100)	45	(100)

either a case or control, we were generally able to get leftover bottles and boxes or to identify the brand name of the product (naturally, this was not the case when caretakers reported having given no antibiotic or medication). In a small study of reliability the k statistic for antibiotic history was 0.9, but a formal z-test failed to reject the null hypothesis. This k statistic measured the degree of agreement between the results of the two interviews. The null hypothesis tested was that the histories of antibiotic use collected by different interviewers were independent so they agreed by chance (i.e., the underlying k = 0). The test statistic was provided by the ratio of the observed k over the standard error of the observed k, a ratio that follows the standard normal distribution.

No differences were found between cases and controls with regard to the socioeconomic variables, maternal employment outside of the home, or gender. Variables that were found to have an association with case-control status and that exhibited some potential for confounding the association found between case outcome and antibiotic use were the duration of the illness episode, the severity of illness, low weight-for-age, cessation of breast-feeding before onset of illness, whether or not a physician was visited during the illness, and maternal age (Table 2). The account that follows considers each of these six potentially confounding factors—individually at first and then jointly with antibiotic use.

Duration of Illness

Information on duration of the illness episode was available for 64 of the 65 case-control pairs. Sixty-one percent of the cases but only 17% of the controls had illnesses that lasted less than five days. In 34 pairs the control's illness lasted

more than five days while the case's illness did not. The reverse was true of only 6 pairs, yielding an estimated odds ratio of 5.7 with a 95% confidence interval of 2.1–17.3.

Unpaired stratification indicated that the duration of illness might modify the association between antibiotic administration and case-control status. Therefore, we have presented the unmatched stratified analyses in order to better describe the modification by illness duration. This unmatched analysis should be biased toward the null hypothesis within any strata.

In the "less than five days duration" strata there were 37 fatal cases, of which 11 received antibiotics. There were also 11 control cases in this strata, of which 10 received antibiotics. The unmatched odds ratio was thus 24 with a 95% confidence interval of 2.5–167.0.

In the "greater than five days duration" strata, the effect of antibiotic use was notably diminished. There were 25 fatal cases in this strata, of which 17 received antibiotics; and there were 53 control cases, of which 46 received antibiotics. The unmatched odds ratio was thus 3.1 with a 95% confidence interval of 0.8-11.5. The difference between the odds ratios in these two strata was tested using the Breslow and Day test and was found to be nearly significant at p = .09.

A matched analysis of the association between antibiotic use and illness outcome, stratifying for duration of illness, yielded similar results. However, of 43 matched sets in the stratum of shorter duration, the denominator was 0, although the Mantel-Haenszel adjusted OR was still significant. A conditional logistic regression analysis of the effect of antibiotics, controlling for duration, yielded a point estimate odds ratio of 19.6 with a 95% confidence interval of 2.6–149.4.

There could be further confounding within the "less than five day" group. To maximize the completeness of our con-

Table 2. A comparison of some selected characteristics of fatal ARI cases and matched controls in the 1986–1987 Naucalpan-Tlaxcala study.

