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A comparison of 'cough and cold' and pneumonia: risk factors for pneumonia in children under 5 years revisited

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Original Report

A comparison of 'cough and cold' and pneumonia: risk factors for pneumonia in children under 5 years revisited

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Objectives: The aim of this study was to identify and measure the risk factors differentiating upper respiratory infection from pneumonia.

Methods: The World Health Organization's acute respiratory infection case management criteria were used. We studied 259 cases of pneumonia (cases) and 187 cases of 'cough and cold' (controls) among children under 5 years of age at a large tertiary-care hospital in Gilgit, Pakistan. While previous studies used healthy controls, in this study we used controls who had mild infection ('cough and cold').

Results: In the multivariate logistic regression analysis, lack of immunization (adjusted odds ratio (AOR)=1.54, 95% CI 1.0, 2.3), previous history of pneumonia (AOR=1.77, 95% CI 1.16, 2.7), younger age (AOR for each preceding month in children aged up to 59 months=1.01, 95% CI 0.99, 1.03) and malnutrition (wasting) (AOR=2.2, 95% CI 1.0, 5.23) were revealed as important risk factors for pneumonia.

Conclusions: Some of the factors reported in previous studies that used healthy controls were not found to be significant when 'cough and cold' children were used as controls. Nonetheless, malnutrition, younger age, low coverage of immunization and also early childhood mismanagement and respiratory damage were found to be significant factors for development of pneumonia.

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INTRODUCTION

The case management criteria for classification of acute respiratory infections (ARIs) of the World Health Organization (WHO) are based on severity of infection. The clinical spectrum ranges from 'cough and cold' to life-threatening illnesses such as pneumonia. The WHO estimates that ARIs cause 3 million deaths annually in children below 5 years of age worldwide.[1–3] Most ARI deaths occur in developing countries and are mostly due to pneumonia.[4–9] It is important to note that the overall incidence of ARI is similar in developed and developing countries. However, the incidence of pneumonia is greater in developing countries, and the mortality rate is higher as compared to developed countries.[10]

Adequate case management can substantially reduce pneumonia mortality,[11] and is advocated by the WHO as the main control strategy. It is also important, however, to consider preventive strategies. The preferred solution for decreasing ARI mortality will ultimately depend on preventing pneumonia from occurring in the first instance, by reducing risk factors.[10,12] Unfortunately, insufficient and inadequate information has been the main hindrance to the adoption of preventive strategies.

There have been inadequacies in the design of studies to identify the risk factors for pneumonia. Most studies have employed well children from the same neighborhood or those who visited vaccination clinics as controls. Therefore, these studies have identified the risk factors for the acquisition of respiratory infection. Many other studies have identified factors for mortality due to pneumonia, and have compared children who died and who did not die from pneumonia.[13–16] Therefore, it is still not known why for some children ARI becomes more severe than for others.

Research studies have identified a number of risk factors for pneumonia in children under 5 years old. However, there are inconsistencies regarding the information on identified risk factors. Comparative studies conducted in 10 developing countries, including Pakistan, by the Board on Science and Technology for International Development (BOSTID) concluded that

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risk factors for pneumonia perform differently in different societies and study populations. Many studies have identified acute lower respiratory infections (ALRIs) as the outcome, and did not explicitly focus on pneumonia. Studies have used dissimilar criteria for diagnosing both ALRI and ARI, which has made the comparison of risk factors among different studies difficult.[17]

In order to plan interventions to prevent pneumonia, a study design is required that measures factors that contribute to the development of pneumonia. One way of clarifying this is to use a design in which a comparison is made between pneumonia and mild infection such as 'cough and cold'. Pursuing the logic just outlined, the aim of this study was to identify risk factors for pneumonia by taking 'cough and cold' subjects as controls.

