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Childhood acute lower respiratory tract infections in Northern Nigeria: At risk factors

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Abstract*: Background:* Childhood Acute Lower Respiratory Tract Infection (ALRTI) remains an important public health problem in the developing world, with significant morbidity and mortality a challenge. An understanding of risk factors in the development of childhood ALRTI may offer clues to prevention of the disease; identify conditions that lead to progression to severe disease, complications and even death in a child receiving treatment.
Aim: to determine risk factors for ALRTI among Under five children hospitalized.
Methods: A prospective study of children aged 2-60 months admitted into hospital with diagnosis of pneumonia and bronchiolitis from November 2011 to September 2012 at the National Hospital, Abuja, Nigeria. With a questionnaire data on socio- demographic and potential risk factors for ALRTI were obtained.
Results: A total of 50 children aged 2-60 months were enrolled, 92.0 % had pneumonia while 8.0% had bronchiolitis. 86.0% of pneumonia subjects were 24months and below, while all those with bronchiolitis were infants. 43(86.0%) of subjects were hospitalized in the rainy season. The weights for height z score was less than minus 2 in 12 (24.0 %) of the subjects. Significant risk factor for ALRTI was the use of kerosene and solid fuel for domestic cooking, 33 (66.0%), p value 0.0001; Mortality was four percent among the infants.
We conclude that younger age under 24 months and exposure to hydrocarbon and biomass from indoor pollution was contributing risk factors for ALRTI in Under five children.

Key words: Acute lower respiratory tract infection, risk factors, hospitalization, under-five.

Introduction

Acute lower respiratory tract infection (ALRTI), primarily pneumonia and bronchiolitis remains a major cause of childhood morbidity and deaths worldwide[1, 2]. Of the estimated 7.6 million deaths in children younger than five years worldwide in 2010, infectious diseases caused 68 percent (5·970 million), with the largest percentages due to pneumonia; 18percent, 1·575 million[1, 2]. Approximately one-half of children younger than five years of age with community-acquired pneumonia (CAP) would require hospitalization[3].
Oyejide CO et al[4] gave an acute respiratory tract infection annual incidence rate of 6.1 to 8.1 episode per year in under five children from a low socioeconomic community in Nigeria, and Yilgwan CS et al[5] reported that 50 percent (39/78) of the children admitted with ARIs were under five children. In a large community-based study conducted by Denny and Clyde, the annual incidence rate of pneumonia was 4 cases per 100 children in the preschool-aged group, 2 cases per 100 children aged 5-9 years, and 1 case per 100 children aged 9-15 years[6]. The WHO Child Health Epidemiology Reference Group (CHERG) estimated the median global incidence of clinical pneumonia to be 0.28 episodes per child-year[7]. This equates to an annual incidence of 150.7 million new cases, of which 11-20 million (7-13%) are severe enough to require hospital admission[7].

Several definite risk factors have been attributed to ALRTI, that include low birth weight for age of less than 2500 grams, prematurity, incomplete immunization against common childhood diseases especially within the first 12months of life, malnutrition of weight -for -age- z -score ≤ 2, lack of exclusive breast feeding in the first six months of life, indoor air pollutants from domestics biomass fuel, presence of coughing sibling (s) at home, overcrowding in bedrooms and schools[8-12]. Other likely risk factors are parental experience as care giver, presence of concomitant disease such as sickle cell anaemia, asthma, HIV/AIDS, diarrhoea diseases and zinc deficiency, while possible risk factors are maternal education, rainfall (humidity) and altitude (cold weather), vitamin A deficiency, attendance to day care,

outdoor pollution and birth order[8-12]. These risk factors for ALRTI could be further categorized as either environmental or constitutional. Maternal education, exposure to fumes/ smoke, exposure to siblings with respiratory infections and dampness in the home as environmental, while constitutional determinants would include gender, atopic predisposition and ethnicity[13]. The agents for most bronchiolitis and pneumonias in children presenting for emergency care are *respiratory syncytial virus (RSV), Streptococcus pneumonia (SP),* and *Haemophilus influenzae* type b (HiB) outside the neonatal period[7-12]. Most children treated with ALRTI have mild to moderate disease and are treated as outpatients with full recovery. However, when pneumonia is severe or very severe, hospitalization is indicated, especially among young infants in the presence of danger signs and compromised immunity, to reduce mortality. Mortality rates from respiratory tract infections are not only more prevalent but more severe, accounting for more than 2 million deaths annually with pneumonia being the number one killer of children in developing societies[8, 14]. The aim of this study therefore was to determine associated risk factors for ALRTI among hospitalized Nigerian children.