Variable (exposed group in parentheses)	Subjects exposed			Discordant pairs				
	Cases		Controls		Exposed	Exposed	Matched pair odds ratio	Logistic regression adjusted odds ratio ^a
	No.	(%)	No.	(%)	cases	controls	(95% CI)	(95% CI)
No antibiotics								
during ARI episode	35	(55)	8	(12)	29	1	29 (3.9-213.0)	28.5 (2.1-393.4)
Duration of ARI								
episode (<5 days)	39	(61)	11	(17)	34	6	5.7 (2.1-17.3)	6.9 (1.1-45.1)
Low weight-for-age								
(<-2 SD)	19	(33)	5	(9)	14	3	4.7 (1.1-29.4)	8.1 (0.8-84.0)
Chest retractions								
during ARI episode	33	(52)	25	(38)	5	14	0.4(0.8-0.2)	0.1 (1.2-0.01)
Maternal age								
(<20 years)	19	(30)	10	(15)	16	7	2.3(0.8-7.0)	7.6 (1.4-79.2)
Breast-feeding stopped								
before onset								
of illness	40	(61)	26	(40)	20	6	3.3 (1.2-10.8)	_
Physician not visited								
during ARI episode	16	(25)	9	(14)	13	5	2.6 (0.8-10.1)	
Mother worked outside								
of home	22	(34)	15	(23)	13	5	2.0 (0.8-10.1)	
Low birth weight								
(<2,500 g)	9	(16)	6	(10)	8	4	2.0 (0.5-10.2)	_
Household without								
piped water	57	(88)	51	(78)	12	6	2.0 (0.6-7.0)	-
Monthly family								
income (< US\$100)	32	(49)	25	(39)	16	9	1.8 (0.7-4.8)	
Household without								
refrigerator	46	(71)	41	(63)	14	9	1.6 (0.6-4.3)	
Sex (male)	39	(60)	36	(55)	16	13	1.2 (0.5-2.9)	
Maternal education								
(<complete primary)<="" td=""><td>26</td><td>(40)</td><td>27</td><td>(41)</td><td>11</td><td>12</td><td>0.9 (0.3-2.4)</td><td>~</td></complete>	26	(40)	27	(41)	11	12	0.9 (0.3-2.4)	~

^aAdjusted for the remaining variables that list odds ratios.

trol over such confounding by the duration of illness factor, we made five unpaired strata of children whose illnesses lasted 1, 2, 3, 4, and 5 or more days. The summary Mantel-Haenszel odds ratio was 4.4 with a 95% confidence interval of 1.6–12.5. A conditional logistic regression controlling the effect of antibiotic use for duration of illness with an interaction term was attempted but failed to converge.

Severity of Illness

Although strict clinical criteria were applied in enrolling both cases and controls in the study, the controls showed some

evidence of actually having had more severe illness than the cases. Information on severity was missing for one death. Fever was present historically in 66% (42) of the cases as compared to 92% (60) of the controls. Cyanosis was present in 33% (21) of the cases and 38% (25) of the controls. Chest retractions were present in 52% (33) of the cases and 74% (48) of the controls. Cough was present in 33% (21) of the cases and 39% (25) of the controls. In a matched pair analysis, 14 pairs were found where chest retractions were present in the control but absent in the matched case. The reverse situation was found in only 5 case-control pairs. These latter findings indicate a significantly higher reporting of severe respiratory illness symptoms in the controls than in the cases (OR = 0.4, 95% CI = 0.8–0.2). The presence of chest retractions was a consistent difference in the disease severity reported for cases and controls, and one that was systematically screened for by use of clinical slides (Photo 2). In further analyses, chest retractions were used as an index of severity of the episode.

In a conditional logistic regression with antibiotic use and the presence of chest retractions the odds ratio for lack of antibiotic use was 31.4 (95% CI = 4.0-246.8), while that for chest retractions was 0.3 (95% CI = 1.3-0.1).

Low Weight-for-Age

Information on the subjects' weight before onset of illness was available for 57 cases, 57 controls, and 52 matched case-control pairs. (It should be noted that weight-for-age was difficult to obtain within the context of our study's design and could only be crudely classified.) In 14 of the matched pairs the case was over two standard deviations below the expected weight for age while the control was above this two standard deviation limit. In three pairs the reverse situation was found. These data yielded a matched pair low weight-for-age odds ratio of 4.7 (95% CI = 1.1–29.4).

In a conditional logistic regression with low weight-for-age and antibiotic use the odds ratio for no antibiotic administration was 24.8 (95% CI = 3.0-205.4), while the low weight-for-age odds ratio was 5.8 (95% CI = 1.1-30.0).

