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THE EFFECTS OF VITAMIN D SUPPLEMENTATION ON THE INCIDENCE OF PNEUMONIA IN INFANTS AND YOUNG CHILDREN IN KABUL, AFGHANISTAN:
A DOUBLE BLIND RANDOMIZED CONTROLLED TRIAL

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Thesis submitted to the Faculty of Medicine of the University of London for the degree of Doctor of Philosophy (PhD)

Revised July, 2011
DECLARATION

I have read and understood the School's definition of plagiarism and cheating given in the Research Degree Handbook. I declare that this thesis is my own work, and I have acknowledged all results and quotations from the published or unpublished work of other people.

Signed: ______________________________ Date: ..........14.7.2011

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SCOPE OF WORK OF THE CANDIDATE FOR THE PHD

1. Contributed in the final stages of the protocol development.

2. Developed the standard operating procedures (SoP) and the all study forms with input from other co-investigators.

3. Developed the verbal autopsy form into local language, modifying the standard WHO verbal autopsy form, and conducted the interviews with families lost their children during the follow up stage.

4. Piloted the study SoPs and forms and trained all study staff.

5. Managed the day to day running of the project.


7. Reported death cases to data safety monitoring board within 48 hours after a child passed away.

8. Conducted quarterly Oversight Committee Meetings, with members and partners from local and international institutions, and presented quarterly progress of the study.

9. Conducted regular meetings with community and local municipality leaders to communicate day to day progress of the study, as well as, to resolve likely problems in the field.

10. Supervised the clinical part of the study, including conducting weekly meeting with study doctors and supervisor to ensure for quality of data and provide them with sufficient technical support.

11. Developed the sub-studies of risk factors of pneumonia.

12. Supervised the data management and cleaned all the data.

13. Reviewed literature and developed the analysis plan.

14. Conducted the analysis and wrote the report.
WORKS THE CANDIDATE WAS NOT INVOLVED

1. Did not contribute in developing the proposal for this study.
2. Was very less involved in application process for Ethics Review Committee.

REGISTRATION

This trial was registered in NIH ClinicalTrials.gov register with identifier NCT00548379.

PUBLICATION

A paper on primary end point of the study has been submitted to Lancet for publication.
ABSTRACT

Afghanistan has one of the highest infant mortalities in the world, and pneumonia is one of the main killers. Moreover, Dietary intake of vitamin D is low and exposure to sunlight is limited due to widespread use of Burqa by women. Two studies in Ethiopia and India suggest that vitamin D deficiency may substantially increase the risk of severe pneumonia among children under-5. Thus a randomized controlled trial was conducted to assess effects of vitamin D on the incidence of pneumonia.

The study was conducted on 3046 children aged 1-11 months (approximately 1500 per arm), in Kabul, Afghanistan. Intervention group was given quarterly 100,000 IU vitamin D (6 doses in total), and control arm received placebo (olive oil). Active and passive surveillance of pneumonia was done for 18 months.

Time to the first episode in the Vitamin D group was compared to that in the placebo group using log rank tests and proportional hazards models. The incidence rate ratio for the episodes of pneumonia was calculated using Cox proportional hazard models.

Vitamin D had no effect on the incidence of first or only episode of x-ray confirmed pneumonia (RR=1.06, 95% CI: 0.89 – 1.27; p=0.47). The incidence of repeat episodes of x-ray confirmed pneumonia was higher in the vitamin D group (RR=1.68; 95% CI: 1.28 – 2.21; p<0.001). Infants 6-12 months old had a higher incidence of pneumonia compared to those <6 months old (RR=2.01; 95% CI: 1.12 – 3.63). Children of fathers without any formal education had a higher incidence of repeat episodes of pneumonia compared to children of fathers having any formal education (RR=1.67, 95% CI: 1.20 – 2.29).

Vitamin D supplementation is not useful to reduce the incidence of pneumonia in children. The effective implementation of measles, DPT, Hib, and pneumococcal vaccines, and IMCI guidelines remain the key strategy to reduce the burden of pneumonia in Afghanistan.
ACKNOWLEDGEMENT

I would like to extend my thanks to all families who kindly took part in this trial. Thanks to head of municipalities for keeping their support for this project’s field works. I am grateful to Wakils, Mullahs and security in-charges for their endless assistance during field data collection.

I am very thankful to my supervisor, Professor Daniel Chandramohan, Dr Semira Manaseki Holland, and Jane Bruce for their kind assistance and support in all aspects of this study. My special thanks to Jane Bruce for her endless support in data analysis. I am thankful to the entire study staffs, including field supervisors and clinical pediatricians, who patiently performed their daily responsibilities.

I thank Pakistan Institute of Medical Sciences (PIMS), ARI Unit for assisting in interpretation of chest x-rays and thanks to the pharmacy of Aga Khan University (AKU) for their special support in providing this study with vitamin D and placebo syringes.

Many thanks to Francesco Checchi for his technical advice on some parts of my PhD work, and I am very thankful to Asad Rehman from ITD computing, who provided IT support during my PhD work at LSHTM. My special thanks to Annemarie Ter Veen for all her support when I first came to London, and many thanks to Silke Lutzelschwab, who came to Kabul for teaching me Stata.

I would like to thank USAID, Afghanistan and Washington States University for providing me with scholarship to come to London and complete my PhD. I also thank all sponsors of this trial, such as The Welcome Trust, British Council, UNICEF, Roshan, AKHS, and International Association of National Public Health Institution.

Finally, I would love to thank my honorable family, specially my mother, my father, my wife, my lovely two years old son (Ahmad Mutahar Maroof), my brother, and my sisters, who took over all home responsibilities and made it possible for me to come to London and complete my PhD.
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<tr>
<td>AKHS,A</td>
<td>Aga Khan Health Service, Afghanistan</td>
</tr>
<tr>
<td>AKUH</td>
<td>Aga Khan University Hospital</td>
</tr>
<tr>
<td>ALRI</td>
<td>Acute Lower Respiratory Tract Infection</td>
</tr>
<tr>
<td>ARI</td>
<td>Acute Respiratory Tract Infection</td>
</tr>
<tr>
<td>CONSORT</td>
<td>Consolidated Standards of Reporting Trials</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>CSO,A</td>
<td>Central Statistics Office, Afghanistan</td>
</tr>
<tr>
<td>HMIS</td>
<td>Health Management Information System</td>
</tr>
<tr>
<td>IMCI</td>
<td>Integrated Management of Childhood Illness</td>
</tr>
<tr>
<td>IPD</td>
<td>Inpatient Department</td>
</tr>
<tr>
<td>KMU</td>
<td>Kabul Medical University</td>
</tr>
<tr>
<td>LSHTM</td>
<td>London School of Hygiene and Tropical Medicine</td>
</tr>
<tr>
<td>MICS</td>
<td>Multi Indicator Cluster Survey</td>
</tr>
<tr>
<td>MoHE</td>
<td>Ministry of Higher Education</td>
</tr>
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<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
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<tr>
<td>RSV</td>
<td>Respiratory Syncytial Virus</td>
</tr>
<tr>
<td>TLR</td>
<td>Toll-like Receptors</td>
</tr>
<tr>
<td>UAE</td>
<td>United Arab Emirates</td>
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<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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CHAPTER 1: INTRODUCTION

1.1 Burden of Pneumonia

Each year 10.5 million children <5 years of age die worldwide, of which 98% occurs in developing countries (2). Afghanistan has the 3rd highest under-5 mortality in the world (257/1000 Live births) after Sierra Leone and Angola (3). The infant mortality rate was 165/1000 live births in 2005 (3). However a recently published report by Ministry of Public Health (MoPH), Afghanistan showed a marked reduction in under-5 and infant mortalities in 2006 (191/1000 live births and 129/1000 live births respectively) (4). The under-5 mortality rate in district 1 of Kabul city was estimated 0.02 (95% CI: 0.01 – 0.02) per child year in 2008 (5). One of the global Millennium Development Goals is to reduce child mortality by two-third by 2015 compared to 1990 (6). Afghanistan aims a 50% reduction in under-5 mortality by 2015 and a 66% reduction in infant mortality by 2020 compared to the levels observed in 2003. (7).

The number of deaths attributable to childhood pneumonia globally was estimated 1.9 millions in the year 2000 (8). Around 19% of under-5 mortality globally is attributable to pneumonia (9). The incidence of pneumonia in children under-5 years of age has been estimated 0.29 episodes per child-year in developing countries and 0.05 episodes per child-year in developed countries (8). The global annual new episodes of pneumonia is estimated 156 million of which 151 millions episodes occur in developing world (8). Another estimate suggests that the mean annual number of new cases of pneumonia is 146.5 millions in developing countries (10). South-east Asia has the highest incidence of pneumonia in children under-5 (0.36 episodes per child-year) followed by Africa (0.33 episodes per child-year) (8). A multi-indicator cluster survey (MICS) conducted by UNICEF in 2003 in Afghanistan showed that the prevalence of pneumonia in a two week period in children under-5 was 19% (11).
1.2 Vitamin D deficiency - a risk factor for pneumonia

Vitamin D is an essential micronutrient. Its role in regulating bone mineralization is well understood (12). Vitamin D is essential for skeletal development and cellular functions due to its effects on Calcium homeostasis and promoting absorption of calcium from intestine (13). Vitamin D is mainly produced in the skin after exposure to ultraviolet B rays (13). If sun exposure is limited due to different reasons, it can be maintained through the intake of foods and supplements rich in Vitamin D (13).

Recently the function of vitamin D as a key link between Toll-Like receptors activation and antimicrobial responses in innate immunity has been shown (12). Two hospital-based case-control studies from Ethiopia (14) and India (15) suggest that vitamin D deficiency may substantially increase the risk of severe pneumonia among children.

1.3 Prevalence of vitamin D deficiency

Vitamin D deficiency is defined as 25-hydroxyvitamin D level ≤ 20 ng/mL (16). It has been estimated that overall 1 billion people have vitamin D deficiency (16). Nutritional rickets is the main manifestation of Vitamin D deficiency (17), and rickets remains a common disease around the world (18). The prevalence of Vitamin D deficiency rickets, a common problem in many developing countries, ranges from 5 to 45% in children under-5, even where there is abundant sunlight: Turkey (19), Iran (20), Saudi Arabia (21), India (15), (22), China (23), (24), Mongolia (25), Algeria (26), and Nigeria (27), (28). The disease remains an endemic problem in many developing countries and has re-emerged in some developed countries (29). The main risk factors for rickets during infancy include exclusive breastfeeding without vitamin supplementations, dark skin pigmentation, decreased sunlight exposure, winter season, increased latitude, and maternal vitamin D deficiency (18), (30), (31).

In Afghanistan, dietary intake of vitamin D is low and exposure of pregnant women to sunlight is also limited due to the widespread use of Burqa. A small proportion of population with better socio-economic status can afford quality food rich in vitamins and micronutrients. Therefore, foods rich in vitamin D, such as fish and liver, are not
affordable. Moreover, because Afghanistan is a land-locked country with little water resources, fish products are not commonly found in the market. Fortified formulas with vitamin D are not produced in the county, and fortified milk imported from other countries is very expensive. Other dietary sources of vitamin D, such as eggs, are commonly found and consumed by majority of the families. Swaddling of infants that reduces exposure to sunlight is also a common practice (32). Thus young children are at a high risk of vitamin D deficiency.

1.4 The study questions

1.4.1 Primary question

Will 3-monthly vitamin D supplementation reduce the incidence of radiological confirmed pneumonia among <24 month old children living in a socio-economically deprived community of Kabul?

1.4.2. Secondary questions

- Will 3-monthly vitamin D supplementation reduce the incidence of clinical moderate or severe ALRI (IMCI criteria) among <24 month old children living in a socio-economically deprived community of Kabul, Afghanistan?
- Will vitamin D supplementation reduce the incidence of hospital admissions for any severe illness?
- Will Vitamin D supplementation reduce all cause mortality and pneumonia specific mortality in children?
- What are the risk factors for pneumonia in children living in deprived areas of Kabul?

1.5 Outline of the report

In chapter 2 an extensive literature review of epidemiology of pneumonia in children globally and in developing countries specifically, global prevalence of vitamin D deficiency and rickets, the association between Vitamin D deficiency and respiratory diseases, and immunological functions of Vitamin D are presented. The methods of the randomized controlled trial that investigated the protective efficacy of vitamin D against pneumonia.
and the analysis plan are described in chapter 3. The study findings are described in chapter 4. The interpretations and implications of the findings are discussed in chapter 5.
CHAPTER 2: LITERATURE REVIEW

2.1 Burden of pneumonia in children

WHO estimates that the annual episodes of clinical pneumonia are 156 million, of which only 4 million occur in developed countries (8) while 115 million (74%) occurs in 15 developing countries (Table 1; Figure 1) (8). WHO also estimates that up to 20 million new cases of pneumonia are severe and require hospitalization (33). Each year, about 10.5 million children die in the world (6) and 19% of these deaths are attributable to pneumonia (6). In 2008, the annual global under-5 deaths was estimated 8.8 million, of which, 18% was attributable to pneumonia (Figure 2) (34). Afghanistan has a high under-5 mortality rate and high mortality from pneumonia. UNICEF best Estimates1 suggest that 23% of under-5 mortality in Afghanistan in 2005 was attributable to pneumonia.

There is very limited data on the burden of pneumonia in Afghanistan. However there is extensive literature on the epidemiology of pneumonia in the neighbouring country Pakistan. Pneumonia has been the second leading cause of under-5 mortality in Pakistan (35). One in 4 deaths in children under-5 years of age in Pakistan is due of pneumonia (36). In north western of Pakistan that lies 1525m above sea level, the annual pneumonia specific mortality has been estimated 14 deaths per 1000 under-5 children (3 5). A community based surveillance of mortality using verbal autopsy in an area in Karachi found that 33% of deaths in infants and 37% of deaths in children 1-4 years were due to pneumonia(35).

A household surveillance in a low-income area of Karachi from 2007 to 2008 found that the incidence of pneumonia was 0.26 (95% CI: 0.25 – 0.28) episodes per child year (36).

1 The best estimates report was prepared by the ministry of Economy/Central Statistics Office of Afghanistan, and UNICEF Afghanistan Country Office during 2005. The indicator in this report has come from a comprehensive search of all available information in Afghanistan related to women and children. The data has been analyzed and indicators generated are from adjusted survey results and use of models and indirect deductive estimates. The report has been delivered from reanalysis of the Multiple Indicator Cluster Survey (MICS) 2003 by UNICEF and the Government of Afghanistan in addition to information from MICS surveys in 1997 and 2000. The main problems in 2003 survey were problems in sampling frame, unknown total population, less Access to rural remote areas due to security problems, and problems in accuracy of responses due to high illiteracy. In the surveys ARI was measured by asking if any of the children had ARI problems in the two weeks period before the survey day.
A cohort study of 1476 infants in Lahore in 1984 found the incidence of pneumonia to be 22 per 100 child years (35). In 1990, the incidence of pneumonia in children under-5 was found 30 per 100 child years near Gilgit in northern Pakistan (35). A cohort study of 5204 children aged 2-35 months living at high altitudes in Himalayan parts of Pakistan found that the annual incidence of non-severe pneumonia was 29.9 per 100 child years and the annual incidence of severe pneumonia was 8.1 per 100 child year (35).

2.2 Risk factors for pneumonia in children

Various risk factors for pneumonia have been indentified, related to the host, the environment and infections (Table 2) in developing countries (8). Children aged 4 months have higher risk of pneumonia compared to older children. In a cohort study conducted in Northern Pakistan the incidence rate ratio adjusted for altitude, number of children less than 36 month of age at home, and child’s sex was 4.33 (95% CI: 3.53 – 5.32) in 2-5 month old infants compared to children aged 24-35 months (35).

Around 3 billion people use solid fuel as a principle household fuel which is linked to poverty (37). Exposure to extreme level of indoor pollution mainly from burning of biomass fuels for cooking and heating is common in developing countries (6). Use of wood, crop residues and animal dung for heating and cooking (38), which are sources of smoke in the homes that expose children to the high risk of acute respiratory infections, is common in developing countries (38). In 1995, Kirkwood et al. found that indoor air pollution from household use of solid fuels such as wood, animal dung, crop wastes and coal is a risk factor for pneumonia in children (37). A critical review of the studies of association between indoor air pollution from use of biomass fuels and acute respiratory infections showed a significant increase in the risk of acute respiratory infections for children exposed to household biomass smoke compared to those using cleaner fuels. Nine case control studies (n=4311) conducted in South Africa, Zimbabwe, Nigeria, Tanzania, Gambia Brazil, India and Argentina showed that the odds of exposure to biomass smoke was higher in children with pneumonia than healthy controls (odds ratio ranged from 2.2 to 9.9). Four cohort studies conducted in Nepal, Kenya, and Gambia (n=910) also showed a high risk of pneumonia in children exposed to biomass smoke (odds ratio ranged from 2.2 to 6.0). A cohort study in Nepal showed a close relationship between hours/day children
under-2 spent near the stove, and episodes of life threatening acute respiratory infections. Two cohort studies involving 780 and 455 children aged 0-23 months respectively, found that children spending more than 1 hours per day near the fireplace had higher risk of developing ARI grades 1 to 4 compared to those spending less time (OR=2.2, 95% CI: 1.6 – 3.0) (38).

Lack of exclusive breastfeeding during the first 6 months of age is also a risk factor for developing Acute Lower Respiratory Infections (ALRI) and mortality from ALRI (39), (40), (41). A meta-analysis of studies focusing on cause-specific morbidity due to patterns of breastfeeding in children under 6 months old, found that the incidence of pneumonia was 1.79 (95% CI: 1.29 – 2.48) in exclusive breastfed children, 2.48 (95% CI: 0.23 – 27.15) in partially breastfed and 2.07 (95% CI: 0.19 – 22.64) in not breastfed children (40). A review of 6 studies conducted in China, Argentina, Brazil and America focusing on relationship between pneumonia and nutritional factors, found that lack of breastfeeding was a risk factor for pneumonia (41).

A large cohort study of 5204 children 2-36 months old in Himalayan parts of Pakistan found that male gender, high altitude and younger ages were the main risk factors for pneumonia(35). The incidence rate ratio (IRR) of pneumonia for Children living in altitudes of 1980 - 2285 m was higher compared to those living in altitudes of 1675 – 1980 m (IRR= 1.66 and 95% CI: 1.45 – 1.90). Male children had higher incidence of pneumonia compared to that of females (IRR= 1.14 and 95% CI: 1.01 – 1.29). Children 2-5 months had highest IRR of pneumonia (IRR= 4.33 and 95%CI: 3.53 – 5.32) compared to 24 – 35 month old children. (35).

A case-control study of 1300 children under-2 years old from July 1989 to June 1990 in Fortaleza city of Brazil found that malnutrition was the most important risk factor for childhood pneumonia. The odds of weight-for-height Z-score<-3 was 6.75 higher (95% CI: 1.88 – 24.27), and the odds of weight-for-age Z-score<-3 was 4.57 higher (95%CI: 2.93 – 7.13) in pneumonia cases compared to healthy controls (42). Moreover, no breastfeeding (OR=1.69; 95% CI: 1.02 – 2.80) and crowding (total household size of ≥8 persons and the number of children at home if ≥7 children) were also significant risk factors for the
incidence of pneumonia. In this study, there was no association between the risk of pneumonia and the number of persons sleeping in the same room as the index child (42).

High altitude is known to be a risk factor for pneumonia and other lung disease (43). At high altitudes where the oxygen supply is lower, the ability of lungs for getting oxygen to the blood is impaired (43). A retrospective cohort study examining the effect of residential altitude on hospitalization for respiratory syncytial virus infection in Colorado from 1998 through 2002 revealed that children 1-4 years old who resided at high altitude (>2500 m) had a 62% increase in rate of hospitalization compared to those living at low altitude (<1500m) (RR=1.62, P= 0.004). The study concluded that high altitude above 2500 m is a modest predictor of RSV-associated hospitalization (43).