METHODS

Study setting

Gilgit is one of the five districts of Northern Areas (NA) of Pakistan. Gilgit town, situated in Gilgit district, is the administrative headquarters for NA. The District Headquarters (DHQ) Hospital Gilgit is one of the largest government health facilities in the NA, is situated in Gilgit town, and receives patients from the town and nearby NA villages.[18] As an estimate, 48 545 children under 12 years of age visited the outpatient department (OPD) or the pediatric unit of DHQ hospital in 1998. A study conducted in Danyore areas of Gilgit district showed that 17% of the population is below 5 years of age.[19] Another study conducted in Gojal/Hunza/Nagar areas of Gilgit district showed that 38% of the population use government health facilities, which is almost double the average for Pakistan (approximately 20% overall).[20,21] Topographically, NA is mountainous and hilly, and lies at 73 degrees longitude and 35 degrees latitude. The climate of Gilgit district is cold in winter and warm in summer. The average temperature is –1.5°C to +15.0°C in winter (November to February) and +15.6°C to +33.7°C in summer (May to August).[22]

Selection of cases and controls

We enrolled all children between 0 and 59 months of age who were residents of Gilgit district and came to the OPD of the pediatric unit of DHQ Hospital, Gilgit during the study period, February to April 2000, considered to be a peak period for respiratory infections. Two physicians diagnosed the patients according to WHO guidelines. The children who came with a history of cough, difficult breathing or both were assessed and classified accordingly by respiratory rate and danger signs (Table 1). Nursing assistants who had received training on WHO ARI guidelines for the diagnosis of 'cough and cold'/pneumonia for a period of 3 months administered a pretested questionnaire. These questionnaires were administered to caregivers of the children in the local dialect at the time of the visit, and children were given treatment according to the WHO guidelines.[23] In order to avoid misclassification of cases and controls, a 3-day follow-up (the day of enrollment was considered as day 0) was done of patients diagnosed with 'cough and cold' at the time of their visit to the OPD, to see if they developed pneumonia. The nursing assistants contacted those patients who did not return for follow-up, at their homes, in the evening of the third day. On the follow-up date (either in the hospital or at home), the respiratory rate was counted again, and other signs of pneumonia were assessed. Caregivers were asked about any other development in the disease that had occurred during the previous 3 days. Therefore, in effect, children with pneumonia or who developed pneumonia were taken as cases, and those with 'cough and cold' and who did not develop pneumonia during the follow-up period were taken as controls (Figure 1).

Children with symptoms of chronic illness such as known cardiac disease, known renal failure, chronic pulmonary disease, e.g. cystic fibrosis, known bronchiectasis, or cough >30 days (suspected pulmonary tuberculosis), or with previous history of wheezing, were not included in the study. Patients enrolled once in the study were not enrolled again if they came with a subsequent episode of illness during the study period. Children brought from other nearby areas outside

Table 1. Classification of acute respiratory infections

For children 2–59 months of age	
No pneumonia (cough and cold)	1. Respiratory rate per minute • <50 (infants aged 2–11 months) • <40 (children aged 12–59 months) 2. No chest indrawing
Pneumonia	1. Respiratory rate per minute • ≥50 (infants aged 2–11 months) • ≥40 (children aged 12–59 months) 2. No chest indrawing
Severe pneumonia	Chest indrawing with or without rapid breathing
Very severe disease	Unable to drink, convulsions, abnormally sleepy or difficult to wake, stridor in calm child
For children under 2 months of age	
No pneumonia (cough and cold)	1. Respiratory rate per minute <60 (young infants under 2 months) 2. No chest indrawing
Severe pneumonia	1. Respiratory rate per minute ≥60 (young infants under 2 months) or Chest indrawing with or without fast breathing
Very severe disease	Unable to drink, convulsions, abnormally sleepy or difficult to wake, stridor in a calm child