Cessation of Breast-feeding

Whether or not breast-feeding had ceased before the onset of illness could be determined for all the cases and controls. The matched pair odds ratio for failure to breast-feed was 3.3 (95% CI = 1.2-10.8). In a conditional logistic regression with cessation of breast-feeding and antibiotic use the odds ratio for no antibiotic use was 33.3 (95% CI = 4.51-310), while the odds ratio for cessation of breast-feeding was 1.2 (95% CI = 0.4-4.2).

Physician Contact

Information about whether a physician was seen for the illness was lacking in one fatal case. Forty-eight out of 64 cases (75%) saw a physician. Information as to whether antibiotics were used, recorded in 47 of the 48 cases, indicated that only 27 (57%) of these 47 received antibiotics. Fifty-six of the 65 controls (86%) saw a physician. Information about antibiotic use, available for 55 of these 56 controls, indicated that 51 (93%) received antibiotics. Thus the major reason that cases failed to get antibiotics was not because they failed to go to a physician. Rather, they failed to get antibiotics more frequently than controls even when they went to a physician.

In the strata that did not go to a physician, 1 of 15 cases got antibiotics (7%) as compared to 4 of 9 controls (44%). No control of the effect of antibiotics for physician visits is indicated, as this is an intervening variable.

Maternal Age

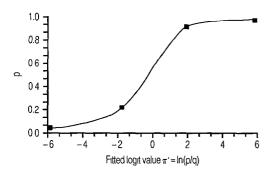
Information regarding maternal age was only missing for one of the fatal cases. In 16 matched pairs the case had a teenage mother while the control did not. The reverse was true in 7 pairs (OR = 2.3; 95% CI = 0.8-7.0). In a conditional logistic regression with maternal age less than 20 years and use of antibiotics, the odds ratio for use of antibiotics was 37.8 (95% CI = 4.6-311.5) while that for maternal age less than 20 years was 3.8 (95% CI = 1.1-13.8).

General Findings

When duration of illness, presence of intercostal retractions, low weight-for-age, and maternal age under 20 years were entered into a conditional logistic regression along with antibiotic use, the odds ratio for antibiotic use was 28.5 (95% CI = 2.1-393.4).

Figure 1 shows the main result obtained by an informal goodness of fit examination. The horizontal axis shows the natural log of the odds of being a case; these values were obtained by plugging each individual's actual values for each variable in the final model into the conditional logistic formula. The vertical axis shows the observed proportion of cases in each quartile. The response function is monotonic and sigmoidal in shape. The Hosmer-Lemeshow chi-square statistic with two degrees of freedom yielded a p value of 0.16, thus failing to reject the hypothesis that the model fit the data. As in any goodness of fit test, a large p value enhances the acceptability of the model.

Figure 1. A chart showing the main result of an informal goodness of fit examination (diagnostic plot of the observed proportion of cases, by quartiles of fitted values, in the final model of the ARI case-control study).



DISCUSSION AND CONCLUSIONS

A central element in the WHO program for control of acute respiratory infections is use of antibiotics. Some public health workers, including the authors, have been skeptical about whether antibiotics could be highly effective in treating an illness that is quite often viral. However, in a manner consistent with other studies (5), the findings reported here suggest a major participation by bacterial infections in severe episodes of ARI. Specifically, the crude etiologic fraction of ARI fatalities among our study children that could have been avoided through antibiotic use was 54%. Even in those cases where antibiotics were used. there is some reason to think that better antibiotic administration might have prevented death.

Our results are consistent with the results of other studies—performed in Pará, Brazil (15), and Tanzania (16)—that have looked at ARI mortality relative to antibiotic use. Both of these studies reported that decreases in severe ARI and infant mortality were achieved with simplified standardized treatments of acute severe respiratory illness episodes in young children. Our study controlled for more extraneous variables than did these other studies.