Afghanistan is a poor country with cold winters. Using solid fuel such as wood, crop residue and animal dung is common as in other developing countries for heating and cooking. Additionally, tobacco smoking indoor in the presence of children, low maternal education, and malnutrition of children are also common. Though no formal studies have been conducted yet to explore the role of these factors on pneumonia and other infectious diseases in children, it is plausible that these factors would impact the incidence of pneumonia in children in Afghanistan.

2.3 Protective factors against pneumonia

Zinc supplementation has been shown to have some protective effect against pneumonia in some settings. A meta-analysis of 4 randomized controlled trials conducted in South Asia showed that administration of oral zinc supplementation daily or weekly significantly reduced the incidence of ALRI in children (RR= 0.80, 95% CI: 0.70 – 0.92) (39). The first study was conducted in 2482 children aged 6 to 30 months in a slum community in New Delhi. Infants were given 10mg and older children were given 20 mg elemental zinc per day for 4 months. Children in both groups got a single high dose of vitamin A (100,000 IU for infant and 200,000 for children). The incidence of pneumonia was lower in zinc supplemented group compared to that in placebo group (OR=0.74, 95% CI: 0.56 – 0.99) (44). The second study was done in children aged 1-6 months in urban slums in Dhaka, Bangladesh. The intervention group (n=152) was given 5mg elemental zinc daily till 24
weeks of age and the placebo group (n=149) was given a liquid containing sucrose, flavors and preservatives. In this study there was no difference in the risk of respiratory diseases in infants with normal baseline zinc concentration. However, among infants with zinc deficiency at baseline, fewer ALRI case were observed in intervention group compared to that in the placebo group (RR=0.30, 95% CI: 0.10 – 0.92) (45).

The third study was also conducted in Bangladesh in 1665 children 2 to 12 months of age. Intervention group was given 70mg zinc weekly for 12 months and the placebo group was given a non-nutritious and vitamin free liquid. The relative risk of pneumonia was 0.83 (95% CI: 0.73 – 0.95) in the zinc group compared to that in the placebo group (46). The last study was done in an urban setting in India in 609 children 6-35 months old. The intervention group was given a daily liquid containing 10mg elemental zinc plus some other elements such as vitamins A, B1, B2, B6, D3, E, and niacinamide for 6 months. Placebo group was given same liquid without zinc. The incidence of ALRI was lower in the zinc supplemented group compared to that in the placebo group (OR= 0.55, 95% CI: 0.33 – 0.90, p=0.02) (47).

The protective effect of Vitamin A against pneumonia has been explored in several studies. In Ecuador, from July 1996 to April 1997, a randomized controlled trial was carried out about effects of low dose vitamin A supplementation on the incidence of ALRI and diarrhea in 400 children aged 6-36 months old. The intervention group received a weekly 100 000 IU vitamin A and the placebo group received weekly syrup with anise flavouring. After 40 weeks, there was no significant difference in the incidence of ALRI between vitamin A supplemented and placebo groups (RR=1.21, 95% CI: 0.81 – 1.82, p=0.35). However, among children underweight at baseline (weight-for-age z-score< - 2 SD), vitamin A supplementation significantly decreased the incidence of ALRI (RR=0.38, 95% CI: 0.17 – 0.85, p=0.01). The incidence of ALRI in children with normal weight-for-age z-score at baseline was higher in vitamin A supplemented group compared to that in placebo group (RR=2.21, 95% CI: 1.24 – 3.93, p=0.005) (48).

The effect of large dose vitamin A on the severity of respiratory diseases was studied in 687 children aged 6 to 60 months old in Tanzania between April 1993 and March 1997. Children admitted to the hospital with non-measles pneumonia were randomly assigned to vitamin A and placebo groups and followed during hospital stay. The intervention group
received one dose of 200 000 vitamin A (half the dose for infants) on the admission day and the second dose on the following day. The placebo group received corn oil. There was no significant difference between vitamin A and Placebo groups in clinical course of pneumonia. Vitamin A supplementation had no significant effect on duration of hospital stay (RR=0.96, 95% CI: 0.82 – 1.12, p=0.58) and number of deaths (RR=1.63, 95% CI: 0.67 – 3.97, p=0.28) between the two groups (49).

In India 1520 children less than 10 years old were randomly assigned to vitamin A and placebo to explore effect of vitamin A on mortality and morbidities such as pneumonia, diarrhea and measles. Half the children was given vitamin A (200 000 IU for children over 1 year old, 100 000 IU for 6-12 month-olds, and 50 000 IU for less than 6 month olds) and half was given placebo (arachis oil) every 4 to 6 months for 15 months. The study showed that vitamin A supplementation did not have a statistically significant effect on reducing incidence of pneumonia (RR=0.69, 95% CI: 0.43 – 1.11, p=0.13). However, children in intervention groups had a significant lower incidence of measles (RR=0.46, 95% CI: 0.29 – 0.74, p<0.001) and diarrhea (RR=0.62, 95% CI: 0.58 – 0.66, p<0.001) (50).

2.4 Sources of vitamin D and its key roles

Vitamin D, also called a pro-hormone or sunlight hormone, is a fat soluble vitamin. Its major biological function is in the formation and maintenance of bones (51), (52). There are two sources of Vitamin D for humans: foods and supplements, and the endogenous synthesis (18). Vitamin D is available mainly in oily fish and to a lesser extent in eggs and liver; breast milk is a poor source (53). Other dietary sources of vitamin D include foods fortified with vitamin D2 (ergocalciferol produced by the ultraviolet irradiation of ergosterol from yeast) or D3 (cholecalciferol produced by ultraviolet irradiation of 7-dehydrocholesterol from lanolin) (30) such as fortified dairy products, infant formula, and breakfast cereals (18) (30). Only less than 10% of vitamin D is derived from dietary sources. The rest of vitamin D is derived by endogenous mechanism (54).

Endogenous synthesis of vitamin D takes place in several steps. The first important step is absorption of Ultraviolet B radiations (wave lengths 290-310 nm) by 7-dehydrocholesterol
in the skin to form pro-vitamin D3. The pro-vitamin D3 rapidly transforms to vitamin D3 (30). Ultraviolet rays trigger synthesis in the skin, which is reduced in darker skins (53), (55), (56). Vitamin D3 is stored in the body fat to be released when there is limited natural production of Vitamin D3 due to the sun irradiation such as winter season (30). Once produced whether vitamin D3 or vitamin D2 will pass the liver for hydroxylation to produce 25-hydroxyvitamin D. This will be hydroxylated further in the first position in kidneys to produce 1, 25 dihydorxyvitamin D, the biological active metabolite of vitamin D. In practice circulatory level of intermediate metabolite of vitamin D (25 hydroxyvitamin D) is used as best indicator of vitamin D sufficiency (57) (58) (30) (59). The half life of 25(OH)D is 2-3 weeks compared to very short half life of its active metabolite, 1,25(OH)2-D, which is only 4 hours (54).

Penetration of the ultraviolet radiations into the skin can be reduced by factors such as dark skin pigmentation, sunscreen, winter season, high latitude (northern latitude), air pollution, confinement indoors, skin covered by clothes, and skin diseases such as ichthyosis (18) (30). The required UV light reduces with distance from the equator to zero at latitudes above 50° in winter (60).

Intestinal absorption of vitamin D is reduced by mal-absorption diseases such as cystic fibrosis and hepatic disorders (30). Taking into account the variation in skin pigmentation between individuals, as well as, the level of sunlight exposure in various latitudes, twice weekly exposure of arms and legs to 5-30 minutes mid-day sunlight in older children, and twice weekly exposure of head and shoulder in infants are probably enough for stimulating adequate production of vitamin D3 (30).

Vitamin D plays important role in maintaining calcium homeostasis (59). Vitamin D3 enhances the intestinal absorption of calcium and phosphorus. The absorption takes place through binding of 1, 25-Dihydroxyvitamin D to vitamin D receptors in small intestine to stimulate trans-cellular absorption of calcium and phosphorus (59) (30). It has also been known that calcium deprivation increases the need of a child to vitamin D, and makes children susceptible to mild vitamin D deficiency (30). Studies have shown that low calcium intake enhances the catabolism of 25(OH) vitamin D through the activation of 24-hydorxylase as a result of elevated 1,25-Dihydroxy vitamin D concentration (61). Vitamin
D is also necessary for mineralization and development of skeleton (59). Genetic factors can affect production of vitamin D in the body. Its main role has been described as polymorphism of enzyme 7-dehydrocholesterol reductase in the skin, cytochrome p450 25-hydroxylase in the liver, and vitamin D binding protein in the circulation. These factors can affect functionality of vitamin D either by interrupting with uptake of 25(OH)D by target cells, or by affecting efficiency of 1α-hydroxylation to produce the active metabolite of vitamin D{1,25(OH)2D} (62).

2.5. Epidemiology of Vitamin D Deficiency

The Institute of Medicine (IOM) and American Academy of Pediatrics (AAP) has defined vitamin D deficiency in infants and children as a serum level of 25(OH) vitamin D below 11ng/mL(27.5 nmol/L) (18) and Vitamin D insufficiency as 25(OH)D <30 ng/mL(75 nmol/L) (18).

A recent review of literatures classifies the vitamin D deficiency status in children based on level of serum 25(OH)D in ng/mL² as follow (54):

a. Severe deficiency: 25(OH)D ≤5ng/mL
b. Deficiency: 25(OH)D 6- ≤14ng/mL
c. Insufficiency: 25(OH)D 15-20ng/mL
d. Sufficiency: 25(OH)D 21-100ng/mL (50-250nmol/L)
e. Excess: >100ng/mL
f. Intoxication: >150ng/mL (>250nmol/L)

More than one billion people in the world have insufficient circulatory level of vitamin D (30). Dietary insufficiency of calcium is common in developing countries (30). Approximately half of the children in the North America are vitamin D insufficient and children in the European countries also seem at risk despite ongoing supplementary efforts (30). Neonatal vitamin D deficiency due to insufficient level of vitamin D in pregnant women is very common (30). Breast milk has lower level of vitamin D as compared to

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cow's milk. Therefore, prolonged breastfeeding in some settings has been associated with vitamin D insufficiency in infants (30). In a newborn baby, concentration of 25(OH) vitamin D is approximately 2/3 of the maternal values (57). The half life of 25(OH) D is around 3 weeks. Therefore, newborns will need exogenous supply of vitamin D after few weeks of the life (57). It has been proposed that high dose vitamin D supplementation for lactating mothers may increase the level of vitamin D in breast milk sufficient to prevent rickets in breast feeding infants (30).

The prevalence of vitamin D deficiency is high in developing countries. In Tehran in a small pilot study during March 1966 in Shahrazad Children's Hospital admitting children from lowest income groups, it was found that 15% of children under 5 years of age (n=82) had evidence of rickets in wrist x-rays (20). In the UAE, Pakistan, and China the prevalence of vitamin D deficiency (serum 25OHD<10ng/ml) in exclusive breastfeeding infants has been reported 82% (n=78), 55% (n=62), and 20% (n=42) respectively (31).

In a case control study of risk factors for pneumonia in a rural community of Bangladesh during the winter season, the mean 25(OH) D level was 36.7nmol/L (95% CI: 30.2 – 43.2) among 29 healthy controls aged 1-6 month. Among these children 28% (95% CI: 10 – 45) had 25(OH)D <25nmol/L, and 50% (95% Cl: 40 – 78) had 25(OH)D < 40nmol/L (63).

A study during the winter of 2005 in Afghanistan showed very high levels of vitamin D deficiency in a poor district in Kabul. The median concentration of 25- hydroxyl vitamin D was 5ng/ml (range 2-25ng/ml) among 108 children aged 6-48 months. Of total, 104 (96.2%) had concentrations below 15ng/ml, the minimum level considered to be sufficient, and 79 (73%) had concentrations below 8ng/ml, a level considered to be significantly deficient (32).

Vitamin D deficiency rickets is associated with 25(OH) vitamin D below 5ng/ml (12.5 nmol/L) (58). It results from impaired bone mineralization in children particularly due to inadequate calcium and phosphorus in the growth palate. (58) Inadequate calcium can cause nutritional rickets in spite of adequate vitamin D status (58). Infants are generally protected from vitamin D deficiency rickets during the first few months of life because
vitamin D metabolites crosses the placenta (57). The peak age for rickets is 3-18 months (57).

The burden of nutritional rickets is greatest in developing countries where it is either underreported or ignored. Cultural practices limit sun exposure in pregnant women and children in spite of abundant sunlight and rickets is common in the middle east particularly in Saudi Arabia (58). In Muslim countries due to cultural beliefs, women wear concealing clothing which minimizes sunlight exposure to them and their children (64). A study done in an urban hospital in Saudi Arabia, revealed that 59% of women (n= 100) delivering and 70% of their newborns had vitamin D deficiency below 25 nmol/L (58).

A study of infants 9-24 months old in India with similar socio-economic conditions and no vitamin D supplementation showed that children (n=26) living in the areas with intensive air pollution had lower serum 25-(OH)D than children (n=31) living in the areas with no air pollution. The mean 25(OH)D in children living in polluted areas was 12.4 ng/ml compared to 27.1 ng/ml in low polluted areas (p<0.001) (65).

In Kuwait, among 858 infants born in a hospital over a period of 2 years, 75 infants (9%) were diagnosed with rachitic rosary by a pediatrician within 24 hours after birth (66) (58). In Turkey, a review of medical records of 42 infants seen in the pediatric endocrinology clinic over a period of 2 years (May 2001 – May 2003) found that children had rickets mainly due to limited sun exposure and low maternal and infantile level of vitamin D (67). In 1999, in a large cross-sectional study for rapid assessment of prevalence of lower limb clinical rickets in Bangladesh, 25891 people 1-20 years old were studied in Cox’s Bazaar. The prevalence of lower limb clinical rickets was found 931 per 100 000 (95% CI 795 – 1067) (68). The monthly incidence of rickets among 1476 infants born between 1984 – 1987 and followed from birth to 24 months of age in Lahore, Pakistan was reported 0.10% (95% CI: 0.06 – 0.14) in a morbidity study (69) (58).

2.6. Immunological roles of Vitamin D

The evidence for profound effects of vitamin D on innate immunity is rapidly growing (70). The increased expression of anti microbial cathelicidin by macrophages and epithelial cells
in response to exposure to microbes depends upon presence of vitamin D (70). In vitro studies have shown that 1,25-dihydroxyvitaminD3, the active metabolite of vitamin D, is important for promoting and regulating immune responses (51), (71), (52). 1,25(OH)2D3 is an immune system modulator and induces expression of the TLR co-receptor CD14 (72), (73). Wang et al showed that 1,25(OH)2D3 directly induced antimicrobial gene expression (cAMP and deficin B2 expression) and highlighted the potential uses of vitamin D in treatment of opportunistic and some antibiotic resistant infections (74).

Sub-clinical vitamin D deficiency is associated with an increased risk of tuberculosis in adults through modification of polymorphisms in the vitamin D receptor (75). Rook and colleagues using cultured human macrophages showed that 1, 25(OH)2 D inhibits the growth of Mycobacterium tuberculosis (76). A study by Lui et al revealed the crucial role of endogenous 1,25(OH)2 D3 produced by macrophages for its anti-mycobacterial capacity (77), (39).

Recent studies have shown that vitamin D activated by expressed enzyme 1-α-hydorxylase from some tissues has important immune-modulatory effects (78). The enzyme 1-α-hydorxylase expressed from lung epithelial cells converts inactive 25-(OH)2 vitamin D3 to the active 1,25-dihydroxyvitaminD3. The active vitaminD3 increases the expression of vitamin D-regulated genes with important innate immune functions (78). These genes include the cathelicidin antimicrobial peptide and the TLR co-receptor CD14 (78). The regulatory effects of vitamin D on innate immunity in the epidermis was detected from expression of cathelicidin in human epidermal keratinocytes induced by 1,25(OH)2D3 (77).

2.7. Vitamin D deficiency and risk of tuberculosis

Recently, an association between vitamin D deficiency and higher risk of tuberculosis has been observed. In a hospital based matched case control study of adult Vietnamese (166 cases and 219 controls), the prevalence of vitamin D insufficiency (25(OH)D<30ng/mL) was higher in TB positive men compared to that in men in the control group (35.45% vs 19.5%; p=0.01). The difference in the prevalence of vitamin D deficiency between female TB cases and controls was not statistically significant (45.3% vs 47.6%; p=0.91) (79). A matched case control study of 72 pairs aged 8-74 years in Greenland found that both high
and low level of serum vitamin D were associated with risk of tuberculosis. After adjusting for alcohol intake and ethnicity, lower level of serum vitamin D \{25(OH) D<75nmol/l\} was highly associated with TB (adjusted OR=6.5; 95% CI: 1.8 – 23.5). Paradoxically higher level of serum vitamin D \{25(OH) D>140nmol/l\} was also associated with risk of TB (adjusted OR=6.5; 95% CI: 1.9 – 22.2). Cases and controls were matched on the basis of age and sex (80).

Recently, a multi-center randomized controlled trial of vitamin D in 146 adults with sputum smear-positive tuberculosis was conducted in London. Half of the patients received 4 doses of 2.5 mg vitamin D3 on days 7, 14, 28 and 42 along with anti TB treatment. The study found that vitamin D significantly hastened sputum culture conversion in patients with tt genotypes of the Taql vitamin D receptor polymorphism(HR=8.09; 95% CI: 1.36 – 48.01; p=0.02) (81).

A double-blind randomized controlled trial was conducted among 192 healthy adult TB contacts in London to determine the effect of vitamin D on enhancing immunity to tuberculosis. Participants were given a single dose of 2.5mg vitamin D and followed for 6 weeks. The primary outcome was measured by assessing ability of whole blood count to restrict luminescence and as a result, growth of mycobacterium in vitro. The trial found that the single dose of vitamin D significantly enhanced ability of participants’ whole blood count to restrict BCG-lux luminescence compared to that in the placebo group. The mean luminescence ratio for intervention group was 0.57 versus 0.71 for placebo group (95% CI: 0.01 – 0.25; p=0.03) (82).

2.8. Association between vitamin D deficiency and pneumonia

High rates of vitamin D deficiency rickets have been found among children admitted to hospital for pneumonia ranging from 43% in Tehran (20), (14) and Kuwait (83), (14) to 50% in Yemen (84). Two hospital-based case-control studies from Ethiopia (14) and India (15) suggested that vitamin D deficiency may substantially increase the risk of severe pneumonia among children aged less than 5 years. The study in Ethiopia which included 1021 children under-5 (521 cases and 500 controls), showed that the prevalence of rickets among children with pneumonia was higher than that of among controls (14); 42% of
pneumonia cases had rickets, compared to 4% of controls (children admitted for other reasons)(OR=22.1; 95% CI: 11.3 – 43.1, P<0.001). After adjusting for several potential confounders (family size, birth order, crowding, and months of exclusive breastfeeding), the OR was still extremely high (adjusted OR=13.4; 95% CI: 8.1 – 24.2, P<0.001) (14).

The role of other possible confounding factors not adjusted for, such as zinc deficiency and severe malnutrition, could not be ruled out in this study.

The Indian study which was conducted in 150 children under-5 years of age (80 cases and 70 controls) to determine whether sub-clinical vitamin D deficiency is a risk factor for ALRI, found that sub-clinical vitamin D deficiency and non-exclusive breastfeeding in the first 4 months of life were significant risk factors for ALRI (15). In this study serum 25(OH) D3 > 22.5 nmol/L (sufficient level) had a protective effect for ALRI compared to that in controls (OR=0.09, 95% CI: 0.03 – 0.24; P<0.001). Small sample size and a lower cut off point (>22.5 nmol/L) compared to commonly used cut off point (> 50 nmol/L) for a sufficient level of serum vitamin D in this study were the main technical limitations limiting its internal and external validity.

In a cohort of 800 young Finnish men serving in a military base, men with a serum 25(OH)D level <40 nmol/L (n=24) had more number of absent days due to respiratory infections than those had higher levels of 25(OH)D (RR=1.63, 95% CI:1.15 – 2.24, p=0.004) (12).