Subjects and Methods

The study was prospective and descriptive of children aged 2 to 60 months old, conducted from November 2011 to September 2012 at the National Hospital Abuja, Nigeria. The hospital is a 350-bed hospital with 80 pediatric beds that provides care for the general public, both inpatient and outpatient care. The calculated minimum sample size[15] was 34. The statistical analysis was both descriptive and inferential at 95% confidence interval, zset at 1.96; p, prevalence taken as 4.35% (Yilgwan CS et al[5] report on ALRTI in under five children)[5] d, tolerable error at 0.05. A total of 50 children were enrolled consecutively with a diagnosis of ALRTI by the principal investigator or a colleague paediatrician. Acute lower respiratory tract infection was diagnosed in a child with history of fever, cough, fast or difficult breathing, chest wall in drawing and abnormal auscultation lung finding (crackles/ crepitations or bronchial breath sounds) with or with an abnormal chest radiographic finding[8,16-18]. Chest radiograph finding were evidence of abnormal pulmonary parenchyma disease as documented by a radiologist. Patients with recurrent wheeze or previous admissions for pneumonia were excluded in view of possible asthma, recurrent pneumonia cases or tuberculosis. Tachypoea was defined as respiratory rate of 50 breaths per minute or more for children 2-12 months and 40 breaths per minutes or more for children aged above 12 months to 60 months[17]. Pulse oximeter measures less than 90% oxygen saturation was defined as hypoxia[17]. Upon recruitment, with a structured questionnaire for each subject, information on the subject's age, sex, immunization status, breastfeeding history, including parental educational level and occupation, family religion, housing type and exposure to smoke were recorded. Weight and height were measured and weight for age and height for age - z- score calculated using WHO standards chart for children aged 0-5 years. All subjects were followed up for at least 6months after discharged from admission at the paediatric respiratory clinic of the department. Informed written or oral consent was obtained from the parents and the study was approved by the National Hospital Abuja Ethics Committee. Data was analyzed and means, standard deviation, percentages and tables described for continuous variables, and categorical variables were described using a Chi square test with a p value level of 0.05 set as significant.

Results

A total of 50 children aged 2 to 60 months were recruited for the study. 50 (M 24, F 26) were admitted and treated for ALRTI (pneumonias 46, bronchiolitis 4). The four subjects with bronchiolitis were aged 10 weeks (F), three months (M, F) and seven months old (M). Of the 22 males with pneumonia, 14(63.6%) were aged 2-12months; 7(31.8%) 13- 24 months; while of the 24 females, 14(58.3%) were aged 2-12months and 8 (33.3%) were aged 13- 24months. Forty three (86.0%) of the study subjects were aged 24months and below, with none above 49 months. The mean ± SD weights and heights for subjects aged 2-12months was 7.06 ±1.30kg and 65.81 ± 6.20cm for all males and 6.73 ±1.97kg and 65.63 ±7.39cm for females. The weights and heights distribution for both males and female did not show any significant differences (tables 1and 2). Seven (29.2%) of the males had a weight for height z score < -2.0, while 5(19.2%) of the females had weight for height z score < - 2.0. The peak period of ALRTI hospitalization was between the months of May to October, height of the rainy season, with 43(86.0%) admissions.

Table 1: Age, Sex and Weight Distribution of ALRTI Subjects

Ages (months)	No (%)	Male Mean ±SD Wt(kg)	Female Mean± SD Wt(kg)	P value	95% CI
2-12	28(56)	7.06 ±1.3	6.73±1.97	0.5376	.033(-0.7559 – to 1.4159)
13-24	15(30)	9.1±1.17	9.59±1.02	0.8637	0.1(-1.1336 to 1.3336)
25-36	5(10)	13.5±0.3	11.6±2.26	0.3432	1.9(-7.7435 to -7.7485)
37-48	2(4)	14±0	12.5±0		

The weight distribution of the males and female subjects did not show any significant difference in table 1

Table 2: Age, sex and height distribution of ALRTI subjects

Ages (months)	No (%)	Male Mean ±SD Ht(cm)	Female Mean± SD Ht(cm)	P value	95%CI
2-12	28(56)	65.81±6.2	65.63±7.39	0.9454	0.18(-5.1683 to 5.5283)
13-24	15(30)	80.29±6.65	81.43±6.67	0.7461	-1.14(-8.5857 to 6.3057
25-36	5(10)	94±4	94±1.63	1	0.0(-7.7435 to 7.7485)
37-48	2(4)	105±0	103±0		

The Height distribution of the males and female subjects did not show any significant difference in table 2.