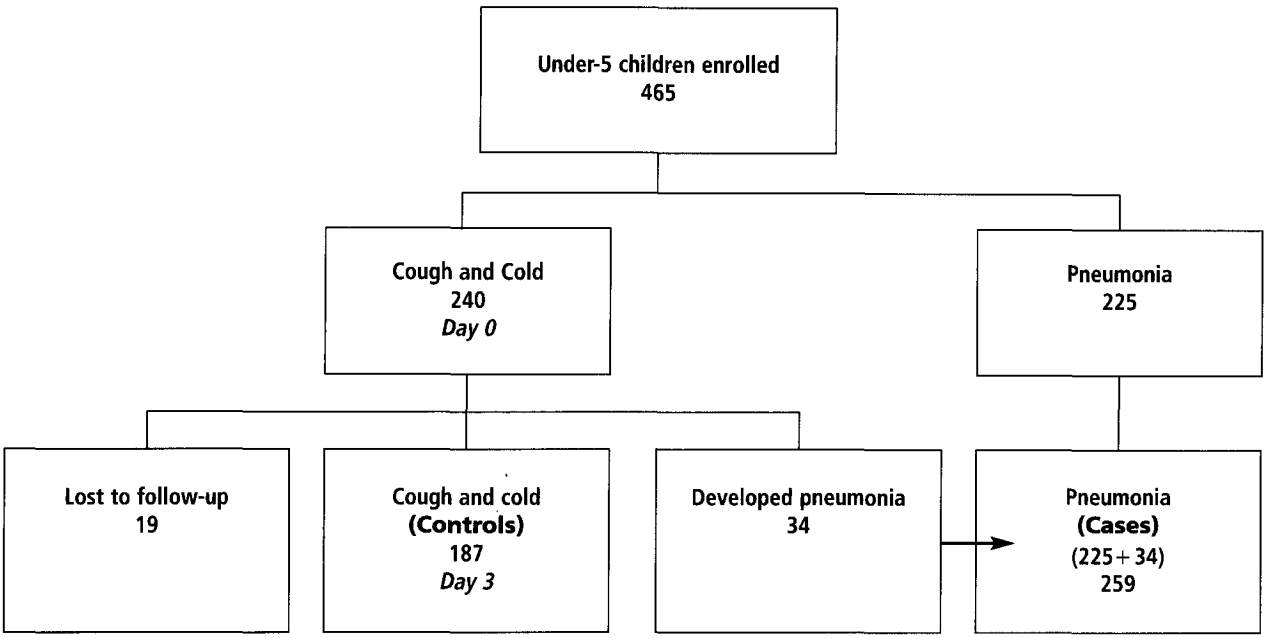

Figure 1. Patient enrollment organogram.

Gilgit district were not included in the study, due to potential difficulty regarding follow-up.

Anthropometric assessment

Body weight in kilograms and height in centimeters of the child were recorded according to recommended standard procedures.[24] Older children (≥2 years) were weighed on a bathroom spring weighing scale in a standing position, with the child's heels together and weight distributed evenly on both feet, while the <2-year-old children were weighed in the lying position on a cradle spring scale. The instrument used to measure height was a metric rule over a vertical wood board, placed against the wall for a child who was ≥2 years old, while a horizontal wood board was used for children <2 years old. As recommended by the WHO for international use, the reference standard was taken from children in the USA.[25]

Sample size

The prevalence of potential risk factors for 'cough and cold' (controls) subjects in this study was considered to be in the range of 20–65%. Pneumonia (cases) and 'cough and cold' (controls) were considered at a ratio of 1 : 1. To detect an odds ratio of ≥2, at alpha of 0.05, with study power (1-beta) of at least 80%, a total of 342 ($n1+n2$) cases and controls was required.[26] Adjusting for potential non-response of 10%, a final sample size of 376 (188+188) was required to detect the putative risk factors.

Data management and analysis

Data were entered using the Epi-info 6 statistical package. The SPSS (version 10) was utilized to analyze the data. We used the chi-square test for bivariate analysis of cross-tabulations to measure crude odd ratios with 95% confidence intervals. For continuous variables, we utilized the two-sample *t*-test to look at differences between means and calculated standard errors of the mean (SE) and 95% confidence intervals for differences between means.