The cytokines released during influenza episode could disrupt the epithelial layer of the lung, leading invasion of streptococcus pneumonia and streptococcus pyogenes to grow and cause pneumonia (85). A randomized controlled trial of vitamin D supplementation conducted among 334 school children in Japan in 2008-2009, found that the relative risk of influenza A infection for school children taking 1200 IU/day vitamin D3 compared to placebo group was 0.58 (95% CI: 0.34 – 0.99; p=0.04) (86).

In 2007, a hospital based study of the effect of a single dose 100,000 IU vitamin D3 supplementation along with antibiotic treatment for pneumonia in 453 children 1-36 months old in Kabul found that the risk of having a repeat episode of pneumonia within 90 days after treatment was lower in the vitamin D supplementation group compared to that in
placebo (RR=0.78; 95% CI: 0.64 – 0.94, p=0.01) (87). In this study although children were recruited by experienced pediatricians, cases were not confirmed radiographically. Thus possible misclassification of pneumonia initially, as well as, during the follow up visits could not be ruled out.

2.9 Potential adverse effects of vitamin D supplementation

Vitamin D can cause acute and chronic intoxication mainly due to its hypercalcemic effects. Acute intoxication is associated with nausea, vomiting, dehydration, anorexia, apathy, polyuria, polydipsia, hypotonia, constipation, corneal clouding, hypercalcemia and hypercalceuria (88),(89),(90), (91), (92). Prolonged vitamin D intoxication affects kidneys resulting in nephrocalcinosis, renal colic, renal failure, and neurological disorders (93), (94), (92). Studies focused on adverse effects of vitamin D are limited; however, cases of acute and chronic vitamin D intoxication in adults and children have been documented through case reports from different countries (95). A review of 21 clinical trials comparing the risk of vitamin D from a low daily dose (3800 IU/day) to a very high daily dose (100,000 IU/day) in adults, concluded that prolonged intake of 10,000 IU/day of vitamin D3 as upper limit is less likely to increase the risk of adverse effects in the general population; however, the capacity of circulating vitamin D-binding protein might affect the safety of vitamin D intake (96) (94).

Three-monthly oral doses of 100,000 IU of vitamin D have been proven to be safe and effective in alleviating vitamin D deficiency in high risk normal or ricketic children. In a randomized controlled trial in Istanbul, Turkey to compared the effect of oral calcium, high dose vitamin D, and combination of these two in treatment of nutritional rickets in 42 children 6-30 months in a hospital, it was found that a single high dose of intramuscular vitamin D (300 000 IU) together with oral calcium was a safe and effective regimen (97). In France the circulating level of 25(OH)D was measured in 70 neonates given 500 - 1000 IU oral vitamin D2 per day for 3 months. It was found that daily administration of 500-1000 IU oral vitamin D2 did not induce any risk of vitamin D over load during the first 3 months of life (98). In Paris, 30 neonates were assigned either to single 5mg (200 000 IU) cholecalciferol at birth or to 2.5mg cholecalciferol at birth, 3 months and 6 months after birth. Venous blood were collected from all after administration of each dose and at various
times to measure serum vitamin 25(OH) D. Both regimens provided similar protection against vitamin D deficiency without any risk of vitamin D overload (99). In another study, 80 full-term neonates born in a maternity hospital in Paris from April to July 1994 were assigned either to 500 IU/day or 1000 IU/day of oral ergocalciferol to compare the effectiveness of these two regimens in correction of subclinical vitamin D deficiency. Both regimens were found to be effective in raising serum vitamin D level in a desired level without posing any sign of vitamin D overload (100). The dosage of vitamin D used in different trials along with main end points, study outcomes and references are summarized in table 3.

2.10 Rationale for the study

Afghanistan has very high under-5 and infant mortality rates (191/1000 live births and 129/1000 live births respectively) and probably pneumonia contributes to a significant proportion of these deaths. The incidence of pneumonia (0.29 episodes per child-year) (8) and the prevalence of vitamin D deficiency rickets (5 to 45%) are also high in children under-5 in developing countries. It is plausible that vitamin D deficiency is a risk factor for pneumonia in some settings and therefore Vitamin D supplementation may reduce the risk of pneumonia in children. Although studies in India and Ethiopia have revealed an association between sub-clinical vitamin D deficiency and lower respiratory tract infections in children, these observations from case control studies are not robust enough to causal inference and to make policy recommendation for routine vitamin D supplementation for children in developing world. Thus a randomized controlled trial of vitamin D supplementation was needed to assess the potential beneficial effects of this intervention on the incidence of pneumonia. If it is shown that vitamin D supplementation can reduce the incidence of pneumonia, it can be incorporated into child health schemes.
CHAPTER 3: METHODS

3.1 Study Country

Afghanistan is a land-locked country situated in southern Central Asia, surround by Pakistan in the south, south-east and partly in the north-east, Iran in the West, and Turkmenistan, Uzbekistan, and Tajikistan in the North (101). The total land area of Afghanistan is estimated 251,700 square mile (around 647,500 sq km), and is composed of 34 provinces. The country has extreme climatic conditions – very cold winters and very hot summers. The climate varies from one area to another area according to altitude.

The total population of Afghanistan is estimated 29,863,000 (3). Fifty two percent of the population is aged ≤ 17 years old (102). The average number of persons in a household is 7.4. Only 28% of people aged >5 years can read (102). Only 31% of the population has access to safe drinking water in the whole country but it is 71% in the capital, Kabul (102). National access to electricity from different sources is 23%, and access to different sources of electricity in the capital is 61%. During the summer, animal dung and bushes are the common source of energy for cooking in the country (23%), while during the winter the common source is firewood (35%). (102). Firewood is also the main fuel for heating during the cold season in the country (39%). Agriculture is the main source of income in Afghanistan - 47% of households are engaged in agriculture (102).

The main exports of the country are opium, nuts, hand-woven carpets, wool, cotton, pelts and gems (101). The country is composed of 4 main ethnic groups-Pashtuns (38%), Tajiks (25%), Hazaras (19%), Uzbeks (6%). Ninety nine percent of Afghans are Muslims (101). The life expectancy at birth is 47 (3). Afghanistan Central Statistic Office estimated the GDP per capita of Afghanistan US $ 290 in 2005 (103). Two decades of civil war lost country’s opportunity for socio-economic development. Recent estimates of human development index ranks Afghanistan second from the last (7).
3.2 Study area

The trial was conducted in Kabul, which lies in a narrow valley along the Kabul River. It is located at 34°31 latitude North and 69°11 longitude East. Kabul is 1,800 m above sea level (104). During the winter (December-March) the average duration of sunlight is 6 hours, minimum temperature -8°C and maximum temperature 2°C. During the summer (June-August) the average duration of sunlight is 12 hours, minimum temperature 16°C and maximum temperature 33°C³. Kabul is a multi-ethnic and multi-cultural city. Tajiks Sunnites forms the majority, followed by Shiite Hazaras and Farsiwans (105).

According to UNICEF, the under-5 population in Kabul in 2003 was 441,000, and the under-5 mortality rate was 155/1000 live births. The annual number of births was 110,126, and maternal mortality ratio was 700/100,000 live births in 2003. The female literacy rate was 35%, and the measles vaccination coverage was approximately 88% in 2003(106). Kabul city is composed of 18 city districts (Nawahi Shahri) in which 403,800 households live.

The vitamin D supplementation trial was conducted in 5 districts of Kabul - the whole of district 1, major part of district 7, and small parts of districts 2, 3, and 8 (Table 4). The vast majority of the study population lived in Districts 1 and 7. District 1 is the nearest area to the study hospital (Maiwand Teaching Hospital), with majority of its population from Hazara ethnic group and socio-economically deprived. This is old part of Kabul with narrow, shaded lanes often with roofed tops between high walled mud houses; most houses have small courtyards with high walls and so for much of the day the courtyard is shaded from sun. The total population living in district 1 in 2005 was estimated 65,900 by CSO (107). The population of district 7 in 2005 was estimated 25,300. People in district 7 are from different ethnic groups. In districts 1, 2, 3 and 7, majority of the people live in hilly sites making their life very difficult especially in the winter.

³ Source: BBC weather, December 18, 2008 (http://www.bbc.co.uk/weather/world/city_guides/results.shtml?tr='110&2=1)
3.3 Study Design

This was an individually randomized double blind placebo controlled trial. The trial design is summarized in figures 3, 4 and 5.

3.4 Study Population

Children aged 1-11 months living in districts 1, 2, 3, 7 and 8 of Kabul city.

3.5 Inclusion and exclusion criteria

3.5.1 Inclusion criteria

- 1 to 11 month-old children living in the study areas
- Parents gave consent to take part in the study

3.5.2 Exclusion criteria

- The family was expecting to move far away from the study area within 18 months after recruitment
- The child was diagnosed with rickets or was known to have received a course of vitamin D treatment in the past 3 months before recruitment
- The child had Kwashiorkor or Marasmus

3.5.3 Temporary exclusion criteria

- Children who had diarrhea, vomiting, or pneumonia were enrolled 2 weeks after recovering from the illness

3.6 Primary End Point

First x-ray confirmed pneumonia=: history of cough + (increased respiratory rate for age\(^4\) or chest x-ray evidence of pneumonia.

\(^4\) RR/min≥60 (<2 months age), ≥50 (2-<12 months age), ≥40 (12-59 months age)
\(^5\) Not drinking/breastfeeding, convulsion, vomiting everything, lethargic/unconscious, stridor in a calm child
3.7 Secondary End Points

- Clinical pneumonia = history of cough + (increased respiratory rate for age or chest in drawing or any danger sign) detected at OPD, IPD or fortnightly house visit.
- Repeat clinical pneumonia = any new case meeting the criteria of clinical pneumonia diagnosed \( \geq 30^6 \text{ days} \) after the first episode of pneumonia, detected at the OPD, IPD or fortnightly house visits.
- Repeat x-ray confirmed pneumonia = any new case meeting the criteria of first x-ray confirmed pneumonia occurring \( \geq 30 \text{ days} \) after an episode of x-ray confirmed pneumonia.
- Severe pneumonia = cough + chest in drawing detected at the OPD or IPD.
- Very severe diseases = cough + any danger signs detected at the OPD or IPD.
- Hospitalization for any diseases.
- All cause and pneumonia specific mortality.

3.8 Sample size

The expected incidence of the first or only episode of pneumonia in the placebo group was based on the following assumptions: (1) the incidence of acute lower respiratory infections (ALRI) in the placebo group will be 0.65/child/year (10); (2) 12% of the ALRI will be pneumonia (10); (3) 25% of pneumonias will be repeat episodes during the 18 month follow-up period. (4) Thus the incidence of the first or the only episode of pneumonia in the placebo group will be 0.0585/child/year \((0.65 \times 0.12 \times 0.75)\). We assumed a 35% reduction in the incidence of pneumonia in the vitamin D group given that 73% of children have vitamin D deficiency in the study area (32), and that the incidence of pneumonia is 10 times higher in vitamin D deficient than in normal children (14) (15). A study with 80% power and 95% significance to detect a 35% reduction in the incidence of pneumonia compared to the placebo group required 22079 child months per group (108). Since each child would be followed for 18 months, assuming a 20% loss to follow-up, the study.

\(^6\) Time for next episodes of pneumonia has been taken from the Gambian Study “Epidemiology and clinical features of pneumonia according to radiographic findings in Gambian children” [1] and a study conducted in Pakistan[35]
required 1472 children per group. In order to facilitate randomization and allocation of staff this figure was rounded to 1500 child per group.

Box 1: Definition of outcomes

**DEFINITION OF THE STUDY OUTCOMES**

Primary End Point was the first x-ray confirmed pneumonia plus clinical diagnosis of pneumonia (history of cough + (increased respiratory rate for age or chest in drawing or any danger sign). For x-ray confirmed pneumonia, the standard definition by WHO was used as following:

"The presence of a dense or fluffy opacity that occupies a portion or whole of a lobe or of the entire lung, and/or the presence of fluid in the lateral pleural space between the lungs and chest wall (1).

For the secondary outcomes, repeat clinical pneumonia was defined as any new case meeting the criteria of clinical pneumonia ≥30 days after the first episode of pneumonia, detected at the OPD, IPD or fortnightly house visits. Severe pneumonia = cough + chest in drawing detected at the OPD or IPD. A very severe disease was cough + any danger signs detected at the OPD or IPD.

Bronchiolitis: history of cough + wheezing with or without increased respiratory rate for age or chest in drawing detected at OPD, IPD. An episode happening within 30 days after previous episode was counted as duplicate of that episode and excluded.

### 3.9 Community Sensitization

Each study district was composed of several subunits called Gozar. A Gozar had 10-15 streets and approximately 500-700 households. Each Gozar had a head called Wakil who was selected by people in that area. In addition each study district had 2-3 mosques headed
by a mullah and a local security office (Hawza). The study field supervisors and I met the head of local municipalities, Wakils, and Mullahs in study district and explained the study objectives and procedures. A project information letter in local language was distributed to all community leaders to sensitize them to the aims and benefits of the study to the communities. Additionally, a supporting letter from the Ministry of Public Health (MoPH) was given to the head of municipalities to solicit their cooperation and letter from the local authorities sent to all Wakils for their support to the project. After initiation of the project, the field supervisors held regular monthly meetings with Wakils and head of municipalities to update them on project progress. At end of the study, the project management team met the head of municipalities and the head of communities and informed them on successful ending of the study.

3.10 Ethics Consideration

The study was approved by Ethics Review Board of the Ministry of Public Health (MoPH), Afghanistan, and the Ethics Committee of the London School of Hygiene and Tropical Medicine. The application form for review board of MoPH, Afghanistan is attached in annex 1. All study tools, including study consent form were submitted to the review boards for verification and approval. Because this study followed the previous pilot study of vitamin D and pneumonia in the same field and clinical setting in Kabul in 2007, to some extent the review board in the Ministry of Public health, Afghanistan was aware about the technical details of the study. The approval letter from MoPH Ethics review board is attached in annex 2. The ethics committee of LSHTM also reviewed the study, and approved all procedures, safety, and technical features of the study. The approval letter by LSHTM Ethics committee is attached in annex 3.

The study was reviewed by two technical monitoring committees: The first was called Oversight Committee, and was based in Kabul. The committee had members from MoPH, MoHE, Maiwand Teaching Hospital, UNICEF, WHO and London School of Hygiene and Tropical Medicine, all based in Kabul. The members were provided with study progress report each quarter, in addition to regular oversight committee meetings held quarterly in the beginning, and 6 monthly later on. In the meetings,
addition to study progress, members were updated on number of children died during the past quarters of the study and the possible causes of deaths.

The second monitoring committee, data safety monitoring board (DSMB) had two members from London School of Hygiene and Tropical Medicine (Prof Christopher Whitty and Dr Sarah Steadke), one member from Afghan MoPH ethics committee (Dr Mir Lais Mustafa), and representative from an independent research organization in Kabul affiliated with John Hopkins University (Dr Philippe Bounhoure). The DSMB discussed the safety and other technical points during the first phone conference call in the beginning of the trial and approved the trial design, SOPs and time table of the study. The DSMB noted that this is a low risk trial because vitamin D is widely used and it has a good side effect profile.

The DSMB agreed that all deaths and any other serious adverse effects (SAEs) for which a causal link to the study drugs cannot be ruled out should be reported to the DSMB chair within 48 hours of identification by email. A summary of all other SAEs should be reported quarterly to the DSMB by the study team. The DSMB decided that no formal interim analysis of the effect of vitamin D on the incidence of pneumonia is required due to low risk. However the incidence of SAEs was monitored by the DSMB and if a substantial difference has been observed between the study groups, a formal statistical analysis would have been carried out by the DSMB.

The study team reported all deaths to DSMB members within 48 hours, which contained a member from ethics committee of MoPH, Afghanistan as well. All other hospital admissions were reported to DSMB members quarterly.

Before starting the trial, technical details of the study were discussed with community leaders, such as Mullah's and Head of Shuras, as well as, with head of local municipalities to see if they might have any concern. The community leaders did not raise a particular concern about any aspect of the study, rather, promised to provide as much support as they could.

Half of the trial area was part of the vitamin D pilot study done in 2007. Therefore, majority of people in those parts knew about vitamin D. In other parts of the study, few
concerns were raised by people during the follow up. Some of families were concerned whether vitamin D might cause infertility in their children. Some other families thought vitamin D is too strong for their children and make their kids highly sexually active when they grow up. The study field supervisors met the families that raised such concerns and assured them that vitamin D does not have such adverse effects. Other than these two points, no other concerns were raised in the communities.

Data Safety and Confidentiality

- All staff was trained in the principles and practices to maintain confidentiality. All staff had signed a confidentially clause as part of their employment contract.
- All data forms were kept in locked cupboard that was accessible to the data manger and PIs only
- The personal information of all study children were kept in a separate data form which was linked to the rest of data form through a unique coding, so that access to the personal data was limited to the data manager and PIs only.
- All hard copies of the study data forms (questionnaires) will be disposed after 10 years. Only study investigators will have access to electronic copy of the data

3.11 Training of study staff

3.11.1 Assessment of clinical parameters by field workers

From October - November 2007, 42 female field workers, and 3 field supervisors were trained in IMCI guidelines, and standard operating procedures of the trial. Participants worked in groups and learnt how to assess respiratory rates, chest in drawing, skin pinch, and other clinical measurements. In addition, the field workers were given clinical demonstration of dehydration and malnutrition in children admitted to the Indira Gandhi Institute of Child Health in Kabul.

3.11.2 Consenting and completing study forms

The field staff practiced the process of consenting and obtaining written consent in groups of six. The study staff role played and practiced in pairs the process of completing all study forms including the consenting form. All study forms were translated into the local
language (Dari) and were field tested. During the field testing field workers did the interview in pairs, and each pair interviewed 3 to 4 families with each study form over a period of 2-3 days. After each day of field practice, field workers discussed their findings and the study forms were amended if deemed to be necessary.

3.11.3 Clinical assessment of children at the study hospital

The study protocol, standard operating procedures and the study forms were discussed with the three study clinicians and two senior clinical supervisors. Then they were trained along with field workers in IMCI guidelines using video clips and clinical demonstration. The consistency in counting respiratory rate and observing chest in drawing was assessed by comparing the study clinicians’ observations with that of the trainer.

3.11.4 Radiography

Four study radiographers were trained in standard techniques of radiography by an expert WHO consultant. The training consisted basic theories of radiography and its physics rules, and practice of taking X-rays at the appropriate positions and optimum level of exposure to x-ray radiation.

3.11.5 Collecting venous blood samples

One study phlebotomist was trained on how to take consent for collecting blood samples, how to fill the blood collection form, and how to take care of blood samples drawn before transporting to the laboratory for centrifugation and freezing.

3.11.6 Refresher Training

All field workers and field officers were given refresher training for two days in June, 2008 in measuring clinical parameters and completing study forms. Refresher training was conducted on 23rd December 2008 for field staff. The aim was to refresh on how to collect correct information about indoor air pollution. One-day training was conducted for field staff on 25th March 2009. The training was a refresher session about anthropometric measurements such as weight, height, and head circumference, as well as, refreshing on use of breast feeding, and economic status forms. The training included practical sessions at Pediatric ward of Maiwand Teaching Hospital and preceded the administration of these
forms in the field. Subsequent refresher trainings were undertaken for field and clinical staff during last two quarters of the study to assess the quality of work and resolve if there were some technical problems.

3.12 Screening, Consenting and recruitment

Three supervisors sketched and counted the total number of houses in the study areas. There were approximately 14000 houses. The study area was divided into 3 study zones (district 1 as zone one, districts 7 and 8 as zone two, and districts 2 and 3 as zone three) and allocated to one supervisor for day to day running of the project. Each study zone was divided into 4 sub zones, and each sub zone was assigned to 1 recruitment team consisting of 10 field workers and 1 team leader. The field workers worked in pair and visited all households in their allocated area. If a family had a child aged between 1 and 11 months, they marked the number of eligible children on the door. If a family did not have any eligible child, they marked zero on the door. If an eligible child was absent on the day of visit, the team returned on the next day to recruit the absentee child into the study.