Overall breast feeding rate was 96.0, p value <05; 15 (30.0%) were exclusively breast fed for 6months and mean duration for ever breastfeeding was 9.12 ± 5.55 months. 92.0%, p value <0.5; had completed immunization for age according to the National Programme of Immunization (NPI) schedule. 4(8.0%) of family members had a history of smoking tobacco, use of multivitamin supplementation, 10(20%); while use of kerosene or fire wood/ coal as cooking fuel was 66.0%; p value < 0.05. The religion of the families were 13(26.0%) Islam, and 37(74.0%) Christians; p value 0.0022. Housing types was 94.0% western; p value <0.05; 43(86%) of the families were urban settlers (table 3).

Table 3: Risk and benefit Factors for ALRTI

Variable	No 50 (%)	x^2	P value	95%CI
Ever breastfed 15(30%had ex Bf for 6months)	48(96)	29.524	<0.0001*	0.8654 to 0.9889
Immunization	46(92)	28.227	<0.0001*	0.3297 to 0.596
Smoker in the house	4(8)	0.973	0.3304	0.0315 to 0.1884
Multivitamin usage	10(20)	4.867	<0.0001*	0.1124 to 0.3304
Kerosene/wood usage	33(66)	9.084	<0.0001*	0.2159 to 0.4683
Christianity	37(74)			
Islam	13(26)	3.1	0.0022*	
Mud	3(6)			
Western	47(94)	4.7	<0.0001*	
Urban	43(86)			
Semi urban	1(2)			
Rural	6(12)			

*Significant, (p<0.05) shown in table 3

The mean maternal age was 30.80 ± 6.06 years, while 72.0% of the fathers and 67.0% of the mothers had educational level post secondary, while average number of people in the homes was 5.70 ± 2.56, and 30(60.0%) having >3-≤6 person per room. 26 (52.0%) families were from socioeconomic classes (SEC) 1, 16(32.0%) SEC2 and 8(16.0%) SEC3, p value 0.30068, x^2 7.2234, df 6 (table 4).

Major clinical features were fever, cough, chest crackles, tachypoea and tachycardia with abnormal chest x-ray findings shown in table 5. Mean ± SD respiratory rate (RR) was 55.54± 15.69 for all patients. The RR was significantly higher for those below 12 months, (p=0.002) shown in table 6. Mean heart rate (HR) for all patients were 135.56 ± 19.10. HR was not significantly difference between the ages 2-12 months and 12-59 months.

Forty four (88.0%) patients had abnormal chest radiographs. Two had repeated convulsions with Spo2 levels below 85.0%. Pneumothorax, emphysema and pleural effusion were found in two each, who had chest tube insertion for drainage. Repeat chest radiograph at four weeks follow up showed complete resolution of parenchyma lesions. There were two deaths, a male and female, from pneumonia, aged six months and below (table5).

Table 4: Socio- economic as risk factors for ALRTI in Subjects

Variable	Mean ± SD; N (%)	x^2	P value
Mother's Age (years)	30.80 ± 6.06		
Father's Age (years)	38.63 ± 7.17		
Parental Education		1.976	0.3726
Primary			
Father	4(8)		
Mother	7(14)		
Secondary			
Father	14(28)		
Mother	12(24)		
Tertiary			
Father	32(64)		
Mother	31(62)		
Number of people in the home	5.70 ± 2.56		
Rooms in the home	2.10 ± 1.18		
No in home			
1-3	8(16)		
>3-≤6	30(60)		
>6	12(24)		
SEC1	26(52)	x^2	P value
SEC2	16(32)	7.2234 ,df	0.300685
SEC3	8(16)	6	

SEC –socioeconomic levels 1, 2, and 3. *The socioeconomic status show a significant difference; (p<0.05) as shown in table 4