Factors we were able to control for included the duration of illness, the severity of illness, low weight-for-age, socioeconomic status, the subject's age, and maternal age. The duration of illness probably modifies the effect of antibiotic use, but this study yielded inconclusive evidence of that. Therefore, we decided to control the effect of antibiotics for the duration of illness. The greatest risk from failure to receive antibiotics occurs in the early stage of the illness. Accordingly, we controlled for the possibility that controls had more time in which to receive anti-

biotics than did cases simply because they survived further into the illness. This was done through an unmatched analysis stratifying the duration on each day of illness up to five days and calculating a Mantel-Haenszel summary odds ratio. Even though this analysis was biased toward the null hypothesis by failing to take case-control pairing into account, it still showed antibiotic use to have had a significant effect.

Our data indicate that the severity of illness was greater among the controls than among the cases. This finding is confusing and might cast doubts on the interviewing process as a source of bias. Perhaps interviewers applied less strict criteria when excluding cases from the study than when excluding controls. It is also possible that the history of the illness episode tended to be more complete for the controls than for the cases. In either event, control for severity of illness still indicates antibiotic use had a significant effect; appropriate data relating to severity of illness are included in Table 2 to show that this observed difference was taken into account in reporting the effect of antibiotic use.

As noted above, weight-for-age data were hard to obtain and could only be crudely classified. We see no strong basis, however, for differential weight-forage misclassification. It was demonstrated recently that when major physical symptoms of acute lower respiratory infection like those considered in our study were taken into account, the specificity of the "verbal autopsy" was high (17). Important differences exist between our study population and that studied by Kalter et al. (17) that may preclude generalization of their results to our data; however, theirs is one of few reports on the validation of methods that has been published in this important research area.

Some reports have pointed out the importance of malnutrition and indicators

of low socioeconomic status in ARI prognosis (18, 19). When controls are selected from neighboring or nearby homes, as was done in our study, some important degree of socioeconomic status matching may exist. Then, although key socioeconomic differences may exist and may play an important role in ARI, these differences may not confound other reported associations. In our study, even when several potentially confounding factors were taken into consideration jointly in a conditional logistic regression with little power, the effect of antibiotic use remained strong and significant. Other variables that should be explored by future research include types of treatment other than antibiotic therapy that young children receive (physiotherapy, rehydration, etc.). In our study treatments such as these were received by very few subiects.

The possibility that selection or observer biases could have affected the validity of the finding about antibiotic effects has to be considered. In particular, since only 49% of the potential cases were enrolled in the study, we must consider the chances of selection bias affecting our major relationship of concern. Indeed, incompleteness of death registration in slum urban and rural areas might even have increased the proportion of cases not included. Nevertheless, in general we feel that such cases which were not enrolled were likely to have come from the poorest and least socially stable strata of society and were therefore less likely than enrolled cases to have received antibiotics.

There is also another selection bias that could have influenced our finding. That is, families might have taken their children to hospitals outside of the registration areas where cases were sought for this study. Some of those children might have died in these outside hospitals, either as inpatients or while in emergency rooms.

And while these children would not have been enrolled in the study, they would have been more likely to receive antibiotics.

To assess the possibility that this latter bias affected our results, we made a comparative study of the proportions of deaths occurring at home and in hospitals among our study subjects and among Naucalpan fatalities registered for 1987. Deaths in this latter descriptive study were ascertained using all deaths registered in Naucalpan and not just those recorded for the registration districts included in our main study. We found that the proportion of all Naucalpan children dying from pneumonia and influenza who died at home was 68%, exactly the same as the percentage of case-control study children who died at home. Moreover, only 17% of all Naucalpan infant deaths from pneumonia and influenza were found to have occurred among hospital inpatients. These data indicate little chance that selection bias caused by referral of hospitalized cases could have influenced our findings.

Recall bias might have arisen if the families of fatal cases were less able than the families of controls to remember medications used. Normally, however, we would think that recall bias would affect the results in the opposite direction (i.e., a case's mother recalling all too well a product she blamed for her child's death). Interviewer bias could also have been involved, in that interviewers might not have probed for antibiotic use history with the same thoroughness in dealing with cases as they did in dealing with controls. In this regard it is reassuring to note that there was agreement between the antibiotics cited on the attending physicians' prescriptions and those identified through caretaker recollections and leftover medications.