Study children were enrolled from 6th November to 2nd December 2007. If a family had an eligible child, the field worker explained the objectives of the project and its benefits to the family and child. If a family was interested in their child to be in the study, the field worker read details of the study procedures from the information sheet and asked the mother if she was willing to participate. In addition to mother a second person (mostly child’s father) was also requested to give consent. If both parents gave consent, they were requested to give their thumb prints in the consent form, in the presence of a witness who also either signed or thumb printed the consent form. For each child, two consent forms were filled: one copy was given the family and the second one was filed in the project office (Annex 4).

If a family consented, data on socio-demographic characteristics of the child and parents (age, education, profession and occupation), height, weight, head circumference, and illness history were collected using the recruitment form (Annex 5). If a family did not consent, or the inclusion criteria was not met, the field workers collected socio-demographic characteristic of parents and the reasons for not consenting in recruitment forms.
Each field worker enrolled approximately 10 children daily, and each study child was provided with Photo ID card. The parents were requested to bring the photo ID card whenever the child was brought to the study hospital for consultation. The photos on the ID cards were updated on a 6-monthly-basis due to rapid growth of the children. Families were provided with a contact number on the ID card to call in case they face any problem in the hospital or if they need to contact the project management. (Annex 6).

A pictorial signs and symptoms card was given to the mothers at recruitment to record health problems of their children in between home visits by field workers. The card included pictorial signs of cough, fever, skin rash, vomiting and diarrhea for mothers to better recognize and recognize the health problems. The pictorial card was in a matrix format – the pictures of the signs were on the top of columns and the days between the fortnightly visits by field workers were in the rows. The mothers were asked to tick the corresponding box of sign and the date if a child had any illness. The pictorial cards were replaced fortnightly. (Annex 7).

All information included in the study forms was approved by study Ethics Review Boards prior to application in the field.

3.13 Randomization and concealment

An independent statistician randomized study number 0001 to 3050 in variable blocks to vitamin D and placebo in equal numbers (block of 20 with equal ratio) and gave it to a pharmacist in AKUH hospital in Karachi. The Pharmacist in AKUH prepared the vitamin D and Placebo and filled in syringes labeled with unique ID numbers provided by the independent statistician. Syringes for vitamin D group were filled with 100,000 IU vitamin D3 in 1 ml olive oil, and syringes for placebo group had only 1 ml olive oil. The dosage of vitamin D was the same for children in all age groups and the same dose was filled to respective syringes for all 6 rounds. The labeling included the manufacturing and expire dates of the vitamin D/placebo contents for each round. The syringes were freshly prepared and transported to the study site on quarterly basis. For each round, the syringes were transferred up to 2 weeks prior to the starting date of dose administration, and the syringes were transferred to study site under manufactures’ recommended temperature and storage conditions.
At recruitment, the field workers allocated one syringe to each child sequentially. The study number for each recruited child was the unique code number of the syringe that was administered at round one for each child. The vitamin D and the placebo (olive oil) were of same color (pale yellow) and same quantity (1ml) and therefore all project staff, as well as, the families were blinded to vitamin D and placebo status of the syringes. During the subsequent round each child was administered vitamin D or placebo from a syringe that had his/her unique ID number by a pair of field workers. One field worker checked the label of the syringe whether it was the same ID number recorded in the Photo ID card and it was verified by the second field worker before giving the content of the syringe to a given child. If a family had two children in the study, the field workers took out only one syringe from their bag at one time to avoid mistakes in administration of the intervention (see SoP 5 Annex 8).

Vitamin D or placebo was administered quarterly. The first dose was in November, 2007, the second in February 2008, the third in May 2008, the fourth in August and the fifth dose in December 2008. The sixth dose was given in March 2009. In each round vitamin D administration form was used to record the details of drug administration (Annex 9).

3.14 Active surveillance

Study children were visited at home fortnightly to assess their health status and also to determine health seeking behavior and practices. In each home visit, field workers asked about signs and symptoms during the past two weeks, the treatments given to the child, and where the child was taken for any illness (two-weekly assessment form – annex 10). Field workers also checked chest in drawing, body temperature, signs of dehydration by skin pinching, and counted respiratory rate. The pictorial cards given to the family on the last visit was checked whether mothers marked the signs and symptoms child had, as well as, if the marked signs corresponded to the signs mother mentioned about health status of her child during the past two weeks. Regretfully, most mothers were either forgetting to mark the signs and symptoms in pictorial cards, or losing the card, making it a less effective approach. Nevertheless, in each home visit, the families were provided with a new pictorial card in order to keep them engaged to the study. If a child was absent during the household visit an absentee form (Annex 11) was completed to determine the period
families were absent from the study area, where they lived in that period, if the child got any serious illness in absent period and to determine when they returned to the study area. Moreover, information about risk factors of pneumonia such as breast feeding, economic status, indoor air pollution, family crowding, anthropometric measures, and exposure to cigarette smoke was collected in different seasons during the fortnightly visits according to study schedule. Over all 36 two-weekly home visits were performed from the beginning till end of project in May 2009.

Verbal autopsy interviews with families that lost their child during the study were conducted 40 days after the child’s deaths. WHO-standard verbal autopsy form was translated into local language, and used for interviews. All death cases were coded according to ICD-10 WHO standard format and reported to data safely monitoring board. I coded the causes of death in Kabul, and the study supervisor at LSHM (Daniel Chandramohan) verified the coding before those cases were reported to DSMB. The details of death cases with ICD-10 codes are summarized in Table 16.

3.15 Passive surveillance

Study children were brought to the hospital either if a field worker referred him/her, or if parents themselves thought their child was sick. Children brought to the hospital were first seen at OPD irrespective of severity of their illness. At OPD the study doctors identified children from the photo ID card and the bracelet in their hands. If the bracelet was missing, or the ID card did not have the photo, the attending study doctor confirmed the child ID using the records in the study office with the assistance of study supervisors. Full clinical history about past two weeks, health seeking and treatments given prior to attending the hospital and all clinical signs including respiratory rate, and chest recession were collected using the OPD form (Annex 12).

Patients with serious conditions were referred from OPD to IPD for admission according to the study protocols (Annex 13). At admission first a full history of sign and symptoms, treatments given at home, and place of treatment were collected. Then a full clinical, laboratory and x-ray examinations were conducted as appropriate and all the data was recorded in the IPD form (Annex 14). The data on prognosis and the final diagnosis was
completed at discharge. If a family refused admission, appropriate treatment was advised at home, and was asked to come back for follow up in two days.

All children with clinical diagnosis of pneumonia were advised chest x-ray. In the x-ray form (Annex 15) the study number, date of chest x-ray and position of chest x-ray were recorded. The chest x-rays were archived and sent to radiographers in the ARI unit of Pakistan Institute of Medical Sciences (PIMS) for assessment. All chest x-rays were read by two radiologists independently. The findings of the two radiologists were compared by the radiology coordinator and if there was a discrepancy between the two radiologists the x-ray was read by a third radiologist independently. The diagnosis agreed by any two radiologists was deemed to be the final diagnosis.

3.16 Vitamin D/Placebo Administration

All doses of Vitamin D (100,000 IU D3) and Placebo were successfully administered to children, who were present in the study at each round. Only a few protocol violations happened and these were immediately reported to study management and recorded. As already mentioned, the same drug dosage (100,000 IU D3) was freshly ordered from Karachi Pharmacy Department for each round and they filled the syringe for each round using the same randomization list provided by our independent statistician. We did not have the resources to monitor the work of the pharmacy department at AKU and to check whether the right amount of vitamin D was filled in each syringe. We did not do quality check of the contents of a random sample of syringes because it was very expensive. However we collected blood samples from a randomly selected 600 children to compare the level of serum vitamin D in two groups. The comparison of the serum vitamin D levels between the two groups was used as a proxy to determine the quality and contents of the syringes. The total doses administered each round and the protocol violations happened are shown in the CONSORT chart (Figure 3).
3.17 Vitamin D Adverse Effects

During 18 months of project implementation, no signs of vitamin D over dosage or adverse effects was detected or reported. All field workers and field supervisors closely monitored the drug administration processes to detect any over dosage. When contents of a syringe were administered to a child in each round, the respective field worker observed the children for at least half an hour for sign and symptom of vitamin D over dosage listed in vitamin D administration form. Moreover, families were asked to contact the respective field worker, field supervisor or project management team if the child experienced any delayed adverse events. All families were provided with contact telephone numbers of the management team, field workers and field supervisors. Two extended focused group discussion were conducted with pediatricians from two pediatric hospitals to ask for their opinions and concerns about vitamin D intoxication and all its aspects such as predisposing factors, toxic doses etc. The findings are discussed in discussion section.

3.18 Reading of chest x-rays

Three radiologists from ARI unit of Pakistan Institute of Medical Sciences (PIMS) read the study chest x-rays using the standard WHO vaccine trial protocol. They used WHO Proforma for Standardized Interpretation of pediatric chest radiographs for the diagnosis of pneumonia(bacterial) (109). The radiologists were trained by WHO and had the experience of working with international research projects. The results from each reader were entered into database by data manager and their opinions were compared. If two readers agreed on the same result, that was reported as the final result. If two independent readers did not agree on the same results, those x-rays were passed to the third radiologist for confirmation. A case was confirmed as pneumonia if unilateral or bilateral infiltration or consolidation with or without effusion was observed in x-rays by two independent readers. Figure 6 shows two samples of chest x-rays diagnosed as significant pathology for pneumonia, and figure 7 shows two samples of chest x-rays where one of the two readers disagreed to diagnose as pneumonia, and they were confirmed as pneumonia after third reader’s opinion.

3616 chest x-rays were read by independent radiologists. 833 x-rays were reported positive for pneumonia. The positive cases of pneumonia were matched with clinical data to see if
the date for each case matched with the records a child was seen either in OPD or IPD. Of
833 x-rays with positive pneumonia, 19 cases (10 from vitamin D and 9 from Placebo
groups) did not match with OPD, IPD or two weekly home visit data and were dropped
from analysis. Of 814 positive chest x-rays, 440 were from vitamin D and 337 were from
Placebo groups. The agreement between the two independent radiologists was reasonable
(Kappa= 0.85, P< 0.001) and the total chest x-rays interpreted by two readers as either
pneumonia or non-pneumonia is summarized in table 30. 258 x-rays were read by 3rd
radiologists because of the discrepancy in the findings of the first two readers. The third
reader’s reading was taken as the final diagnosis.

3.19 Blood sampling and assessment of serum vitamin D levels

We collected around 120 blood samples 5 times during the 18 months of project’s
implementation. Children were randomly selected for each round. The time for blood
sampling was arranged to account for pharmacodynamic and seasonality of vitamin D
deficiency. All families were asked for consent before drawing the blood. From each child
up to 5ml blood was drawn and stored in a vacutainer tubes inside the cold vaccine carrying
box before transferring all samples to a clinic. In the clinic samples were immediately
centrifuged and the plasma was kept in a separate tube refrigerated. Both the phlebotomist
in the field and the nurse in the clinic filled a form recording child’s unique ID, amount of
blood/plasma drawn and the date. A total of 668 blood samples were drawn, of which 345
were from vitamin D and 323 from placebo groups. The samples were transferred to
Manchester hospital for measuring serum vitamin D level. The list of samples was given to
the lab technologist without disclosing the study codes.

The serum 25(OH)D levels were determined by IDS-iSYS Multi-Discipline Automated
Chemiluminescent assay (Immunodiagnostic Systems Ltd, Boldon, Tyne and Wear UK) at
Manchester Royal Infirmary, Supra-Regional Vitamin D Reference Laboratories accredited
to ISO9001:2000 and ISO13485:2003 and participating in the Vitamin D Quality
Assurance Scheme (DEQAS).

Of 668 sample serums, 632 (332 from vitamin D and 300 from placebo groups) were able
to be tested. The rest of samples were not enough for processing.
3.20 Assessment of contextual and potential risk factors of pneumonia

Data on child’s currently breastfeeding status, and reasons for not breastfeeding were collected twice during the project life using the breastfeeding form (Annex 16). Data on number of people sleeping in the child’s bedroom were also collected and recorded in the same form. The section on breastfeeding status was repeated in the second winter.

In the beginning of winter 2007, the level of indoor air pollution was assessed by asking about smoking in the family, cooking and heating system (Annex 17). Exposure to cigarette smoke was assessed as one of potential risk factor for pneumonia. Additionally, indoor air pollution was assessed by measuring what type of heating device a family used during the winter, as well as, how long each device was on during a day on average (section 3.22.2).

The socio-economic status of the households was assessed by ownership of common assets. Using the principle component analysis, we developed the wealth index based on household characteristics and assets. From this index, wealth quintiles were obtained ranging from least poor to poorest as a final measure of economic status of a household (section 3.22.2).

Mother’s total birth was determined by asking about total death and living children she had (Annex 18). In this study, total alive children were used as a measure of crowding in addition to number of people sleeping in the child’s bedroom.

Baseline nutritional status was assessed by measuring weight of children at recruitment (form A, annex 5). In this study the weight for age z-score was used for assessing the nutritional status (section 3.22.2). Age of children, as well as, mothers’ and fathers’ education as influencing factors for pneumonia was assessed at recruitment (form F, annex 2).
3.21 Data Entry and Data Processing

All data collection forms were manually checked daily and errors were corrected by the respective field worker. Some forms that required cross-checking with the families were taken back to the families for completion. Only the field worker who completed a given form was allowed to correct data errors in that form. If the respective field worker was not available, the field supervisors and the project manager were authorized to correct the data errors if appropriate.

Data were checked again at data entry point. If any mistake or inconsistency was found, the form was sent back to the field for correction. Data entry was done parallel to data collection. The database was developed using Microsoft office Access 2003 with necessary validation rules to avoid data entry errors. All forms were entered twice by two different data clerks. The data management team developed a query system in database to detect if there was any inconsistency between first and second entries. If the system was detecting any error, the data assistant was checking the forms to determine the problem and correct it. I also checked all data in Kabul during the preliminary analysis to find out if there was any data entry error or data inconsistency, and proper feedback was provided to data management team for respective corrections. The database was backed up on a daily basis to avoid any data loss. Statistical analysis was undertaking by using statistical data management package Stata, version 10. The main analysis was carried out in the basis of intention to treat, but per protocol analysis was also conducted to compare the result with that of intention to treat. The identity of study subjects was not revealed to all investigators and institutions involved with project’s analysis part such as blood tests and x-ray interpretation till all the analysis was performed.

3.22 Study Timeline

The enrolment started on 7th November 2007 and completed on 2nd December 2007. The first dose of vitamin D/placebo was administered at recruitment and the rest of the doses were given 3 monthly. The last dose was given in February 2009. The active and passive surveillance ended in May/June 2009. Date entry, data cleaning and data archiving were finished in October 2009.
3.23 Analytical methods

3.23.1 Baseline characteristics

The frequencies and percentages of baseline characteristic that are binary/categorical variables (age of the child, mothers’ and father’s education, marital status and working status) were compared between the two study groups using Chi square test. The distributions of continuous variables (child’s age) were compared between the groups using means (and SD) or medians (and inter-quartile range). The distribution of potential risk factors of pneumonia namely child’s age, mother’s education, father’s education, families economic status, indoor air pollution and exposure to cigarette smoke, family crowding, breast feeding and nutritional status were also compared between the two groups using Chi square test to assess the robustness of randomization. The background characteristics were compared between children with no episode of pneumonia, single episode of pneumonia and multiple episodes of pneumonia. A logistic regression model was used to test the association between potential predictors and single or multiple episodes of pneumonia.

3.23.2 Potential Risk Factors for Pneumonia

The following potential risk factors for pneumonia were measured: Indoor air pollution (exposure to cigarette smoke and type of heating device), lack of breastfeeding, crowding (number of people sleeping in child’s bed room, and number of alive children from the same mother), malnutrition (weight for age z-score), poverty (household’s asset ownership), child’s age, mother’s education, and fathers’ education. Analysis method for each risk factor is described below:

Indoor air pollution

Indoor air pollution was measured by a composite variable derived from the type of heating device used by families and the length of time the device was on in 24 hours of the past week during winter season on average. Indoor air pollution was quantified by an air pollution score ranging from 0 to 5. The scoring matrix is shown in Table 6. The indoor air pollution score from each source was summed up and categorized into no/low pollution (score <0.5), medium (score 0.5-2) and high pollution (score 3-5).
Malnutrition
Nutritional status was measured by baseline weight for age z-score. Using the standard WHO reference weight for age, nutritional status was categorized as follows: No Malnutrition: Weight for age Z-Score ≥ -1; Mild Malnutrition: Weight for Age -2 ≤ Z-score <-1; Moderate Malnutrition: Weight for age -3 ≤ Z-score <-2; Severe Malnutrition: Weight for age Z-Score < -3

Lack of breastfeeding
A child was defined as not breastfed if he/she had never been breastfed or if he/she was ever breastfed but not currently breastfed (one month after recruitment at time of interview)

Crowding
Crowding was measured by two separate variables. Overcrowding was defined either if ≥ 5 people were sleeping in child’s bedroom or if a family got ≥8 children alive from the same mother. Total number of people sleeping in child’s bedroom was classified into three categories (≤ 2, 3-4, or ≤ 5 peoples sleeping in child’s bedroom). Number of children alive from the same mother was also classified into three categories (≤ 3, 4-7, or ≤ 8 children).

Exposure to cigarette smoke
Was measured by child’s exposure to the number of cigarettes all family members smoked inside the child’s room on average on a daily basis and categorized as follow: none; exposed to 1-9 cigarettes per day; 10-19 cigarettes per day or exposed to ≥ 20 cigarettes per day.

Economic status
Economic status was assessed by total assets a family owned. A principle component analysis was carried out using the asset information. All assets were tested for association among each other to check for consistency. Study children were classified into five economic quintiles:

a. Better off (Highest quintile)
b. Less poor
c. Poor
d. Very poor
e. Poorest (Lowest quintile)
**Child's age**
Child’s age at recruitment was considered as a risk factor for pneumonia. Children were classified into three age groups based on age at enrolment: <2 months; 2-5 months; 6-12 months.

**Mother's and father's education**
Mother’s and father’s education were measured by asking if they had any formal education or not.

**3.23.3 Person Time At risk and End points**
A clinical episode of pneumonia was defined as those cases observed in: 1) the 2 weekly visit records; 2) the outpatient records; and 3) the inpatient records according to the criteria for the first and repeat episodes of pneumonia (text box on definition of the study outcomes). The time to an episode was calculated as time from recruitment or previous episode allowing at least 30 days (35), (1) between two episodes to be counted as a new episode. An episode happening within 30 days after previous episode was counted as duplicate of that episode and excluded. If a child was not seen for more than 45 days at the two weekly visits or at the OPD/IPD records, they were censored for that period of the study. Such a child could reenter the study when next seen. Any overlap between episodes reported in the 2 weekly visits, outpatients or inpatients was accounted for with an inpatient episode taking first priority and an outpatient episode second.

Children who were missed during the follow up visits were included in intention to treat analysis if they re-appeared any time during the follow up or the final home visit at the end of the study. If not present in the final home visit, they were censored from the point they were last seen either in the hospital or home.

For the primary endpoint, data on chest x-rays were combined with clinical data to measure the rate of first and repeat episodes of x-ray confirmed severe and non-severe pneumonia in vitamin D and placebo groups. The same criteria were applied for censoring and accounting for repeat episodes as mentioned above.
Rate ratios for the first episode of pneumonia for the Vitamin D group were compared to the placebo group using Cox proportional hazard models. Time to the first episode in the Vitamin D group was compared to that in the placebo group using log rank tests and proportional hazards models. Percent failure, incidence rate ratios (with 95% CI’s) together with numbers of cases and censored children were given at specified time points (every three months). Kaplan Meier plots were used to display the survival curves for both groups. Initial models were used to determine the effect of Vitamin D compared to placebo (unadjusted for other factors) on the primary outcome.