Table 5: Distribution of the Clinical features

Clinical features	Number	Percent
Fever	50	100
Cough	49	98
Crackles	49	98
Fever	46	92
Chest in-drawing	46	92
Pallor	17	34
Cyanosis	4	8
Abnormal Chest xray	44	88
Tachypoea (cycles/min) Mean ±SD	55.54 ± 15.69	
Heart rate (beats/min) Mean ±SD	135.56 ±19.10	
Pneumonia	46	92
Bronchiolitis	4	8
Deaths	2	4

Table 6: showing the Respiratory rate (RR) and Heart rate (HR) of the age groups of the children with ALRTI

Ages	Mean RR	N	Std. Deviation	Fisher's exact	Sig
2-12 months	61.43	28	15.074	10.747	0.002*
>12-59months	48.05	22	13.311		
Total	55.54	50	15.690		
Ages	Mean HR	N	Std. Deviation	Fisher's exact	Sig
2-12 months	138.93	28	17.668	2.020	0.162
>12-59months	131.27	22	20.392		
Total	135.56	50	19.104		

*The RR was significant for the children 12 months and below with ALRTI (p=0.002), while HR was not significantly different between the children ages 2-12 months with those age 12-59 months shown in table 6.

Discussion

This report was hospital based to investigate risk factors associated with ALRTI. Acute lower respiratory tract infection, mainly pneumonias and bronchiolitis have been previously highlighted as a common cause of childhood morbidity and mortality encountered in several children emergency care settings[1,2,5- 8,11,17,20,21]. Similar to other reports[5,12,17, 20- 22], this report had 86 percent of children with pneumonia aged two years and below, while bronchiolitis remaining a disease of infancy. In the Yilgwan CS et al report on 39 Under five children hospitalized with acute respiratory infections (ARIs), bronchiolitis was among infants; while those with pneumonia were mostly 0-11 months old, 42.1percent; 12- 36 months, 72.7 percent and all (100 percent) aged 36 months[5]. Our report did not record any patient above 49months old. Symptoms of fever, cough, fast and difficult breathing, convulsions; with signs of tachypnoea, tachycardia, chest in-drawing and crackles, and abnormal chest x-ray findings, were similar to other reports[5, 8,16,19]. The World Health organization (WHO) recommends the use of increased respiratory rate as early sign for diagnosis of pneumonias[17]. The mean ± SD respiratory rate in this series was 55.54 ± 15.69 for all patients and 61.43 ±15.07 for 2-12months olds (p value 0.002).

This report show that tachypoea was significant for ALRTI in the 28 (56.0%) patients aged 2-12months when compared to those above 12months. A rapid respiration in infants should be considered a high point for suspicion and early treatment of ALRTI in infants. This view is supported by the WHO guideline for diagnosis and management of childhood acute respiratory infections[17]. However, an earlier report by Tagbo BN et al[22] on 101 children of which 52 (51.5percent) had radiological evidence of pneumonia, 38 (73 percent) had respiratory rate ±50/minutes, while 43 (83 percent) had respiratory rate ±40/minutes. They found respiratory rate to be least reliable as an indicator of pneumonia in children 2-11 months (p value >0.005). They suggested that it was due to wide variation in respiratory rates in the younger child compared to those aged 12-35 months (p value <0.005) where it was highly sensitive predictor of pneumonia. An abnormal radiological finding in patients with pneumonia was found in 44 (88 percent) in this report. This is much higher than the WHO reported 34.3 percent rate for clinical diagnosis of radiographic pneumonia in children presenting to a pediatric emergency department[23]. Severe pneumonia with danger signs were seen among the subjects. The presence of severe or very severe disease is an indication for hospitalization in childhood pneumonia[17]. However, hospitalization can be affected by parents' care seeking behavior, access to hospitals, financing, and medical professionals' threshold for admission which varies widely within and across geographic settings[16].

Breastfeeding rate was over 90 percent, (p value <0.05) with exclusive breast feeding of six months in 15 (30.0percent). An adequate period of exclusive breast feeding followed by continued breast feeding and an appropriate complementary feeding has been shown to protect young infants against respiratory tract infections, while a lack of breast feeding predisposing young infants to pneumonias and diarrhea diseases[8-12]. Compared with breastfed infants, formula-fed infants have been shown to face higher risks of infectious morbidity in the first year of life, because they lack specific and innate immune factors provided in human milk which protect against infection, particularly against the common respiratory pathogens, such as *Haemophilus influenzae* and *Streptococcus pneumonia*[24,25]. Reported vaccination rates among study subjects was over 90 percent (p value <0.05), mainly covering the six antigens used in the National programme on immunization schedule. An effective immunization would be expected to protect children from respiratory tract infections such as pertussus and measles and invasive diseases. However, the immunization coverage during the period of study did not include the routine use of pentavalent vaccine that is inclusive of pneumococcal antigens and Heamophilus influenza type b. These agents have been shown to contribute significantly to childhood pneumonias and other invasive diseases[8,11,26], Evidence show that a significant reduction in pneumonias can be achieved with the pentavalent vaccine in children and HIV positive individuals[26,27].