Multivariate logistic regression analysis was carried out to evaluate the combined effect of multiple risk factors, adjusting for confounding variables. We included in the multivariate model all the variables that had shown any biological, social or behavioral significance in the literature. Apart from this, we also made some use of univariate results, and selected the variables that showed some statistical meaningfulness. For that selection, we used a conventional cutoff P-value of ≤0.25.[27] While selecting for variables on statistical cutoff, we were careful not to compromise on any variable which was biologically of potential importance apart from its statistical significance.

RESULTS

We enrolled 465 under-5 children who fulfilled the entry criteria for the study. On enrollment day (counted as day 0), out of 465 children, 225 (48%) were diagnosed as having pneumonia (pneumonia, severe pneumonia or very severe disease), and 240 (52%) were diagnosed as having 'cough and cold'. In the follow-up, on the third day (day 3 from enrollment day), we were not able to trace 19 'cough and cold' patients, who did not return to the OPD and were also not traceable during the follow-up visit at their homes. Thirty-four of the 'cough and cold' patients developed pneumonia during the 3-day follow-up and were therefore excluded from controls

and included as cases. Therefore, analysis was accordingly done on 259 pneumonia (cases) and 187 'cough and cold' (controls) under-5 children (Figure 1).

We collected information regarding the duration of illness, presence of fever, vomiting, and diarrhea. The mean duration of illness of cases was greater compared to controls. Cough was present in 95% of cases and in 97% of controls, while difficult breathing was present in 38% of cases and in only 15% of controls. Vomiting and diarrhea were more common in cases compared to controls, 32% and 33% versus 15% and 23% respectively. Fever was common in both cases and controls, 95% and 92% respectively (Table 2).

There was a significant difference between the mean ages of cases and controls; the ages of cases were lower compared to controls. In our study, we did not find any significant difference in pneumonia with gender of the child. Also, we did not find any significant association of education of parents with pneumonia in the child. Similarly, occupation of the fathers was not significantly associated with pneumonia. There was also no association of increase in number of under-5 siblings with the development of pneumonia compared to children with 'cough and cold' (Table 3).

Wasting was found to be associated with pneumonia. Being underweight and stunting were not significantly associated with the development of pneumonia when compared to 'cough and cold' (Table 4).

Children born at home were more likely to develop pneumonia than were children born at health facilities.

Table 2. Distribution of pneumonia (cases) and 'cough and cold' (controls) subjects in relation to duration and symptoms of illness[a]

	Cases (n=259) n (%)	*Controls (n=187) n (%)*
Duration of illness (in days)[b]	4.6±0.22	4.19±0.26
Cough		
Present	245 (94.59)	181 (96.74)
Absent	14 (5.40)	6 (3.20)
Fever		
Present	247 (95.36)	172 (91.97)
Absent	12 (4.63)	15 (8.02)
Difficult breathing		
Present	98 (38.43)	28 (15.05)
Absent	157 (61.56)	158 (84.94)
Vomiting		
Yes	81 (31.76)	28 (15.05)
No	174 (68.23)	158 (84.94)
Diarrhea		
Yes	84 (32.81)	42 (22.70)
No	172 (67.18)	143 (77.29)
Respiratory rate[b]	55.75±0.76	37.05±0.51

[a]Decreased numbers in cells are due to non response.
[b]Continuous data are given as mean±SE.

Table 3. Distribution of pneumonia (cases) and 'cough and control' (controls) subjects according to the sociodemographic factors, with corresponding odds ratios[a]