Violation of the assumptions of proportionality in the Cox models were assessed via model Schoenfield residuals and examined graphically with plots of a survival transformation over time.

Similar analysis was carried out for repeat episodes and all other secondary outcomes.

Effect of potential risk factors of pneumonia, such as, child's age, mothers and fathers education, economic status, family crowding, breastfeeding status, indoor air pollution, child’s sex, exposure to cigarette smoke, and malnutrition (weight for age z-score) were assessed on the rate of first and repeat episodes of severe and non-severe x-ray confirmed pneumonia using Cox regression model. Only covariates with a significant effect in unadjusted analysis were kept in the adjusted model.

3.23.4 Per Protocol Analysis

We conducted 3 different per protocol analyses. The first was based on initial study protocol where children in vitamin D and placebo groups who received two consecutive doses of the drug within 60 days or more than 120 were excluded, and the remaining of children were kept for analysis. In the second per protocol analysis, only the children who received at least 4 consecutive doses of the drug at the right time (interval between doses was not less than 60 days and not more than 120 days) were kept for analysis. In the third per protocol analysis we planned to restrict the analysis to those children who had received all 6 doses at the right time, but we were unable to do this because no children had received all 6 doses at the right time. Therefore the third analysis was restricted to children who had received 5 doses of the drug in the right time. In per protocol analyses, children whose
randomization was violated (received the wrong dose or received a high dose of vitamin D from other sources) were excluded.
CHAPTER 4: RESULTS

4.1 Trial profile

From 14000 households sketched in the study area, 3060 children were assessed for eligibility and 3046 (1524 children in vitamin D group and 1522 children in placebo group) were recruited in the study. Of 14 children excluded, 2 children did not meet the inclusion criteria and 12 children/families did not want to participate. Of 2 children, one was suffering from severe malnutrition, and the second had received a high dose of vitamin D within 3 months before recruitment. Those who refused to participate (12 families), either did not want to go to study hospital or did not want field workers to go to their houses. Some of them did not participate without any reason. The reasons for exclusion from the study and the follow up rate are shown in Figure 3. After the first quarter refusal and lost to follow up was 34 in vitamin D group and 26 in placebo group. Three children had died from Vitamin D group and 2 children from placebo group. At the end of second quarter, refusal and lost to follow up increased to 35 in vitamin D and 41 in placebo groups. Six children died in vitamin D group and 1 child from placebo group. Before the 4th quarter, we had 45 children lost to follow up and refused to participate in vitamin D group and 47 children of those in placebo group. One child from vitamin D group and one from placebo group had died. After the 4th quarter 50 children were refusal and lost to follow up in vitamin D group and 72 children in placebo group. Only 2 children had died from Placebo group. By the end of study in May 2009, we had a total 206 children refusal and lost to follow up in vitamin D group and 207 children in placebo group. The cumulative deaths in vitamin D group was 10 and in placebo group was 7 (Figure 3). In final follow up visit in May 2009, 2616 (1312 vitamin D and 1304 placebo) children were present in the study and 17 had died. (Figure 3). The number of children lost to follow up during the study was pretty low and many children lost, rejoined the study later and rates were similar between the two groups (Figure 3).
4.2 Socio-demographic characteristics of study children

The mean age for study children in vitamin D group was 6.2 months (95% CI: 6.02 – 6.34) and for children in placebo group was 6.2 (95% CI: 6.04 – 6.35) at recruitment (Table 7). In both vitamin D placebo groups almost half of the children were male (53.2% and 51.2% respectively).

Majority of mothers in vitamin D and placebo groups were aged 20-39 years (90.7% and 88.9% respectively). More than half of mothers in both groups did not have any formal education (62.4% and 65.2% respectively) (Table 7). Of mothers, who attended any formal education, the majority studied until grade 6 (primary school) in both groups (51.5% in vitamin D group and 48.5% in placebo group). In comparison to mothers, more than half of fathers in both groups had attended any formal education (71.2% in vitamin D and 70.4% in placebo groups). More than 90% of fathers in both groups were currently working (Table 7). More than 95% of mothers in both groups were currently married and the only wife of their husbands. Majority of fathers in both groups were from Tajik nationality (69.7% in vitamin D versus 70.5% in placebo groups). All baseline characteristics were evenly distributed between vitamin D and placebo groups and the slight differences were not statistically significant.

4.3 Baseline Potential Risk Factors

The distributions of potential risk factors of pneumonia at the baseline in the two groups are shown in Table 8. As expected almost all risk factors were evenly distributed between vitamin D and placebo groups. The distribution of poverty was similar between the groups. In vitamin D group 10.8% of families were in the better of group compared to 10.4 % in placebo group. Similarly, 16.7% in vitamin D group and 15.5% in placebo groups were in the poorest group. Similar percentages of children in both groups were malnourished (44.9% in vitamin D and 44.1% in placebo groups); of whom, 5.7% of children in vitamin D group and 5.1% in placebo group were severely malnourished (weight for age z-score). Exposure to number of cigarettes smoked inside the child’s room was similar, and 57% of children in both groups were not exposed to any indoor cigarette smoke. Only 4.7% in vitamin D and 4.9% in placebo groups were exposed to more than 20 cigarettes smoked per
day inside the child’s room. Similar number of people was sleeping in child’s bed room. Percentage of 5 or more people sleeping in child’s bedroom in vitamin D group was 41.1% in comparison to 39.5% in placebo group. Almost 60% of children in both groups were currently breastfed. In vitamin D group 47.8% of children were exposed to high indoor air pollution compared to that of placebo (48.9%).

4.4 Characteristics of children in comparison to episode of pneumonia

Overall, 82% of the study population (2496 children) did not get any episode of pneumonia during the 18 months of study follow up. Those who got only a single episode of pneumonia composed 13% of the population (395 children), and only 5% of the study population (155 children) got multiple episodes of pneumonia (two or more episodes) (Table 9). Number of children with first or only episode of pneumonia was higher in placebo group, while more children in vitamin D group got multiple episodes of pneumonia (Figure 8 and Table 10).

Among children who had ≥2 episodes of pneumonia the proportion of 9-12 month old children was higher than that among children who had no episodes of pneumonia or just one episode of pneumonia. (44.5% vs. 27%). Similarly, nearly quarter of children (23.9%) having ≥2 episodes of pneumonia were from the poorest socio-economic quintile while the proportion of children in the poorest quintile was relatively lower among those who had no episodes of pneumonia (15.3%) but these differences were not statistically significant. The proportion of children exposed to high indoor air pollution was higher among those who had no episodes of pneumonia (43.4%) or one episode of pneumonia (44.3%) while this was lower among children who had ≥2 episodes of pneumonia (38.1%). ≥ 5 people sleeping in the same room as the child was higher among the children who had ≥2 episodes of pneumonia (50.9%) compared to that among children who had no pneumonia (39.3%). Father’s lack of formal education was lower (27.6%) in children who did not get any episode of pneumonia compared to that for children who got a single episode of pneumonia (34.4%) and those who got two or more episodes of pneumonia (40%). The percentage of children who had vitamin D was higher in children who had two or more episodes of pneumonia (58.1%) compared with those who had a single episode of pneumonia (47.3%) or did not have an episode of pneumonia (49.9%) (Table 9).
After adjusting for background characteristics that were statistically significant in unadjusted model, child's age, indoor air pollution and vitamin D were the only predictors of multiple episodes of x-ray confirmed pneumonia. Age 9-12 months at enrolment was a strong predictor of multiple episodes of pneumonia (adjusted OR 3.4; 95% CI: 1.4 – 7.9, p=0.03) compared to children with no episodes of pneumonia (Table 10). Children exposed to medium or high indoor air pollution appear to be protected from multiple episodes of pneumonia compared to children exposed low air pollution (Table 10). The exposure to vitamin D is a predictor of multiple episodes of pneumonia compared to those who were exposed to placebo (OR 1.7; 95% CI 1.1 – 2.8).

The incidence rate of x-ray confirmed pneumonia was highest in winter, followed by spring, autumn and summer seasons (Figure 9). The incidence was higher in vitamin D group compared to that in the placebo group in winter, spring and autumn seasons. The incidence in summer was almost the same for both groups (Figure 8).

4.5 Primary Endpoint

The incidence rate of first or only episode of x-ray confirmed all severe and non-severe pneumonia in vitamin D group was 0.145 per child year (95% CI: 0.129 – 0.164), and in the placebo group was 0.137 per child year (95% CI: 0.121 – 0.155). The incidence rate ratio was 1.06 (95% CI: 0.89 – 1.27; p=0.47) (Table 11).

The incidence rate of first or only episode of x-ray confirmed severe pneumonia in vitamin D and placebo groups were almost the same 0.02 per child per year (95% CI: 0.01 – 0.03). The incidence rate ratio was 1.1(95% CI: 0.73 – 1.72, p= 0.58). The incidence rate of first or only episode of x-ray confirmed very severe diseases including very severe pneumonia in vitamin D group was 0.006 per child year (95% CI: 0.003 – 0.011) and 0.004 per child year (95% CI: 0.002 – 0.008) in the placebo group. The incidence rate ratio was 1.45(95% CI: 0.61 – 3.39, p= 0.39). (Table 11).

The survival graph (Figure 10) of time to the first or only episodes of x-ray confirmed severe and non-severe pneumonia shows that children in both vitamin D and Placebo groups had almost similar probability of survival without an episode of pneumonia. The
incidence rate ratios together with confidence limits for primary end points are graphically presented in Figure 12.

The test for non proportional hazards was not significant with \( p > 0.05 \).

4.6 Secondary Endpoints

4.6.1 Repeat Episodes of X-Ray Confirmed Pneumonia

The incidence rate of repeat episodes of x-ray confirmed severe and non-severe pneumonia in vitamin D group was 0.07 per child per year (95\% CI: 0.06 – 0.08) compared to 0.04 per child per year (95\% CI: 0.03 – 0.05) in the placebo group. The incidence rate ratio was 1.68 (95\% CI: 1.28 – 2.21; \( p < 0.001 \)) (Table 12). The incidence rate of repeat x-ray confirmed severe pneumonia was 0.004 per child per year (95\% CI: 0.002 – 0.009) compared to 0.003 per child per year (95\% CI: 0.001 – 0.007) in placebo group. The incidence rate ratio was 1.25 (95\% CI: 0.49 – 3.17; \( p = 0.63 \)). There were not repeat episodes of very severe diseases in both groups (Table 12). The incidence rate ratios together with confidence limits for repeat episode of severe and non-severe x-ray confirmed pneumonia are graphically presented in Figure 13.

4.6.2 First or only Episode of clinical Pneumonia

The incidence rate of first or only episode of severe and non-severe clinical pneumonia in vitamin D group was 1.38 per child per year (95\% CI: 1.30 – 1.47) compared to 1.46 per child per year (95\% CI: 1.37 – 1.55) in placebo group. The incidence rate ratio was 0.95 (95\% CI: 0.87 – 1.03; \( p = 0.27 \)). The incidence rate of first or only episode of severe clinical pneumonia in vitamin D group was 0.08 per child per year (95\% CI: 0.07 – 0.10) which was similar in placebo group 0.08 per child per year (95\% CI: 0.07 – 0.09). The incidence rate ratio was 1.08 (95\% CI: 0.86 – 1.35; \( p = 0.49 \)). The incidence rate of first or only episode of clinical very severe diseases in vitamin D group was 0.08 per child per year (95\% CI: 0.07 – 0.09) which was comparable to that in the placebo group 0.09 per child per year(95\% CI: 0.07 – 0.10). The incidence rate ratio was 0.90 (95\% CI: 0.72 – 1.12; \( p = 0.36 \)) (Table 11). The incidence rate ratios together with confidence limits for first or only severe and non-severe clinical pneumonia are graphically presented in Figure 14.
4.6.3 Repeat Episodes of Clinical Pneumonia

The incidence rate of repeat episodes severe and non-severe clinical pneumonia in vitamin D group was 1.15 per child per year (95% CI: 1.11 – 1.19) compared to 1.08 per child per year (95% CI: 1.04 – 1.13) in the placebo group. The incidence rate ratio was 1.06 (95% CI: 1.00 – 1.12; p= .04) (Table 12). The incidence rate of repeat severe clinical pneumonia in vitamin D group was 0.02 per child per year (95% CI: 0.01 – 0.03) compared to 0.03 (95% CI: 0.02 – 0.04) in placebo group. The incidence rate ratio was 0.92 (95% CI: 0.63 – 1.35; p=0.68). The incidence rate of repeat clinical very severe diseases in vitamin D and placebo groups was almost the same 0.02 per child per year (95% CI: 0.01 – 0.03). The incidence rate ratio was 1.12 (95% CI: 0.72 – 1.74; p= 0.59) (table 12). The incidence rate ratios together with confidence limits for repeat episode of severe and non-severe clinical pneumonia are graphically presented in Figure 15.

4.6.4 All Episodes of X-ray confirmed Pneumonia

The incidence rate of all episodes of x-ray confirmed severe and non-severe pneumonia in vitamin D group was 0.195 per child year (95% CI: 0.177 – 0.216) and in the placebo group was 0.161 per child year (95% CI: 0.144 – 0.179). The incidence rate ratio was 1.22 (95% CI: 1.05 – 1.41; p=0.008) (Table 13). The incidence rate of all episodes of x-ray confirmed severe pneumonia in vitamin D was 0.027 per child year (95% CI: 0.021 – 0.036) and in the placebo groups was 0.023 per child per year (95% CI: 0.017 – 0.031). The incidence rate ratio was 1.17 (95% CI: 0.79 – 1.72, p= 0.42). The incidence rate of all episodes of x-ray confirmed very severe diseases including very severe pneumonia in vitamin D group was 0.006 per child year (95% CI: 0.003 – 0.011) and 0.004 per child year (95% CI: 0.002 – 0.008) in the placebo group. The incidence rate ratio was 1.44 (95% CI: 0.61 – 3.39, p= 0.39). (Table 13).

4.6.5 All Episodes of Clinical Pneumonia

The incidence rate of all episodes of clinical severe and non-severe pneumonia in vitamin D group was 1.656 per child year (95% CI: 1.601 – 1.713) and in the placebo group was 1.594 per child year (95% CI: 1.540 – 1.650). The incidence rate ratio was 1.04 (95% CI: 0.99 – 1.09; p=0.11) (Table 13). The incidence rate of all episodes of clinical severe
pneumonia in vitamin D group was 0.103 per child year (95% CI: 0.090 – 0.118) and in placebo groups was 0.100 per child per year (95% CI: 0.087 – 0.115). The incidence rate ratio was 1.03 (95% CI: 0.85 – 1.25, p= 0.73). The incidence rate of all episodes of clinical very severe diseases including very severe pneumonia in vitamin D group was 0.095 per child year (95% CI: 0.083 – 0.110) and 0.101 per child year (95% CI: 0.088 – 0.116) in the placebo group. The incidence rate ratio was 0.94 (95% CI: 0.77 – 1.15, p= 0.57). (Table 13).

4.6.6 Time to repeat episodes of pneumonia after vitamin D/Placebo administration

To determine whether a higher rate of repeat x-ray confirmed pneumonia in vitamin D compared to placebo group was due to recent vitamin D supplementation and a high serum vitamin D, we measured the mean time (number of days) to repeat episodes of x-ray confirmed pneumonia after the most recent dose of vitamin D or placebo. The mean number of days to a repeat episode of pneumonia post vitamin D was 63.5 (95% CI: 47.2 – 79.8) and that in the placebo groups was 67.1 (95% CI: 44.5 – 89.7). The difference in mean number of days was not statistically significant between the two groups (P-value = 0.39) (Table 14).

4.6.7 All Cause and Pneumonia specific Mortality

By end of project’s implementation in May 2009, 17 children had died due to different causes. Of those, 10 cases were from vitamin D and 7 cases were from Placebo groups. The mortality rate in the study cohort was 4.2 (95% CI: 2.4 – 6.7) /1000 child year with 4.9 (95% CI: 2.4 – 9.1) /1000 child years in vitamin D and 3.4(95% CI: 1.3 – 7.1) /1000 child years in placebo groups. The mortality rate ratio was 1.42 (95% CI: 0.49 – 4.41; p=0.24). The difference in the all cause mortality rate between the two groups was not statistically significant. However the study was not powered enough to detect an effect of vitamin D on reducing mortality. Three children in vitamin D group and 2 children in placebo group died due to pneumonia associated with other health problems. Two cases from vitamin D group and 2 cases from Placebo died due to some other bacterial conditions such as bacterial meningitis and septicemia. The rest of death cases in both groups happened either due to chronic non-infectious reasons or due to accidental causes. Of these, 2 children died due to head trauma (TV fallen on child), one child was chocked by pill, two children died from possible congenital heart disease and neonatal jaundice respectively, one child was
suffocated by mattress while sleeping, and another child died due to neuroblastoma. The
detailed causes of mortality derived from verbal autopsy are shown in Table 17.

4.6.8 Hospitalization for any diseases

The incidence rate of first or only episode of hospital admission in vitamin D group was
0.07 per child per year (95% CI: 0.06 – 0.08) which was the same for placebo group. The
incidence rate ratio was 1.00 (95% CI: 0.79 – 1.27, p= 0.99). The incidence rate of repeat
hospital admission for vitamin D group was 0.02 per child per year (95% CI: 0.01 – 0.03)
and almost the same for placebo group {0.03(95% CI: 0.02 – 0.04)}. The incidence rate
ratio was 0.79 (95% CI: 0.53 – 1.19, p= 0.26) (Table 18). The probability of survival
without an episode of hospital admission was similar between the two groups (Figure 11),
and the test for non proportional hazards was not significant (p>0.05).

The mean number of days of hospitalization for various illness was 0.7 (95% CI: 0.4 – 1.0)
compared to 0.8(95% CI: 0.5 – 1.1) in placebo group (Table 19). Almost 80% of children in
both groups hospitalized for different illnesses were discharged in within a day. Number of
hospitalization days ranged from 0 - 10 days in vitamin D group (SD=1.9) compared to 0 -
7 days (SD=1.8) in placebo group. Almost 4% of children in vitamin D group and 5% in
placebo group were hospitalized for severe pneumonia (IMCI criteria). Febrile convulsion
cased 1.8% of hospitalization in vitamin D group and 1.7% in placebo group. Equal
number of children from both groups (15 children from each group) was hospitalized for
bronchiolitis. Bronchial asthma caused 0.7% of admissions in vitamin D group and 0.8% of
that in placebo group. Finally, admission for Urinary Tract Infection (UTI) was 1.1% in
vitamin D group and 1.4% in placebo group. The causes for hospitalization are summarized
in Table 19.

4.7 Per protocol analysis based on initial protocol:

Majority of study children (97%) entered the per protocol analysis using the initial protocol
criteria discussed in section 3.23.4. Of those, 49.9% were from the vitamin D group and
50.1% from the placebo group.
The results from per protocol analysis of x-ray confirmed and clinical severe and non-severe pneumonia using the initial protocol are not very different from those of intention to treat analysis:

**4.7.1 First or only Episode of X-Ray confirmed Pneumonia**

The incidence rate of first or only episode of x-ray confirmed all severe and non-severe pneumonia in vitamin D group was 0.14 per child year (95% CI: 0.12 – 0.16), compared to 0.13 per child year (95% CI: 0.12 – 0.15) in the placebo group. The incidence rate ratio was 1.06 (95% CI: 0.88 – 1.27; p=0.54). (Table19). The incidence rate of first or only episode of x-ray confirmed severe pneumonia in vitamin D group was very similar to that in placebo group: 0.024 per child year (95% CI: 0.018 – 0.033) in vitamin D group versus 0.028 per child year (95% CI: 0.014 – 0.028) in the placebo group. The incidence rate ratio was 1.23 (95% CI: 0.79 – 1.91; p=0.35). The incidence rate of first or only episode of x-ray confirmed very severe diseases including very severe pneumonia in vitamin D group was 0.006 per child year (95% CI: 0.003 – 0.012) compared to 0.005 per child year (95% CI: 0.002 – 0.009) in the placebo group. The incidence rate ratio was 1.33 (95%CI: 0.56 – 3.17; p= 0.51) (Table 20).