The socio-economic class of the parents was not a significant risk factor in this report (p value 0.30065). This can be deduced from the findings of over 65 percent of mothers having post secondary education, non- overcrowded living conditions as 76 percent of home have one to six persons in a room, and 52 percent families are of upper social class, who mainly are urban dwellers, living in western type housings. Only 24 percent having more than six occupants in a room. Exposure to indoor smoke from use of hydrocarbon and solid domestic fuel was found a significant environmental risk for respiratory tract infections[13], though exposure to passive smoking from tobacco use was low. Other environmental risk factors such as role of day care and siblings contact were not assessed in the present study as limitations. The rainy season weathers are associated with drop in ambient temperatures when most of the patients were enrolled (86.0 percent). Home dampness in the presence of moulds, water leakages, and moisture on walls and ceiling were not assessed, but a few families in the present study lived in mud type housing and in rural settings which would contribute to dampness during the rainy season.

This report shows that some of the ALRTI patients were stunted, with weight for height z score less than minus two. Malnutrition has been highlighted as a significant cause of childhood illnesses that include pneumonia. This can be as micronutrient or macronutrient deficiencies. Vitamin D has been shown to both increase the severity and overall prevalence of acute lower respiratory infections and is an important factor in determining the mortality rates from severe forms of respiratory infections[28].

Another earlier report found vitamin D deficiency in infants exclusively breast fed[29]. Micronutrients deficiencies may be multiple, many of which function as cofactors or regulatory molecules in immune or inflammatory cascades (e.g. vitamins C, D, selenium)[30]. However, these deficiencies will further predispose to anaemia in childhood. This supports the several micronutrient interventions programs in use to both protect and prevent children from developing acute lower respiratory infections. The aetiology of malnutrition in the present study was not assessed. Thirty four percent of the study subjects had clinical pallor which would contribute to malnutrition. There were two deaths among infants with very severe pneumonia. Sewlyn et al also reported that the incidence and case-fatality of ALRTI were consistently higher among younger children aged less than 18 months[12].

Conclusion

Young age of less than 24months, exposure to solid fume from indoor pollutants, are important risk factor for subjects with ALRTI among those hospitalized.