	Cases (n=259) n (%)	*Controls (n=187) n (%)*	*Odds ratio (95% CI)*
Age (months)[b]			
Mean	11.6±SE 0.74	14.3±SE 1.04	−2.63 (−5.14, −0.12)
Gender			
Male	165 (63.70)	121 (65.24)	1.07 (0.72, 1.58)
Female	94 (36.29)	65 (34.75)	1.00
Mother's education (years of schooling)			
0	178 (69.26)	116 (62.70)	0.43 (0.22, 0.85)
1–5	24 (9.33)	20 (10.81)	0.55 (0.23, 1.32)
6–10	39 (15.17)	25 (13.51)	0.42 (0.19, 0.95)
11 or more	16 (6.22)	24 (12.97)	1.00
Father's education (years of schooling)			
0	99 (39.28)	61 (33.15)	0.78 (0.48, 1.27)
1–5	23 (9.12)	18 (9.78)	0.99 (0.48, 2.04)
6–10	65 (25.79)	54 (29.34)	1.05 (0.63, 1.77)
11 or more	65 (25.79)	51 (27.71)	1.00
Father's occupation			
Government service	109 (43.95)	73 (40.55)	1.15 (0.76, 1.73)
Private service	139 (56.04)	107 (59.44)	1.00
Number of children under 5 years			
3 or more	68 (26.45)	37 (19.84)	1.44 (0.92, 2.28)
<3	189 (73.55)	149 (80.16)	1.00

[a] Decreased numbers in cells are due to non response.
[b] Mean ages of children in months and difference of means and 95% CIs of difference are calculated.

Table 4. Distribution of pneumonia (cases) and 'cough and cold' (controls) subjects according to nutritional factors, with corresponding odds ratios[a]

		Cases (n=259) n (%)	*Controls (n=187) n (%)*	*Odds ratio (95% CI)*
Underweight (WAZ)	<−2 SD	49 (20.16)	30 (16.30)	1.32 (0.81, 2.21)
	≥−2 SD	194 (79.83)	154 (83.69)	1.00
Wasting (WHZ)	<−2 SD	19 (7.81)	7 (3.80)	2.35 (1.01, 5.71)
	≥−2 SD	224 (92.18)	177 (96.19)	1.00
Stunting (HAZ)	<−2 SD	84 (34.56)	52 (28.26)	1.36 (0.9,2.03)
	≥−2 SD	159 (65.43)	132 (71.73)	1.00

[a]Decreased numbers in cells are due to nonresponse and exclusion due to −6 SD limit.
WAZ, weight-for-age *Z* score; WHZ, weight-for-height *Z* score; HAZ, height-for-age *Z* score.

Children with a history of chest illness in the neonatal period and children with previous history of pneumonia were more likely to develop pneumonia. A history of previous measles was not significantly associated with the development of pneumonia (Table 5).

In order to measure the protective effect of colostrum on the development of pneumonia, we asked about the initiation of breastfeeding of the child after birth. Our hypothesis was that if the mother initiated breastfeeding in the first 72 h, then the child must have received colostrum. Initiation of breastfeeding of a child in the first 72 h after birth appeared to be protective, but this was not statistically significant. Children without immunization appeared to be at increased risk of pneumonia compared to those who were immunized, but the result was not statistically significant in univariate analysis (Table 5).

In order to assess the contribution of these factors to the overall variance while controlling for confounding, multiple logistic regression analysis was conducted. In the final multivariate model, younger age, lack of immunization, previous history of pneumonia and wasting were found to be significant factors for the development of pneumonia compared to 'cough and cold'. Among children up to 59 months of age, extrapolating from a regression analysis, pneumonia was 1.01 times (1%) more likely to develop with each preceding month, as age decreases. Children with pneumonia were 1.54 times more likely to lack immunization than 'cough and cold' children. Children with previous history of pneumonia were about twice as likely to develop pneumonia. Also, children with pneumonia were about twice as likely to have wasting than 'cough and cold' children (Table 6).