**4.7.2 Repeat Episodes of X-Ray Confirmed Pneumonia**

The incidence rate of repeat episodes of x-ray confirmed severe and non-severe pneumonia in vitamin D group was 0.07 per child year (95% CI: 0.06 – 0.08) compared to 0.04 per child year (95% CI: 0.03 – 0.05) in the placebo group. The incidence rate ratio was 1.69 (95% CI: 1.27 – 2.25; p <0.001) (Table 20). The incidence rate of repeat x-ray confirmed severe pneumonia in vitamin D group was 0.005 per child year (95% CI: 0.003 – 0.010) compared to 0.003 per child year (95% CI: 0.001 – 0.007) in the placebo group. The incidence rate ratio was 1.67 (95% CI: 0.61 – 4.59; p=0.31) (Table 21).

**4.7.3 First or only Episode of clinical Pneumonia**

The incidence rate of first or only episode of severe and non-severe clinical pneumonia in vitamin D group was 1.01 per child year (95% CI: 0.94 – 1.07) compared to 1.03 per child year (95% CI: 0.96 – 1.09) in the placebo group. The incidence rate ratio was 0.98 (95% CI: 0.89 – 1.07; p=0.68). The incidence rate of first or only episode of severe clinical pneumonia in vitamin D group was 0.09 per child year (95% CI: 0.07 – 0.10) which was
similar in placebo group 0.08 per child year (95% CI: 0.07 – 0.09). The incidence rate ratio was 1.11 (95% CI: 0.88 – 1.40; p= 0.38). The incidence rate of first or only episode of clinical very severe diseases in vitamin D group was 0.08 per child year (95% CI: 0.06 – 0.09) compared to 0.09 per child year (95% CI: 0.07 – 0.11) in the placebo group. The incidence rate ratio was 0.86 (95% CI: 0.68 – 1.08; p=0.21) (Table 20).

4.7.4 Repeat Episodes of Clinical Pneumonia

The incidence rate of repeat episodes severe and non-severe clinical pneumonia in vitamin D group was 1.17 per child year (95% CI: 1.12 – 1.22) compared to 1.08 per child year (95% CI: 1.04 – 1.13) in the placebo group. The incidence rate ratio was 1.08 (95 CI: 1.01 – 1.14; p=0.02 (Table 20). The incidence rate of repeat severe clinical pneumonia in vitamin D group was 0.024 per child year (95% CI: 0.017 – 0.032) compared to 0.023 per child year (95% CI: 0.017 – 0.031) in placebo group. The incidence rate ratio was 1.04 (95% CI: 0.68 – 1.59; p=0.84). The incidence rate of repeat clinical very severe diseases in vitamin D group was 0.022 per child year (95% CI: 0.016 – 0.030) which was similar to that in the placebo group 0.020 per child year (95% CI: 0.014 – 0.028). The incidence rate ratio was 1.10 (95% CI: 0.71 – 1.72; p=0.66) (Table 21).

4.8 Per protocol analysis with at least 4 consecutive doses of vitamin D/placebo

Assuming 4 consecutive quarterly doses of drug would cover all 4 season during a year, we restrict the analysis for children who received at least 4 consecutive doses of vitamin D or placebo in the right time. Using this criteria, 69% of the study cohort entered the per protocol analysis (2111 children). Of those, 50.3% was from vitamin D group and 49.7% from placebo group.

The results from this analysis for x-ray confirmed severe and non-severe pneumonia were very similar to that using the initial protocol presented earlier, while the results for clinical pneumonia were slightly different in two. The results are described below:

4.8.1 First or only Episode of X-Ray confirmed Pneumonia

The incidence rate of first or only episode of x-ray confirmed all severe and non-severe pneumonia in vitamin D group was 0.14 per child year (95% CI: 0.13 – 0.18), compared to
0.13 per child year (95% CI: 0.11 – 0.15) in the placebo group. The incidence rate ratio was 1.12 (95% CI: 0.91 – 1.37; p=0.26). (Table 21). The incidence rate of first or only episode of x-ray confirmed severe pneumonia in vitamin D group was 0.025 per child year (95% CI: 0.018 – 0.035) in vitamin D group versus 0.019 per child year (95% CI: 0.013 – 0.028) in the placebo group. The incidence rate ratio was 1.29 (95% CI: 0.80 – 2.11; p=0.28). The incidence rate of first or only episode of x-ray confirmed very severe diseases including very severe pneumonia in vitamin D group was 0.006 per child year (95% CI: 0.003 – 0.012) compared to 0.005 per child year (95% CI: 0.003 – 0.011) in the placebo group. The incidence rate ratio was 1.23 (95% CI: 0.49 – 3.12; p=0.65) (Table 22).

4.8.2 Repeat Episodes of X-Ray Confirmed Pneumonia

The incidence rate of repeat episodes of x-ray confirmed severe and non-severe pneumonia in vitamin D group was 0.07 per child year (95% CI: 0.06 – 0.09) compared to 0.04 per child year (95% CI: 0.03 – 0.05) in the placebo group. The incidence rate ratio was 1.75 (95% CI: 1.29 – 2.39; p <0.001) (Table 22). The incidence rate of repeat x-ray confirmed severe pneumonia in vitamin D group was 0.006 per child year (95% CI: 0.003 – 0.012) compared to 0.002 per child year (95% CI: 0.001 – 0.006) in the placebo group. The incidence rate ratio was 3.29 (95% CI: 0.91 – 11.96; p=0.07) (Table 23).

4.8.3 First or only Episode of clinical Pneumonia

The incidence rate of first or only episode of severe and non-severe clinical pneumonia in vitamin D group was 1.39 per child year (95% CI: 1.29 – 1.49) compared to 1.51 per child year (95% CI: 1.40 – 1.62) in the placebo group. The incidence rate ratio was 0.93 (95% CI: 0.84 – 1.03; p=0.19). The incidence rate of first or only episode of severe clinical pneumonia in vitamin D group was 0.09 per child year (95% CI: 0.08 – 0.11) compared to 0.07 per child year (95% CI: 0.05 – 0.08) in the placebo group. The incidence rate ratio was 1.31 (95% CI: 1.01 – 1.71; p= 0.04). The incidence rate of first or only episode of clinical very severe diseases in vitamin D group was 0.07 per child year (95% CI: 0.05 – 0.08) compared to 0.09 per child year (95% CI: 0.08 – 0.11) in the placebo group. The incidence rate ratio was 0.74 (95% CI: 0.57 – 0.95; p=0.02) (Table 22).
4.8.4 Repeat Episodes of Clinical Pneumonia

The incidence rate of repeat episodes severe and non-severe clinical pneumonia in vitamin D group was 1.18 per child year (95% CI: 1.12 – 1.23) compared to 1.11 per child year (95% CI: 1.05 – 1.16) in the placebo group. The incidence rate ratio was 1.06 (95% CI: 0.99 – 1.14; p=0.07 (Table 22). The incidence rate of repeat severe clinical pneumonia in vitamin D group was 0.03 per child year (95% CI: 0.02 – 0.04) compared to 0.02 per child year (95% CI: 0.01 – 0.03) in placebo group. The incidence rate ratio was 1.30 (95% CI: 0.82 – 2.08; p=0.23). The incidence rate of repeat clinical very severe diseases in vitamin D group was 0.022 per child year (95% CI: 0.016 – 0.031) which was very similar to that in the placebo group 0.023 per child year (95% CI: 0.016 – 0.031). The incidence rate ratio was 0.99 (95% CI: 0.61 – 1.59; p=0.96) (Table 23).

4.9 Per protocol analysis with at least 5 consecutive doses of vitamin D/placebo

None of study children had received all 6 consecutive doses of vitamin D/placebo in the right time. The maximum number of consecutive doses received in the right time was five. Restricting the analysis for this sub group, 64% of the study cohort entered the per protocol analysis under above criteria (1971 children). Of those, 50.2% was from vitamin D group and 49.8% from placebo group.

The results from this analysis were very similar to that from the analysis restricted to children who received at least 4 consecutive dose of vitamin D/placebo in the right time.

4.9.1 First or only Episode of X-Ray confirmed Pneumonia

The incidence rate of first or only episode of x-ray confirmed all severe and non-severe pneumonia in vitamin D group was 0.14 per child year (95% CI: 0.12 – 0.16), compared to 0.13 per child year (95% CI: 0.11 – 0.15) in the placebo group. The incidence rate ratio was 1.06 (95% CI: 0.85 – 1.31; p=0.61). (Table23). The incidence rate of first or only episode of x-ray confirmed severe pneumonia in vitamin D group was 0.03 per child year (95% CI: 0.02 – 0.04) in vitamin D group versus 0.02 per child year (95% CI: 0.01 – 0.04) in the placebo group. The incidence rate ratio was 1.32 (95% CI: 0.81 – 2.16; p=0.26). The incidence rate of first or only episode of x-ray confirmed very severe diseases including
very severe pneumonia in vitamin D group was 0.005 per child year (95% CI: 0.002 – 0.010) compared to 0.006 per child year (95% CI: 0.003 – 0.011) in the placebo group. The incidence rate ratio was 0.87 (95% CI: 0.31 – 2.39; p= 0.78) (Table 24).

4.9.2 Repeat Episodes of X-Ray Confirmed Pneumonia

The incidence rate of repeat episodes of x-ray confirmed severe and non-severe pneumonia in vitamin D group was 0.07 per child year (95% CI: 0.06 – 0.09) compared to 0.04 per child year (95% CI: 0.03 – 0.05) in the placebo group. The incidence rate ratio was 1.75 (95% CI: 1.26 – 2.39; p <0.001) (Table 24). The incidence rate of repeat x-ray confirmed severe pneumonia in vitamin D group was 0.007 per child year (95% CI: 0.004 – 0.013) compared to 0.002 per child year (95% CI: 0.001 – 0.006) in the placebo group. The incidence rate ratio was 3.31 (95% CI: 0.91 – 12.03; p=0.06) (Table 25).

4.9.3 First or only Episode of clinical Pneumonia

The incidence rate of first or only episode of severe and non-severe clinical pneumonia in vitamin D group was 1.39 per child year (95% CI: 1.29 – 1.49) compared to 1.51 per child year (95% CI: 1.41 – 1.63) in the placebo group. The incidence rate ratio was 0.93 (95% CI: 0.84 – 1.03; p=0.17). The incidence rate of first or only episode of severe clinical pneumonia in vitamin D group was 0.09 per child year (95% CI: 0.08 – 0.11) compared to 0.07 per child year (95% CI: 0.05 – 0.09) in the placebo group. The incidence rate ratio was 1.32 (95% CI: 1.01 – 1.74; p= 0.04). The incidence rate of first or only episode of clinical very severe diseases in vitamin D group was 0.07 per child year (95% CI: 0.05 – 0.08) compared to 0.09 per child year (95% CI: 0.08 – 0.11) in the placebo group. The incidence rate ratio was 0.70 (95% CI: 0.54 – 0.93; p=0.01) (Table 24).

4.9.4 Repeat Episodes of Clinical Pneumonia

The incidence rate of repeat episodes severe and non-severe clinical pneumonia in vitamin D group was 1.17 per child year (95% CI: 1.11 – 1.22) compared to 1.10 per child year (95% CI: 1.05 – 1.16) in the placebo group. The incidence rate ratio was 1.06 (95% CI: 0.99 – 1.13; p=0.10) (Table 24). The incidence rate of repeat severe clinical pneumonia in vitamin D group was 0.03 per child year (95% CI: 0.02 – 0.04) compared to 0.02 per child year (95% CI: 0.01 – 0.03) in placebo group. The incidence rate ratio was 1.29 (95% CI: 0.80 – 2.10; p=0.29). The incidence rate of repeat clinical very severe diseases in vitamin D
group was 0.023 per child year (95% CI: 0.016 – 0.032) which was very similar to that in
the placebo group 0.024 per child year (95% CI: 0.016 – 0.032). The incidence rate ratio
was 0.99 (95% CI: 0.61 – 1.61; p=0.98) (Table 25).

4.10 Effect of risk factors on the incidence of pneumonia

The univariate analysis showed a statistically significant association of first or only episode
of x-ray confirmed severe and non-severe pneumonia with child’s age, indoor air pollution,
family crowding, and father’s education (Table 26). After adjusting for all risk factors,
child’s age and indoor air pollution were strongly associated with first or only episode of x-
ray confirmed severe and non-severe pneumonia. The incidence of pneumonia was higher
in 6-12 month old infants compared to that in infants <2 months of age (RR=1.73; 95% CI:
1.04 – 2.89; p=0.04). The incidence rate ratio of pneumonia in children exposed to high
indoor air pollution was lower compared to children exposed to low indoor air pollution
(RR=0.80; 95% CI: 0.62 – 1.04, p=0.003) (Table 26).

The univariate analysis showed that child’s age, economic status, indoor air pollution,
nutritional status, mother’s any formal education, father’s any formal education and vitamin
D were potential risk factors for the incidence of repeat episodes of x-ray confirmed severe
and non-severe pneumonia (Table 27). However in the multivariate analysis after adjusting
for the effects of covariates, only father’s education, vitamin D and indoor pollution were
associated with the risk of repeat episodes of pneumonia. The incidence rate ratio in
children exposed to high indoor air pollution was lower compared to those children who
had low exposure to air pollution (RR=0.69; 95% CI: 0.49 – 0.97, p=0.001). The incidence
rate ratio for children whose fathers did not have any formal education was higher
(RR=1.68; 95% CI: 1.21 – 2.32, p=0.002) compared to children whose fathers had some
formal education. Surprisingly, vitamin D was found to be a significant risk factor for the
incidence of repeat all x-ray confirmed pneumonia. The incidence rate ratio of repeat
episodes of pneumonia in children who got vitamin D was 1.93(95% CI: 1.40 – 2.65,
p<0.001) compared to children in the placebo group (Table 27).

Indoor air pollution, family crowding and father’s education showed significant association
with the incidence rate of first or only episode of x-ray confirmed severe pneumonia. After
adjusting for other factors, low indoor air pollution was highly associated with incidence rate of first or only episode of x-ray confirmed severe pneumonia. The risk of first episode x-ray confirmed severe pneumonia was almost 65% lower in high pollution group (RR=0.37, 95% CI: 0.18 – 0.73, p=0.002) compared to that in low pollution group (Table 28).

Univariate analysis revealed a statistically significant association between father’s education and the risk of first or only episode of x-ray confirmed very severe diseases, however, this association was not significant when adjusted for the effect of the other risk factors (Table 30).

4.11 Episodes of Bronchiolitis

The overall incidence of bronchiolitis (definition given in box 1) in this study was 0.10 per child year (95%CI: 0.09 – 0.12). The incidence in vitamin D group was 0.116 per child year (95%CI: 0.095 – 0.114) and in the placebo group was 0.089 per child year (95%CI: 0.071 – 0.112). The incidence rate ratio was 1.28 (95% CI: 0.95 – 1.72, p=0.11) (Table 32).

The incidence of bronchiolitis was highest in the winter followed by spring, summer and autumn seasons respectively. The incidence was higher in vitamin D group for all seasons, except the summer, but these differences are not statistically significant (Figure 16).

4.12 Effect of vitamin D supplementation on serum vitamin D level

Of 668 blood samples drawn and sent for testing, 637 samples (334 from vitamin D and 303 from placebo groups) were tested. The quantity of blood in the remaining samples was not enough for processing. Almost 90% of children in vitamin D group tested had a high level of serum vitamin D (50-250nmol/L) one week after the first dose of vitamin D administration (Table 33). Among these, one child got a very high level of serum 25(OH)D more than 250nmol/L.
Seventy one percent of children in Vitamin D group tested had a serum 25(OH) D level (50-250nmol/L) 2 months after administration of the first dose compared to only 17% of children in the placebo group with such a level. Ninety three percent of children in Vitamin D group tested had a serum 25(OH) D level 50-250nmol/L 2 weeks after administration of the third dose compared to only 53% of children in the placebo group with such a level (Table 33).

The proportion of children having serum 25(OH) D levels 50-250nmol/L decreased to 42% three months after the administration of the first dose of vitamin D and to 51% four months after the administration of the 6th dose of vitamin D. However only 23% of children in the placebo group had serum 25(OH) D levels 50-250nmol/L three months after administration of the first dose (table 33). The mean level of serum 25(OH) D three months after the first dose was 55.5 nmol/L in vitamin D group compared to that in the placebo group which was 39.6 nmol/L (Table 34).

Over all, children in Vitamin D group got a higher serum concentration of 25(OH) D compared to that in the placebo group, particularly immediately after receiving vitamin D supplements. Number of children with severe and moderate vitamin D deficiency was higher in placebo group compared to that in vitamin D group. Of 303 children in control group, 17.5 % had severe vitamin D deficiency (25(OH) D <20nmol/L), 49.8% had vitamin D insufficiency (25(OH) D 20-<50 nmol/L), and 32.3% had a normal level of vitamin D (25(OH) D ≥50nmol/L). Only 2 out of 334 children in vitamin D group (0.6%) had a very high serum 25(OH) D (>250nmol/L) considered undesirable.

Figrue 17 shows the mean level of serum 25(OH) D in different seasons in a sample of study children. Almost in all seasons the mean serum 25(OH) D level was higher in vitamin D group compared to that in placebo group. The placebo group had the lowest serum 25(OH) D levels during the winter followed by autumn season. Interestingly, the mean level of 25(OH) D was not that different in summer between the two groups (Figure 17).
CHAPTER 5: DISCUSSION

5.1 Primary and secondary end points

Despite some previous evidence of an association between low serum vitamin D level and pneumonia in children, this study found no effect of vitamin D on decreasing incidence of first or only episode of x-ray confirmed severe and non-severe pneumonia (RR=1.06, 95% CI : 0.89 – 1.27, p= 0.47). Surprisingly, the incidence rate of repeat x-ray confirmed severe and non-severe pneumonia was higher in the vitamin D group compared to that in placebo group (RR=1.68, 95% CI: 1.28 – 2.21; p <0.001). Similarly, the incidence rate of all x-ray confirmed severe and non-severe pneumonia was also higher in the vitamin D group compared to that in the placebo group (RR=1.22, 95% CI: 1.05 – 1.41; p=0.008). These results from intention to treat analysis are consistent with those in all 3 types of per protocol analysis. These findings are at odds to the observations in two case-control studies in India and Ethiopia, where children with low vitamin D level had higher rate of pneumonia compared to those with normal level of vitamin D(14), (15). However, lower sample sizes, difference in study design, and role of other possible confounder factors in those two case-control studies could be the possible reasons for the inconsistency between the previous case control studies and our randomized controlled trial.

The incidence rates of repeat episodes of both x-ray confirmed or unconfirmed severe and non-severe clinical pneumonia in vitamin D group were higher compared to that in the placebo group in intention to treat analysis. However, in the per protocol analyses of those who received at least 4 or 5 consecutive doses of the drug in the right time, the higher risk of repeat clinical pneumonia in the vitamin D group was not statistically significant. Nonetheless, the finding in intention to treat analysis is in contrary to results of a study of vitamin D supplementation along with antibiotics for children admitted with pneumonia in a hospital in Kabul. In that hospital based randomized controlled trial, vitamin D significantly reduced the incidence rate of repeat episodes of clinical pneumonia in children in the vitamin D group compared to the placebo group (RR= 0.78; 95% CI: 0.64 – 0.94, p=0.01) (87). However, the sample size in that study was much lower(456 children) and blood samples were not collected to check if the intervention group really had a higher serum vitamin D level and whether the effect was due to vitamin D. Nevertheless, the
higher incidence of repeat episodes of pneumonia, and as a result, the incidence of all x-ray confirmed severe and non-severe pneumonia in the vitamin D supplemented group does not seem plausible given that repeat episodes of pneumonia were reduced by vitamin D supplementation to children with pneumonia in a population with similar socio-biological characteristics. It is important to consider whether regular vitamin D supplementation reduced immunity and thereby increased incidence of pneumonia. However, since the incidence of first episode pneumonia did not differ between the vitamin D and placebo groups in this trial, higher rates of repeat pneumonia could not be explained by this phenomenon. Moreover, the mean number of days to repeat episodes of pneumonia after the latest vitamin D/placebo dose was similar between the two groups, which is inconsistent with the notion that a high level of vitamin D increased the risk of repeat episodes of pneumonia in the supplemented group (Table 14).