If we accept that antibiotics can prevent many deaths from ARI among chil-

dren, the findings of this study suggest a need for further research on how that end should be achieved. It is clearly not enough just to get ARI patients to see a physician. They must also be recognized by the physician as having severe cases, and special arrangements must be made to ensure that they get their antibiotics—rather than leaving the physician's office with a prescription that limited resources cannot fill.

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REFERENCES

- 1. Leowski J. Mortality from acute respiratory infections in children under five years of age: global estimates. *World Health Stat Q.* 1986;39(2):138–44.
- Pío A, Leowski J, Luelmo F. Programa de la Organización Mundial de la Salud de infecciones respiratorias agudas en la infancia. Bol Of Sanit Panam. 1984;96(4):283– 95.
- Cárdenas V. Factors contributing to ARI mortality. ARI News. 1987;1(7):7.
- World Health Organization. International classification of diseases, ninth revision. Geneva: 1978.
- 5. Shann F, et al. Aetiology of pneumonia in children in Goroka Hospital, Papua New Guinea. *Lancet*. 1984;2(8402):537–41.

- 6. Gómez F. Desnutrición. Bol Med Hosp Infant Mex. 1946;3:543.
- Schlesselman JJ. Case-control studies: design, conduct, and analysis. New York: Oxford University Press; 1982:171–226.
- Cole P, MacMahon B. Attributable risk percent in case-control studies. Br J Prev Soc Med. 1971;25:242–44.
- Kuritz SJ, Landis JR. Attributable risk ratio estimation from matched-pairs case-control data. *Am J Epidemiol*. 1987; 125(2):324–28.
- Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22(4):719-48.
- Breslow NE, Day NE. Statistical methods in cancer research (vol 1): the analysis of casecontrol studies. IARC scientific publication 32. Lyon: WHO/IARC; 1980:142–46.
- Kleinbaum D, et al. Epidemiologic research: principles and quantitative methods. Belmont: Lifetime Learning Publications; 1982:412– 15.
- 13. Neter J, Wasserman W, Kutner MH. Applied linear regression models. Second edi-

- tion. Homewood, Illinois, and Boston: Irwin; 1989:594–95.
- 14. Hosmer DW, Lemeshow S. Applied logistic regression. New York: Wiley; 1989:135–72.
- Benguigui Y. Controle das infecções respiratórias agudas em crianças, Pará, Brasil. Bol Of Sanit Panam. 1987;102(1):36–48.
- Mtango FD, Neuvians D. Acute respiratory infections in children under five years: control project in Bagamoyo District, Tanzania. Trans R Soc Trop Med Hyg. 1986; 80(6):851–58.
- Kalter HD, Gray RH, Black RE, Gultiano SA. Validation of postmortem interviews to ascertain selected causes of death in children. *Int J Epidemiol*. 1990;19(2):380– 86.
- Tupasi TE, Velmonte MA, Sanvictores ME, et al. Determinants of morbidity and mortality due to acute respiratory infections: implications for intervention. J Infect Dis. 1988;157(4):615–23.
- Victora CG, Smith PG, Barros FC, Vaughan JP, Fuchs SC. Risk factors for deaths due to respiratory infections among Brazilian infants. Int J Epidemiol. 1989;18(4):918–25.



PAHO Participates in Expo '92

The Pan American Health Organization, along with the Inter-American Development Bank, the Organization of American States, and the Inter-American Institute for Cooperation on Agriculture, joined the more than 100 countries participating in the 1992 Universal Exposition (Expo '92) in Seville, Spain, by creating an Inter-American System exhibit for the Pavilion of the Americas. PAHO's contribution consists of interactive videos, an exhibit on health in the Americas, and a high-tech epidemiologic map that illustrates the spread of disease. Expo '92, which began in April and will-run for six months, is expected to host nearly 20 million visitors.

Source: PAHO Today, January/February 1992, p. 3.