Table 5. Distribution of pneumonia (cases) and 'cough and cold' (controls) subjects according to previous morbidities, breastfeeding and immunization status, with corresponding odds ratios[a]

	Cases (n=259) n (%)	*Controls (n=187) n (%)*	*Odds ratio (95% CI)*
Place of birth			
Home	102 (45.13)	46 (28.75)	2.04 (1.3, 3.14)
Hospital	124 (54.86)	114 (71.25)	1.00
Smoker in the house			
Yes	114 (44.2)	88 (46.9)	0.89 (0.60, 1.33)
No	145 (55.8)	99 (53.1)	1.00
Chest illness in early neonatal period			
Yes	47 (27.64)	18 (11.39)	2.15 (1.20, 3.87)
No	170 (78.34)	140 (88.60)	1.00
Previous history of pneumonia			
Yes	128 (52.24)	77 (42.07)	1.50 (1.02, 2.22)
No	117 (47.75)	106 (57.92)	1.00
History of measles			
Yes	25 (10.04)	12 (6.70)	1.55 (0.76, 3.18)
No	224 (89.95)	167 (93.29)	1.00
Initiation of breastfeeding after birth			
≥72 h	73 (29.43)	69 (38.33)	0.67 (0.45, 1.00)
<72 h	175 (70.56)	111 (61.66)	1.00
Immunization			
No	85 (49.70)	53 (39.25)	1.53 (0.97, 2.42)
Yes	86 (50.29)	82 (60.74)	1.00

[a]Decreased numbers in cells are due to nonresponse.

Table 6. Multiple logistic regression analysis showing factors independently associated with pneumonia

	Adjusted odds ratio (95% CI)
Age (0–59 months)	
For each preceding month, then up to 59th month	1.01 (0.99, 1.03)
Immunization	
No	1.54 (1.0, 2.38)
Yes	1.00
Previous history of pneumonia	
Yes	1.77 (1.16, 2.7)
No	1.00
Wasting (WHZ)	
<-2 SD	2.22 (1.0, 5.23)
≥ -2 SD	1.00

WHZ, weight-for-height Z score.

DISCUSSION

The focus of this study was to identify the risk factors for severe respiratory infection (pneumonia) in under-5 children by taking children with mild ARI ('cough and cold') as controls. Previous studies have utilized healthy children or those who visit vaccination clinics as controls, and therefore mostly have identified risk factors for the acquisition of the respiratory infections.[9] Some other studies have looked at the difference between fatal pneumonia and healthy controls, and therefore have measured the factors associated with fatality from pneumonia.[9,27] The BOSTID group of studies has been instrumental in providing the baseline information regarding the risk factors for pneumonia, but was inadequate for elucidating the risk factors for severe respiratory infection.[17]

In some previous studies there have also been inconsistencies in the diagnosis of ARIs and the use of vague and overlapping case definitions. Some studies have used laboratory and radiologic criteria for the diagnosis of pneumonia, but these have greater potential for subjective interpretation.[28] The use of WHO case management guidelines decreases the potential for misclassification of cases of severe and mild infection. These guidelines are meant to identify severe infections, are simple to apply, and have been established to be sensitive and specific.[29] In addition, rigorous 3-day follow-up, which was agreed following consultation with senior pediatricians, was a useful period for detecting any 'cough and cold' patients who acquired pneumonia. This strategy would have further decreased the potential of misclassification of cases and controls, from which some previous studies have suffered.[28,30,31]

Comparison of results of univariate analysis of this study showed that use of 'cough and cold' children as controls leads to loss of associations for some of the risk factors reported for pneumonia from previous studies. These factors were male gender and sociodemographic characteristics of caregivers.[28,30–32] The figures also suggest that male children may be at a greater risk for acquiring ARI as a whole (both 'cough and cold' and pneumonia) than female children. Also, the association of pneumonia with sociodemographic variables has not been a consistent finding, and some previous studies have not found any association with parent's education.[32] In addition, the general sociodemographic characteristics of people of the NA are more alike than different, which might have contributed to the decreased odds ratio.

Relatively few studies have controlled extraneous factors and used a multivariate approach to analysis. Interpretation of results from the multivariate logistic regression analysis may have different implications for individuals than for the population as a whole. For an individual child, the magnitude of an odds ratio determines to what extent the child is at an increased risk if they have the factor. However, a combination of the magnitude of the odds ratio and the prevalence of the risk factor in the population determines to what extent the occurrence of pneumonia can be attributed to the risk factor.