Among the study children only 13% (395 children) had only one episode of pneumonia and 5% (155 children) had ≥2 episodes of pneumonia while the remaining 82% of children had no episodes of pneumonia at all. The first or repeat episodes of pneumonia do not seem to be due to clustering, or being developed by a specific group of children. In line with main risk factors for repeat episode of pneumonia, child’s age (older age at enrollment) and vitamin D exposure were the main predictors for children with multiple episodes of x-ray confirmed pneumonia. Exposure to vitamin D as a risk factor for repeat episodes of pneumonia needs more investigation for a plausible explanation. Additionally, exposure to high pollution was a protective predictor for children with multiple episodes of x-ray confirmed pneumonia, which was found in the analysis of risk factors for pneumonia as well. Using heating devices with proper chimneys (Figure 18) during the winter producing good heating with minimal smoke could be the most plausible explanation for this finding. Though it shows we did not use an appropriate tool to measure indoor air pollution in this study, this finding is of more value in Afghanistan context, where people cannot afford expensive heating devices or central heating system which costs much more.

Due to the lack of repetitive records of cases with possible chronic cough (cough for more than 30 days), data for chronic lower respiratory infections, particularly pulmonary tuberculosis, could not be presented, which could have been an interesting finding, or might have changed definition of our repeat episodes of pneumonia.
Residual confounders, particularly, outdoor air pollution common in Kabul city, might affect study's outcomes. However all other risk factors of pneumonia were evenly distributed between two arms and the study had a large sample size. Thus the effect of residual confounders is unlikely to be the reason for this unexpected finding.

The compliance rate was satisfactory and loss to follow up due to migration, refusal or death was not remarkable to affect study’s power. The study outcomes were measured by experienced pediatricians, and the primary end point was confirmed by experienced radiologists using WHO standards for defining pneumonia. Despite adhering to WHO protocol for defining X-ray confirmed pneumonia used in vaccine trials, it could be debated whether our definition is specific enough to ascertain pneumonia, particularly because detecting childhood pneumonia is not easy by chest radiographs in the early stages of the disease. Misclassification of pneumonia by radiographs cannot be ruled out. However since the radiologists who read the X-rays were blind to the study groups, therefore, any misclassification is likely to be distributed equally between the two groups. If this type of misclassification had occurred, the power of our study would have reduced. Nevertheless since the incidence rate of first episode of pneumonia using any definition is so similar between the two groups, any reduction in the power of the study would have no influence on our conclusion.

The estimates of serum 25 (OH) D in a random sample of children showed that vitamin D supplementation had indeed raised the level of serum 25(OH) D in intervention group after first and third doses. Therefore, lack of protection against pneumonia is not likely to be due to insufficient supplementation or misclassification of exposure status. Because the trial had a large cohort, and both families and study team were blind on exposure status of study subjects, misclassification of any other causes of raised respiratory rate, such as bronchiolitis, as well as, under/over reporting of outcome would be evenly distributed between the two arms.

The incidence rate of first or only episode of x-ray confirmed severe and non-severe pneumonia in placebo group (IR=0.137 per child year, 95% CI: 0.121 – 0.155) was much higher than that of among 6-51 weeks Gambian children (IR=0.04 per child-year, 95% CI:
The incidence rate of first or only episode of clinical severe and non-severe pneumonia in the placebo group (1.46 (95% CI: 1.37 – 1.55)) was also higher than the incidence of all clinical pneumonia among unvaccinated Gambian children in Gambian pneumococcal vaccine trial (IR=0.287 per child-year, 95% CI: 0.277 – 0.298), compared to children 2-35 months in Himalayan parts of Pakistan where the annual incidence rate of all clinical pneumonia was 0.30 per child-years, and in comparison to overall incidence of pneumonia among under-5 children in south-east Asia (IR=0.36 per child-year) (35), (1), (8). Environmental pollution might be a possible reason why children in Kabul had a higher incidence of pneumonia compared to all other settings.

Using different time periods to define repeat episodes of x-ray confirmed and clinical pneumonia did not affect the results. Both 15 days and 30 days gap between episodes to define an episode of repeat pneumonia produced similar results. The rate ratios for repeat episodes of severe and non-severe x-ray confirmed and clinical pneumonia were almost the same in both scenarios.

The incidence of x-ray confirmed pneumonia was highest during the winter followed by spring season (Figure 9). Though vitamin D deficiency was also high during the winter, the serum vitamin D level was higher in intervention group compared to the placebo group during the spring (Figure 17). Overall, children in placebo group had a desirable serum vitamin D level during the spring and summer seasons, compared to that in winter and autumn, which possibly indicates the role of sun light in producing vitamin D. A higher incidence of pneumonia during the winter and spring is also very typical of countries with cold climate such as Afghanistan.

The rate of hospital admissions was not different between vitamin D and placebo groups. Both first and repeat episodes presented similar rates indicating vitamin D does not reduce not only the risk of pneumonia, but also the risk of other hospital admitted cases such as diarrhea, febrile convulsion, urinary tract infection and other illnesses presented earlier.

The incidence rate of bronchiolitis was not different between the two groups, showing that vitamin D does not reduce the risk of viral infections as well; however more evidences and studies are required to confirm this finding. There might be some misclassification of
bronchiolitis as clinical pneumonia; however, given that our study pediatricians were all experienced clinicians, it is less likely that a case with typical wheezing as a good indicator of bronchiolitis could have been classified as clinical pneumonia.

The incidence of bronchiolitis was highest during the winter, followed by spring and summer seasons in both groups (Figure 16). It shows a typical seasonality of cases with wheezing that peaks during the cold seasons.

Analysis of data from this study about effect of vitamin D on the incidence of first or repeat episode of diarrhea also did not find any significant role of vitamin D on decreasing the incidence of diarrhea. The overall incidence rate of diarrhea was 3.62 (95% CI: 3.46 – 3.79) in the vitamin D group and 3.45 (95% CI: 3.30 – 3.61) in the placebo group. The incidence rate ratio was 1.05 (95% CI: 0.99 – 1.12; p=0.13). The analysis was done based on intention to treat and the results for per-protocol analysis were not different from that of intention to treat. Approximately 80% of children admitted to the hospital for different illnesses were discharged in the same day. This could either be due to lower severity of illnesses as a result of proper referral and counseling our field and clinical staff provided during the visits, or because our clinical staff did not keep admitted children for longer period for economic and bed occupation reasons.

Number of children died during the 18 months of the project was 17, of which, 10 were from intervention and 7 from control groups. Three children in vitamin D and 2 children in placebo groups died due to pneumonia-associated reasons. The number of deaths due to pneumonia is much lower than UNICEF best estimation attributing 23% under-5 mortality to pneumonia in Afghanistan and in north western of Pakistan, where the annual pneumonia specific mortality was estimated 14 deaths per 1000 under-5 children(35).

The overall mortality rate in the study cohort was 4.17/1000 child years (4.89/1000 child years in vitamin D and 3.44/1000 child years in placebo groups) and the probability of dying in 18 months was 2.3% (23/1000 children alive at one month of age). The probability of death in 1-11 month old infants was 1.83%.7 Thus mortality rate in 1-11 month old

7 The probability of death was calculated using survival analysis in Stata. For infants 1-11 months old, the analysis was confined to the time children turned one month old till they turned 12 months old.
infants in our cohort is almost 18/1000 children alive at one month of age. The national infant mortality in 2009 was estimated at 121/1000 (4). Typically 50% of infant mortality occurs before 1 month of life (3). Thus the mortality rate nationally would be 60/1000 alive at one month of age. It appears that the mortality rate in our study cohort is much lower than the expected rate nationally (at least 3 times lower). In 2008 Roberts et al (5) estimated the under-5 mortality rate at 0.018 per child year in the study area using a validation method. In this method all deaths in past 60 days were recorded from key informants and the mortality rate for estimated population was calculated in the area. The mortality rate was validated by comparing it with two independent lists of deaths using capture-recapture analysis method. Assuming infant mortality rate accounts for almost 70% of under-5 mortalities, and approximately 50% of infant mortalities are due to neonatal causes, the mortality rate in age group similar to that in our study cohort (infants over one month at baseline) was roughly 0.006 (95% CI: 0.004 – 0.017) per child year. The mortality estimation by Roberts et al took place in the beginning of this trial in the parts constituting almost 60% of our trial area. Therefore, comparison of mortality rate in our control group with that of determined by Roberts et al could give a rough estimation of the impact the implementation process had on lowering mortality rate in the area. This impact could be explained by reasons such as appropriate two-weekly check up at households, proper referral to study hospital, and appropriate treatment and counseling given to families by our pediatricians. The impact of trials on lowering overall mortality rates has been determined in other studies as well. In Tanzania, during a randomized controlled trial about protective efficacy and safety of three anti-malarial regimens for intermittent preventive treatment of malaria in infants, the estimated child mortality rate among study children (8-16 weeks at enrolment) was found to be 75% lower than the expected child mortality based on national estimates. The reduction in placebo group was remarkable, with only 5 out of 32 deaths happened in placebo group in this study. (110). A cluster randomized controlled trial about effect of IMCI on child mortality and nutrition in Bangladesh found that the overall under-5 mortality in intervention and non-intervention groups dropped to 49.3 and 50.0 per 1000 live births respectively during the last 2 years of the trial compared to 70.0 and 65.6 per 1000 live births respectively during the first 2 years of the trial (111). Thus the vast reduction in all cause mortality observed in our study cohort is not surprising given that the study children were provided the best care possible available at the time in Kabul.
5.2 Risk factors of pneumonia

Analysis of risk factor for pneumonia found different results compared to results found in other studies.

Previous studies detected an association between childhood pneumonia and indoor-air pollution, child sex, family crowding, breastfeeding and severe malnutrition (37), (38), (112), (42). Child’s age was a risk factor for first episode of pneumonia, while number of children sleeping in child’s bedroom, malnutrition, child sex, cigarette smoke, and mother’s education were not significantly associated with pneumonia. Children aged 6-12 months at enrolment had the highest incidence rate ratio of pneumonia (RR=2.01, 95% CI: 1.12 – 3.63) compared to children <6 months of age at enrolment. This finding is at odds to that in a cohort study of children in Pakistan where children 2-5 months had the highest incidence rate ratio compared to reference group aged 24-35 months old (RR=4.33, 95% CI: 3.53 – 5.32) (35). On the other hand, the finding is in line with Gambian pneumococcal vaccine trial where the incidence of x-ray confirmed pneumonia was highest in children aged 12-17 months old (IR=46/1000 child-years, 95% CI: 40 – 54) compared to younger and higher age groups(1). The higher incidence of pneumonia in children higher than 6 months might probably be due to the fact that in Afghanistan children get exposed to environmental risk factors such as outdoor air pollution and extreme cold weather once they start walking and play outdoors.

In this study we did not find child’s sex as a risk factor for pneumonia, while study in Pakistan found that the incidence rate of pneumonia for male children was higher compared to that in females (RR=1.14, 95% CI: 1.01 – 1.29) (35). Surprisingly the incidence of first episodes as well as, repeat episodes of severe and non-severe pneumonia was higher in children with no exposure to high indoor air pollution compared to those exposed to higher indoor air pollution (type of fuel used for heating and the length of time the heating device was on). Children exposed to no indoor air pollution had approximately 50% higher chance of getting first episode x-ray confirmed severe and non-severe pneumonia compared to group exposed to higher pollution. This finding is not in line with findings in previous review of literatures (112) and a study in Nepal, where number of hours per day children spent near fire place was highly associated with risk of acute respiratory infections (38).
The higher rate of pneumonia in children unexposed to indoor air pollution might be either due to information bias, or due to inaccurate measurement of indoor air pollution in this study. It could be possible that a misclassification of indoor air pollution status might have happened as a result of people’s inappropriate reporting of their exposure status or improper recording of families’ exposure by field data collectors. Moreover, the questions and the matrix used for defining and classification of indoor air pollution status might not be specific enough to measure the indoor air pollution status accurately. In other studies, the indoor air pollution have been measured differently, such as hours children spent near fire place (38), time children spent with their mother at cooking place (113). Similarly, the heating device using wood or other solid fuel in our study (Figure18) were designed such that majority of smoke emitted were directed out by a pipe, permitting less/no smoke inside the living room. This could be another reason why using such devices, even using solid fuel, had protective effect for pneumonia probably due to warmth produced inside the rooms children lived and slept. Due to increasing outdoor air pollution in Kabul city as a result of growing number of population, increasing number of second hand cars, inappropriate sanitations system, and too much dust from unpaved streets, the higher incidence of pneumonia could be due to exposure to outdoor air pollution rather than indoor air pollution, which needs further investigation.

Father’s education was found to have a protective effect against the incidence of repeat x-ray confirmed severe and non-severe pneumonia. The role of maternal education on decreasing the risk of infectious diseases in children has been observed in many studies before, but the protective role of father’s education for pneumonia is an interesting observation in this study. It might be due to the fact that men in Afghan context have a dominating role in decision making in various ways. For example their education might play a significant role on determining the early signs of the disease for cases experienced the first episode of the diseases. Similarly, educated fathers could suggest proper indoor measures in the family in order to avoid re-occurrence of disease, such as explaining risk factors of diseases to the rest of family, appropriate warming of the house, and hygienic practices necessary for prevention of microbial diseases. On the other hand, it does not seem plausible that father’s education did not protect children from getting the first episode of disease.
Unexpectedly, children who got vitamin D had higher incidence rate of repeat x-ray confirmed severe and non-severe all pneumonia compared to placebo group. This observation is in contrary to study hypothesis. The matched case control study in Greenland found that high level of vitamin D (>140nmol/L) was associated with the risk of tuberculosis. Firstly, that study was conducted on people aged 8-74 years old, and secondly, the outcome was tuberculosis, which has a different pathophysiology. We did not assess the serum vitamin D levels in the whole study cohort to determine how many children developed high serum vitamin D level after each dose administration. However blood samples from a random sample of children taken at two points showed that only few children developed a very high serum vitamin D level. Furthermore, if high vitamin D level could reduce immunity, it would affect incidence of first episodes of pneumonia as well which was not the case in this study. Although the length of time after a vitamin D dose to produce any immunity effect is not well known, the mean number of days between last dose of vitamin D/placebo and the episodes of repeat pneumonia was also not different between the two groups in this study.

We did not find any association of severe malnutrition with overall x-ray confirmed and non-confirmed severe and non-severe pneumonia. This is inconsistent with findings in a case control study of under-2 year children in some parts of Brazil, where the odds of weight for age z-score<-3 was 4.57 (95% CI: 2.93 – 7.13) higher in pneumonia cases compared to healthy controls (42). One possible reason might be a lower rate of severe malnutrition in our study area and probably in the whole Kabul city as a result of effective interventions against malnutrition in tertiary Pediatric hospitals and local clinics, and free administration of treatment for malnutrition by national and international NGOs for more than a decade. As presented earlier, only 5% in each study group was suffering from severe malnutrition at baseline.

Kabul is a province with an altitude of 1800 m above sea level (104). Previous studies in Pakistan (35)and Colorado (43)found that children living in areas with altitude of more than 1980 m and 2500 m above sea level (respectively) will have a higher risk of developing pneumonia and other respiratory diseases compared to those living in lower altitudes. Though the altitude in Kabul is not higher compared to those cut off points, the incidence of childhood pneumonia is still very high. This indicates that the risk of pneumonia in
others parts of Afghanistan with high altitudes, such as Badakhshan in north-eastern part of the country, might be higher compared to that in Kabul.

5.3 Serum vitamin D levels

The blood test done in a random sample of 303 children in control group showed that 17.5% of children had severe vitamin D deficiency {25(OH) D <8ng/ml}. This finding is different from the findings of a study carried out in similar population in Kabul in 2005 by Manaseki-Holland et al, which showed that 73% of 108 children aged 6-48 months had vitamin D concentration below 8ng/ml (32). Similarly, the study in 2005 found 96.2% of children with vitamin D concentration below 15ng/ml, while our study showed that 50% of children had vitamin D insufficiency {25(OH) D 8-<20ng/ml}. Almost one third of children in control group (32.7%) had a normal level of vitamin D {25(OH) D ≥20ng/ ml}, which suggests a better nutritional status among the study children. This could be partly due to improvement in economic status of families over the 3 year period, or due to the fact that study in 2005 was conducted during a short period in winter season in a smaller sample. Children in intervention group had a higher level of serum vitamin D after administration of vitamin D compared to that in placebo group. This suggests that there was no protocol violation of allocation to respective study groups and also the vitamin D supplementation was effective to raise the serum vitamin D levels. Moreover, a higher serum vitamin D level in intervention group suggests the reliability of syringe contents produced by AKU pharmacy. Any acute or chronic adverse effect associated with vitamin D supplementation was not reported during the study. However, if there was any chronic toxic effect of vitamin D after the study, we were not able to trace them.

In line with previous studies showing that 100,000 IU vitamin D could provide a good protection against vitamin D deficiency without risk of side-effects in infants(99), our study also detected a desirable level of vitamin D among intervention group with no side-effects. Only 0.6% of children in intervention group had a 25OHD level >150ng/ml considered to be high. This suggests that such dosages might increase level of vitamin D to an unexpected levels in few percentages of children with certain social or health background and should be considered in future studies.
5.4 Perceptions of Health care providers

During the life of project we conducted two focused group discussion (FGDs) with pediatricians from two large tertiary pediatric hospitals to explore their ideas about adverse effects of vitamin D after administration of the dose we have been given to our study children. In both FGDs, they thought that only children who receive vitamin D on a daily basis, or more often might develop signs of over dosage. They also commented that from their clinical experience, they have never confronted a case of vitamin D over dosage after 3 consecutive doses of 600,000 IU vitamin D in their patients. They suggested that some children might develop some chronic conditions, such as kidney diseases in long term, which might need further investigation after this study is completed. They thought, it would be a good idea to compare those likely conditions with the level of vitamin D in serum tests carried out in this study to find out if there might be any association.

5.5 Immunological role of vitamin D

The immunological role of vitamin D has been studied previously but needs further investigation. In this study we focused only on association between vitamin D status and incidence of pneumonia in children. We did not explore the exact immunological impact of vitamin D administration through laboratory investigations. Previous studies found that vitamin D has a role on expression of anti microbial cathelicidin by macrophages in response to microbial agents. Additionally, it has been shown that 1, 25(OH) 2D3 is an immune system modulator and promotes the immune responses. The immunological role of vitamin D in response to microbial diseases has not been described in different age groups and we do not know if the physiological mechanisms are similar in adults and children. It is possible that vitamin D might play an import role in enhancing immunity in adults and older children, but less so in infants and young children. It is not clear how long it takes after vitamin D administration to improve the immunological status and body’s immunological responses. We measured the incidence of pneumonia during three months post administration of vitamin D over 18 months in total. Perhaps 3 months might not be long enough to see a substantial impact on children’s immunity and reduction in incidence of microbial diseases. Studies have revealed an association between subclinical vitamin D deficiency and increased risk of tuberculosis in adults (81), (82). Given that tuberculosis is
a chronic illness, one could speculate that vitamin D deficiency might only impact chronic inflammatory processes rather than acute conditions such as pneumonia and diarrhea. Moreover, studies on role of vitamin D on tuberculosis have focused on adults only. As mentioned earlier, the inflammatory processes might not behave same ways between children and adults, and vitamin D might modulate inflammatory processes in adults better and differently than that of children. Further studies of time lag between vitamin D administration and improvement in immune status are needed to evaluate the effect of vitamin D on microbial infections.