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References

1. Rudan I, O'Brien KL, Nair H, Liu L, Theodoratou E, Qazi S, et al Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. *J Glob Health. 2013; 3(1): 010401.*
2. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet. 2012; 379:2151–61.*
3. Margolis P, Gadomski A. The rational clinical examination. Does this infant have pneumonia? *JAMA 1998; 279:308.*
4. Oyejide CO, Osinusi K. Acute respiratory tract infection in children in Idikan Community, Ibadan, Nigeria: severity, risk factors, and frequency of occurrence. *Rev Infect Dis. 1990; 12 Suppl 8:1042-6.*
5. Yilgwan CS, John C, Abok II, Okolo SN. Pattern of acute respiratory infections in hospitalized children under five years in Jos Nigeria. *Niger J Paed 2013; 40 (2):150- 153.*
6. Denny FW, Clyde WA Jr. Acute lower respiratory tract infections in non hospitalized children. *J Pediatr. 1986; 108 (5):635-46.*
7. Rudan I, Tomaskovic L, Boschi-Pinto C, Campbell H. Global estimate of the incidence of clinical pneumonia among children under five years of age. *Bull World Health Organ. 2004; 82(12):895-903.*
8. Rudan I; Boschi-Pinto C; Biloglav Z; Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. *Bull World Health Organ 2008; 86 (5) 408.*
9. WHO/UNICEF. Global action plan for prevention and control of pneumonia (GAPP). Geneva, World Health Organization, 2009.
10. Sazawal S, Black RE. Effect of pneumonia case management on mortality in neonates, infants, and preschool children: a meta-analysis of community-based trials. *Lancet Infect Dis 2003; 3: 547-56* (abstract).
11. Greenwood BM, Weber MW, Mulholland K. Childhood pneumonia – preventing the world's biggest killer of children. *Bull World Health Organ 2007; 85: 502-3.*
12. Selwyn BJ. The epidemiology of acute respiratory tract infection in young children: comparison of findings from several developing countries. Coordinated Data Group of BOSTID Researchers. *Rev Infect Dis 1990; 12 (suppl 8): 870-88 (abstract).*
13. Karevold G, Kvestad E, Nafstad P, Kvaerner KJ. Respiatory infections in school children: co-morbidity and risk factors. *Arch Dis Childhood 2006; 91:391-395*
14. Wardlaw T, Salama P, Johansson EW, Mason E. Pneumonia: the leading killer of children. *Lancet 2006; 368:1048.*
15. Lwanga SK, Tye CY, Ayeni O. Teaching health statistics, lesson and seminar outlines, 2nd Ed. Examples of sample size determination. *World Health Organization, Geneva 1999;76- 78.*
16. Lanata CF, Rudan I, Boschi–Pinto C, Tomaskovic L, Cherian T, Weber M, et al. Methodological and quality issues in epidemiological studies of acute lower respiratory infections in children in developing countries. *Int J Epidemiol. 2004; 33: (6)1362–72.*
17. Integrated management of childhood illness revised chart book. *World Health Organization* 2014. Website http://www.who.int.
18. Bennett NJ, Domachowske J. Pediatric Pneumonia Clinical Presentation. http://emedicine.medscape.com/article/967822. Accessed 24/11/2014.
19. WHO/UNICEF. The integrated Global action plan for pneumonia and diarrhoea (GAPPD). 2013.
20. Ohiaeri CN, Akinsulie OA, and Renner JK. Pattern of presentation and risk factors of acute respiratory infection in Under five old in Mushin Local government area of Lagos State. *Nig Ot J Hosp med 2003; 13:24-26.*
21. Ujunwa FA, Ezeonu CT. Risk Factors for Acute Respiratory Tract Infections in
22. Under-five Children in Enugu Southeast Nigeria. *Ann Med Health Sci 2014; 4: 95-99.*
23. Tagbo BN, Ude AC, Ibe BC. Predictive value of respiratory rate thresholds on pneumonia among preschool children. *Nig J Paediatr 2002; 29 (4):108-12.*
24. Wingerter SL, Bachur RG, Monuteaux MC, Neuman MI. Application of the World Health Organization Criteria to Predict Radiographic Pneumonia in a US-based Pediatric Emergency Department. *Pediatr Infect Dis J. 2012; 31(6):561-4.*
25. Hamosh M. Bioactive factors in human milk. *Pediatr Clin North Am. 2001; 48:69–86.*

26. Alison Stuebe.. The Risks of Not Breastfeeding for Mothers and Infants. *Rev Obstet Gynecol. 2009; 2(4):222–231.*
27. Flannery B, Heffernan RT, Harrison LH et al. Changes in invasive Pneumococcal disease among HIV -infected adults living in the era of childhood pneumococcal immunization. *Ann Intern Med. 2006;(1) 144: 1-9.*
28. Madhi SA, Petersen K, Madhi A, Wasas A, Klugman KP. Impact of human immunodeficiency virus type 1 on the disease spectrum of Streptococcus pneumoniae in South African children. *Pediatr Infect Dis J. 2000; 19(12):1141-1147.*
29. Manaseki-Holland S, Qader G, Isaq Masher M, Bruce J, Zulf Mughal M, Chandramohan D, Walraven G. Effects of vitamin D supplementation to children diagnosed with pneumonia in Kabul: a randomised controlled trial. *Trop Med Int Health 2010;15(10)1148–55.*
30. Dawodu A, Agarwal M, Hossain M, Kochiyil J and Zayed R. Hypovitaminosis D and vitamin D deficiency in exclusively breast-feeding infants and their mothers in summer: A justification for vitamin D supplementation of breast – feeding infants. *J Pediatr 2003;142:169-73.*
31. Maggini S, Wintergerst ES, Beveridge S, Hornig DH. Selected vitamins and trace elements support immune function by strengthening epithelial barriers and cellular and humoral immune responses. *Br J Nutr 2007;98:29-35.*