Exposure of fetuses or young babies to environmental tobacco smoke has been found to be associated with pneumonia in previous studies. In our study area, women are not allowed to smoke for cultural reasons. Also, passive exposure to cigarette smoke and heating oil (wood) was not found to be associated with pneumonia. This may be due to open-spaced and well-ventilated houses in the area. Birth at home and respiratory infection in the early neonatal period (first 7 days after childbirth) were found to be associated with increased likelihood of pneumonia compared to birth in hospitals. This could be due to a higher likelihood of aspiration resulting from deliveries conducted by unskilled attendants at homes. Previous studies also support this finding.[33] In Pakistan and South Asia, more than 80% of deliveries are conducted at home, mostly by unskilled attendants.[21] Our study supports the observation that younger age is associated with increased risk of pneumonia.[17,30] Age was analyzed as a continuous variable, and we propose that the risk of pneumonia is inversely and continuously associated with age (adjusted odds ratio for each preceding month in children aged up to 59 months=1.01, 95% CI 0.99, 1.03).[34–35]

Many studies have linked malnutrition with case fatality (pneumonia mortality).[36–39] Also, differing measurements have been reported from various studies regarding the association of malnutrition and pneumonia.[40–42] Except for some studies that give indirect clues,[43] no study has looked at the association of malnutrition with the development of severity of ARI (pneumonia morbidity). Our study clearly delineates the contribution of wasting to the development of pneumonia, and it implies that acute malnutrition could have the potential to avert the development of pneumonia in populations. Protein deficiency appears to inhibit the formation of specific antibodies and also cause impair-

ment of pulmonary defense mechanisms.[44–45] Our study supports the hypothesis that lack of immunization is an important predictor for the development of pneumonia.[30,36]

Some factors should be kept in mind in the interpretation of these results. This study presumes from the outset that 'cough and cold' is itself a risk factor for the development of pneumonia, and therefore does not address the underlying determinants of this condition. Also, in a case–control study, the possibility of recall bias cannot be eliminated. Nineteen 'cough and cold' children could not be followed, and there was non-response for some questions. Through BOSTID studies, it is known that ARI has a seasonal variation in incidence, and, due to limited time and resources, our study was not able to capture the effect of seasonal variations on the studied factors. Instead, we have focused on the period of highest seasonal incidence of pneumonia in NA. In any given year, however, there is a limited possibility that an epidemic viral pathogen could affect the results. This possibility could be minimized by a year-round study, but this was not feasible. There is, however, no evidence of any difference in risk factors due to different times of the year. Also, most studies of risk factors for pneumonia have been conducted in a limited time frame, especially in winter (similar to this study), due to the higher frequency of cases during these months.

This study helps identify putative factors that may have the greatest potential to prevent the development of pneumonia at the population level. The use of WHO criteria for the diagnosis of pneumonia also has wider applicability for developing countries, where Integrated Management of Childhood Illness (IMCI) strategies and case management guidelines are generally applicable.

Several factors reported from studies that used healthy controls were not found to be significant in this study. These include: gender, number of under-5 siblings, particular socioeconomic variables (e.g. educational status, age of mother, educational status, and father's occupation), some anthropometric measurements (being underweight, stunting), and initiation of breastfeeding within 72 h of birth (i.e. child receiving colostrum). We believe that this reflects the purpose of the present study, which is to assess potential risk factors for progression from mild to severe ARI, utilizing as controls patients with 'cough and cold' rather than the more usual choice of healthy controls.

The data from the present study clearly and independently support the hypothesis that reduction in the prevalence of malnutrition (specifically wasting) would have a substantial impact on the prevention of pneumonia (morbidity), which may be seen as the consequence of progression from milder forms of ARI. Young age of the child and early respiratory damage (in the neonatal period, due to aspiration and/or infection) have significance in the development of pneumonia at other times in early childhood. Our results also support the value of immunization in the control of pneumonia, and the related need to improve Expanded Program on Immunization coverage in the NA of Pakistan.

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