It is possible that effectiveness of vitamin D supplementation to reduce the risk of pneumonia might depend on other factors that we do not know yet, such as deficiency of other important vitamins and minerals as a result of poor dietary resources, or people's lack of knowledge on balanced healthy foods for children. Similarly, the sufficient level of serum 25(OH) D necessary for stimulating immunity in response to infections has not been clearly studied.

The study conducted by Manaseki-Holland and colleagues in the same parts of Kabul in 2007 found that a single dose of 100,000 IU vitamin D along with antibiotics in the active phase of infection can reduce the incidence rate of repeat episodes of pneumonia in young children. Methodological differences such as definition of pneumonia and quality assurance procedures might be possible reasons for this inconsistency in the results between the two studies done in the same population. Nevertheless, this could be because production of cathelicidins in vitamin D depleted children is significantly dependent on stimulation of TLR on macrophages and monocytes by bacterial antigens, and the up-regulation of CYP2BI-hydorxylase and VDR necessary for production of cathelicidins could only take place when vitamin D is supplemented in the active phase of the infection rather than supplemented as a preventive measure. On the other hand, vitamin D might enhance the immunity in chronic infections and certain genotypes such as observed in a recent small multi-center randomized controlled trial of vitamin D in adults with sputum smear-positive tuberculosis in London, UK. The study found that vitamin D significantly hastened sputum culture conversion in patients with tt genotypes (81). Another trial in the UK also found that a single dose vitamin D enhanced immunity to mycobacterium tuberculosis (82). Similarly, the link between vitamin D deficiency and risk of TB was detected among
Vietnamese men. Therefore, the trial needs to be repeated in other settings, where people might be genetically different.

Recent findings on role of vitamin D on enhancing immune response to mycobacterium tuberculosis, and its complementary role on successful treatment of TB suggest that further studies are needed to investigate the beneficial effects of vitamin D in the treatment of TB. Afghanistan has a high annual incidence of TB (168/100 000/year) (114) and high to moderate rate of vitamin D deficiency and thus, Afghanistan is an appropriate setting for such studies.

Vitamin D supplementation did not show any effect on reducing incidence of diarrheal diseases as well, which highly contributes to burden of diseases and mortality in under-5 children in Afghanistan. No study has been done on effect of vitamin D on reducing risk of diarrheal diseases in other parts of the world. Since the effect of vitamin D may depend of genetic variations, further studies in different settings may be needed to confirm or refute this observation.

5.6 Dose of vitamin D supplementation

For convenience of implementation and based on previous studies showing that 100,000 IU vitamin D can provide the best protection against vitamin D deficiency without the risk of over dosage, we decided to use 3 monthly supplementation of 100,000 IU vitamin D in this trial. The trial found that 3 monthly supplementation of 100,000 IU vitamin D was a safe intervention, keeping serum 25(OH)D to a sufficient level necessary for protection against vitamin D deficiency and its further consequences such as vitamin D rickets. Although only few cases of clinical rickets were observed in this study (in both vitamin D and placebo groups), children in more economically deprived parts of the country, where vitamin D deficiency might be higher, could benefit from more frequent administration of vitamin D. Only two children developed a toxic level of serum 25(OH) D (>150ng/mL) immediately after 1st and 3rd doses. These children did not show any signs of vitamin D over dosage, but caution should be undertaken while using such a high dose in the future. On the other hand, such high doses could produce long term side effects, which are not yet known and need to be traced in the future.
5.7 Generalisability of the findings

Findings in this study could be inferred to population with similar background characteristics living in similar settings, however, due to possible genetic variations, these findings might not be generalisable to children in different settings, particularly to settings where the risk of vitamin D deficiency and the incidence of pneumonia are lower. Due to lack of surveillance system and proper studies in Afghanistan, it is difficult to clearly understand similarities and differences of socio-economic status among different parts within the country. As a result, it is not appropriate to generalize findings from this study done in few districts in Kabul to the whole population. Afghanistan is a poor country with lack of quality food and proper living conditions, but findings from this study revealed that people in our study areas were not in extreme poverty and only a small proportion of study children were severely malnourished. Therefore, they might not be a good representative of children of same age group living in other parts of the country, where socio-economic deprivation is more prominent. We found that vitamin D administration increased serum vitamin D in intervention group. Therefore, biologically, it may give similar results if we conduct such studies in other parts of the country with the hypothesis that Afghan children are sharing similar genetic properties, while it may not be applicable to children in surrounding countries where their immune system may react differently in response to vitamin D supplementation.

Despite vitamin D did not reduce the incidence of pneumonia; vitamin D supplementation could be a cheap and effective intervention for improving vitamin D status in poor settings like Afghanistan, particularly due to the fact that such countries are deprived of quality food, such as fortified milk and calcium enriched food resources. Our study revealed that 3-monthly vitamin D administration could keep serum vitamin D in a desired level necessary for body’s metabolism. Because normal level of serum vitamin D is a key for proper intestinal absorption of calcium, children in poor countries could benefit if they are provided with three-monthly oral vitamin D supplementation.
5.8 Alternative Interventions for Control of Pneumonia in Children in Afghanistan

The important recommended strategies by WHO for controlling childhood pneumonia are as follow (115):

- Vaccination
- Case management through implementing IMCI
- Improvement of nutritional status
- Control of indoor air pollution

WHO recommends measles, pertussis, Hemophilus Influenza Type b (Hib) conjugate and pneumococcal conjugate vaccines for prevention of childhood pneumonia (115). The first two vaccines have been introduced to routine immunization programs for many decades in most countries, including Afghanistan, while the Hib and pneumococcal conjugate vaccines are newly introduced to some developing countries, due to its high cost. The efficacy of Hib vaccine determined by case-control studies ranged from 20 to 40% against radiologically confirmed pneumonia (115). Similarly, the efficacy of pneumococcal conjugate vaccine against radiologically confirmed pneumonia has been reported 20 - 37% (115). The Global Alliance for Vaccines and Immunization (GAVI) has been supporting eligible countries for introduction of Hib vaccine. In Afghanistan, for the first time, the Hib vaccine was introduced and supported by GAVI in 2009, and now it is part of routine immunization for children in most provinces (116). The pneumococcal conjugate vaccine has not yet been introduced in Afghanistan. Afghan MoPH annual report 2008 shows that DPT3 and measles vaccinations' coverage reached 85 and 75 percent respectively in 2008 (117). The measles vaccination is delivered through routine immunization programs in clinics along with DPT, as well as, through national immunization campaigns launched each year. Although the MoPH has set higher coverage targets for these vaccines, current insecurity in many parts of the country is a major barrier.

The second strategy for controlling pneumonia is implementation of IMCI. IMCI was first introduced in mid 1990s by WHO and UNICEF in order to reduce mortality due to pneumonia, diarrhea, measles, malaria and malnutrition through immunization, counseling and case management components (111). The effectiveness of IMCI in reducing pneumonia and overall mortality is not well known. In a cluster randomized controlled trial in Matlab, Bangladesh in 2007, the effect of IMCI was studied on childhood mortality and nutrition.
The Study randomly assigned 10 clusters into IMCI and 10 clusters into non-IMCI usual-service groups (total population 350 000) and started implementing IMCI in intervention group in Feb 2002. After 3 years, it was found that the overall mortality was reduced in both intervention and non intervention groups. In the final 2 years of the study, the mortality rate (except deaths happened in first week of life) was 13.4% (95% CI: 14.2 – 34.3) lower in IMCI compared to control areas, but the difference was not statistically significant (p=0.030) (111). In Afghanistan IMCI was introduced in 2003 (118) and its facility component has being implemented by NGOs and governmental health facilities in all 34 provinces since 2008. The community based IMCI has currently being implemented in 17 provinces of Afghanistan. In our study, IMCI guidelines were used for the management of sick children and we noticed a substantial reduction in mortality in both intervention and controls groups compared to the previous estimates. However this reduction in mortality could be due to improved access to health services and not necessarily due to implementation if IMCI guidelines.

Although IMCI has been a useful intervention for controlling the childhood morbidity, in our study, we found that only 10% of all clinical cases of pneumonia (using IMCI protocol) were confirmed as pneumonia by chest x-rays (WHO standard protocol for diagnosis of x-ray confirmed pneumonia). It shows that IMCI protocol is not specific enough for diagnosis of true pneumonia; however, we do not know how strictly the IMCI guidelines were applied in diagnosis of pneumonia by our clinicians. If the IMCI has exactly been followed for diagnosis of pneumonia, it could be a concern for community based health programs, where IMCI is used as a tool for detection and treatment of pneumonia. Moreover, it could be a bigger concern because staff working in communities such as community health workers (CHWs), have little medical knowledge compared to pediatricians, which could predispose to an overestimation of pneumonia episodes, and as a result, over prescription of antibiotics which would lead to antibiotic resistance.

The third component for controlling pneumonia is improving nutritional status. Afghan MoPH has reported the prevalence of under-five underweight as 39.3 % in 2004 (117). Moreover, exclusive breastfeeding is reported 40-70% in Afghanistan (117), which is desirable in a country with low literacy and high poverty rates where families cannot afford expensive fortified infant formulas. The quality of food introduced after weaning remains a
challenge which has significant implications on child’s wellbeing during critical first 5 years of life. Enhancing child nutritional status has been challenged by ongoing insecurity and its economic consequences in Afghanistan. As described before, zinc supplementation has shown better protective effects against pneumonia and diarrhea. Therefore, it could be a reasonable intervention for prevention of pneumonia and child mortality in Afghanistan. The Afghan MoPH has included zinc supplementation in its strategy for the treatment of diarrhea (119), but it has not been introduced in all parts of the country yet. UNICEF, Afghanistan provides zinc supplementation for Afghan NGOs only during diarrhea treatment campaigns. Supplementation of zinc for treatment of pneumonia has not been introduced in Afghanistan so far.

Indoor air pollution in the form of burning solid household fuels, as described in literature review section, is a well-known risk factor for pneumonia in children, particularly if used in simple stoves common in some developing countries. As described in GAPP report 2007, usage of efficient wood stoves with chimney can lower the risk of overall pneumonia by 15% in children less than 18 months of age (115). This fact was revealed in our current trial as well, where children exposed to common stove types with proper chimney using solid fuels had lower risk of pneumonia compared to those exposed to other types of heating devices. In Afghanistan, particularly in Kabul, outdoor air pollution poses a more serious challenge for controlling pneumonia. Due to huge number of second-hand cars, a very high number of streets unpaved, and usage of common unsanitary toilets, children in Kabul are at high risk of all respiratory diseases including pneumonia. Though the Afghan government has recently doubled the number of official off days from one to two days per week to reduce environmental pollution due to car traffic, the problem of unsanitary toilets and unpaved streets remains a remarkable challenge, which requires a substantial economic investment by governmental and private sectors.

5.9 Conclusion

The study did not find a protective effect of 3-monthly supplementation of 100,000 IU vitamin D on reducing the incidence of pneumonia in infants and young children in Kabul.
The high incidence of pneumonia in this study indicates that pneumonia is still a main contributor to the burden of children’s morbidity, and needs more effort to improve the quality of health service provision. Improving the quality of health services is important because our study had a significant impact on reducing all-cause child mortality. The marked reduction in mortality is most likely due to the quality of services we provided, such as proper referral, providing quality medicine, using a standard protocol for diagnosis and treatment of the cases, and finally availability of health care provider when a child was sick and the families needed a medical staff to be there. The last point is more important because my personal experience from working in remote areas of Afghanistan shows that health care providers could not be accessed always except the official time they work in a health center. Due to the fact that children’s diseases, particularly pneumonia, develop very quickly, availability of medical staff during the day and night is very crucial for on-time provision of medical care and prevention of severe disease and death.

Although it is not clear how carefully the IMCI tools were applied for diagnosis of pneumonia, only around 10% of pneumonia cases detected clinically were confirmed by chest radiography. Therefore, programs using IMCI for diagnosis of pneumonia, especially in the community level with majority of their staff with insufficient medical training, should be careful with possible overestimation of pneumonia and over prescription of antibiotics and the consequent antibiotic resistance.

Heating devices commonly used in Afghanistan showed a protective effect for pneumonia. This observation should be studied further and if proved to be correct, this heating device could be promoted further inside the country, and probably in other countries with cold climate and lack of resources for provision of central heating.

Three-monthly administration of 100,000 IU vitamin D was shown to be a safe intervention for keeping a desired level of serum vitamin D for protection against vitamin D deficiency and its further health hazards. However, it did not show an effect on reducing the incidence of pneumonia and other acute infectious conditions such as diarrhea or bronchiolitis. Because the level of serum vitamin D required to producing a desirable immunity necessary for reduction of infectious diseases is not well known, further investigations are needed in...
order to determine a better dosage and dosage frequency to produce a desirable immune effect necessary for combating infections.

Findings in this study could be generalized only to a similar setting and to a similar population and not generalisable to settings with different socio demographic and biological characteristics. Due to differences in genetic features among populations of different countries, it might be worth repeating such a study in other parts of the world.
REFERENCES


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FIGURES

Figure 1: Estimates of incidence of clinical pneumonia in different regions of the world by episodes per child-year

![Bar graph showing incidence of clinical pneumonia in different regions of the world.]


Figure 2: Global causes of child deaths, 2008

![Pie chart showing global causes of child deaths.]

Source: Lancet, Vol 375 June 5, 2010 (34)
Figure 3: Trial Profile

Assessed for Eligibility
N= 3060

Lost to follow-up
N= 34
Died n= 3

Lost to follow-up
N= 35
Died n= 6

Lost to follow-up
N= 45
Died n= 1

Lost to follow-up
N= 50
Died n= 0

Lost to follow-up
N= 262
Died n= 0

Protocol violation = 4

Randomized and given Vitamin in the first round
n=1524

Randomized and given placebo in the first round
n= 1522

Randomized and given Vitamin in the second round
n= 1487

Randomized and given placebo in the second round
n= 1494

Randomized and given Vitamin in the third round
n= 1446

Randomized and given placebo in the third round
n= 1452

Randomized and given Vitamin in the fourth round
n= 1400

Randomized and given placebo in the fourth round
n= 1404

Randomized and given Vitamin in the fifth round
n= 1350

Randomized and given placebo in the fifth round
n= 1330

Randomized and given Vitamin in the sixth round
n= 1088

Randomized and given placebo in the sixth round
n= 1077

End of Project
Lost to follow-up
N= 206
Died n= 10 (cumulative)
Present = 1312

End of Project
Lost to follow-up
N= 207
Died n= 7 (cumulative)
Present= 1304

Excluded n= 14
Not meeting inclusion criteria n= 2
Refused to Participate n= 12
Other reasons n= 0

Lost to follow-up
N= 26
Died n= 2

Lost to follow-up
N= 41
Died n= 1

Lost to follow-up
N= 47
Died n= 1

Lost to follow-up
N= 72
Died n= 2

Protocol violation = 2

Lost to follow-up
N= 252
Died n= 1

Lost to follow-up
N= 206
Died n= 10 (cumulative)
Present = 1312

Lost to follow-up
N= 207
Died n= 7 (cumulative)
Present= 1304

Protocol violation = 1

One case was a severely malnourished child and another had received vitamin D high dose within last 3 months

\(\bigstar\) Did not want to be enrolled in the project for the reasons such as did not want to go to Maiwand hospital, did not want the fieldworkers to come to their house and other with no clear reasons.

\(\bigstar\) - The syringe with code number of 2706 was given to the child with study number of 2707
- The syringe with code number of 1070 was given to the child with study number of 1084
- The syringe with code number of 2393 was given to the child with study number of 2939
- The syringe with code number of 2939 was given to the child with study number of 2393

\(\bigstar\) - The syringe with code number of 1418 was given to the child with study number of 1814
- The syringe with code number of 2335 was given to the child with study number of 2235

\(\bigstar\) - The syringe with code number 2215 was given to the child with code number of 2224

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Figure 4: Study Design and Project Timeline for Intervention and Data Collection Points

1. Enrolled infants 1-11 months old (n=3046), whose parents give consent, and meet the inclusion criteria

2. Randomized individually in blocks to either vitamin D or placebo (n=3046)

**Intervention Group**
100,000 IU Vitamin D at enrolment and then quarterly for 18 months (6 doses in total)

**Control Group**
Placebo (olive oil resembling vitamin D) at enrolment and then quarterly for 18 months (6 doses in total)

**Follow up**

1. Active surveillance for incidence of pneumonia (fortnightly house visits for 18 months)

2. Passive Surveillance for incidence of pneumonia based at the study hospital

3. Collected data on additional risk factors of pneumonia in different seasons during follow up period through fortnightly home visits

4. Took Chest x-rays for suspected cases of pneumonia in the study hospital
Figure 5: Timeline for study interventions, and data collection points

Start date: Nov 2007

Fortnightly active surveillance of pneumonia by home visits
End date: May 2009

Daily passive surveillance of pneumonia at the study hospital

Enrolment randomization

Month 0 (Nov-2007)  month 3  month 6  month 9  month 12  month 15  month 18 (May-2009)

4 weeks 4 weeks 4 weeks 4 weeks 4 weeks 4 weeks
Vitamin D/Placebo dose 1 Vitamin D/Placebo dose 2 Vitamin D/Placebo dose 3 Vitamin D/Placebo dose 4 Vitamin D/Placebo dose 5 Vitamin D/Placebo dose 6

Data collection points and tools

**Enrolment**
1. Vitamin D/Placebo Administration
2. Enrolment Forms
3. Consent Form

**Passive surveillance at hospital**
1. Out Patient Form
2. In-patient Form
3. Chest x-ray Form

**Fortnightly active surveillance**
1. Home visit form

**Once during the active surveillance**
1. Breastfeeding and Living Status Form
2. Sun-exposure and indoor air pollution Form
3. Economic and vaccine status form
4. Sun-exposure Form
5. Breastfeeding and indoor air pollution Form
Figure 6: Chest x-rays from study children diagnosed with significant pathology for pneumonia
Figure 7: Chest x-rays from study children, where one of the two readers disagreed to diagnose them as pneumonia, and were confirmed as pneumonia after 3rd reader's opinion.
Figure 8: Children with x-ray confirmed pneumonia episodes in vitamin D and placebo groups (N=3046)

![Bar chart showing the number of pneumonia episodes per child for placebo and vitamin D groups, with Placebo being higher than vitamin D in most categories.]

Figure 9: Incidence of x-ray confirmed pneumonia by season in vitamin D and placebo groups

![Bar chart showing the incidence rate per child year for vitamin D and placebo groups by season, with Winter having the highest incidence for both groups.]

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Figure 10: Proportion of Children without First or Only Episode of X-Ray Confirmed Severe and Non-Severe Pneumonia during 18 Months

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<thead>
<tr>
<th>Time since recruitment (days)</th>
<th>Number at risk (no of episodes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Vitamin D 1485 (94) 1362 (81) 1246 (8) 1217 (11) 1183 (50) 1086 (16) 0</td>
</tr>
<tr>
<td>90</td>
<td>Placebo 1477 (88) 1375 (82) 1252 (14) 1199 (9) 1169 (39) 1099 (13) 0</td>
</tr>
</tbody>
</table>

Figure 11: Proportion of Children without First or Only hospital admission during 18 Months

<table>
<thead>
<tr>
<th>Time since recruitment (days)</th>
<th>Number at risk (no of episodes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Vitamin D 1477 (34) 1438 (31) 1364 (19) 1303 (8) 1270 (32) 1206 (10) 0</td>
</tr>
<tr>
<td>90</td>
<td>Placebo 1484 (31) 1433 (31) 1363 (24) 1316 (18) 1273 (20) 1201 (10) 0</td>
</tr>
</tbody>
</table>
Figure 12: Comparison of first or only episodes of severe and non-severe x-ray confirmed pneumonia in vitamin D and placebo groups

Figure 13: Comparison of repeat episodes of severe and non-severe x-ray confirmed pneumonia in vitamin D and placebo groups
Figure 14: Comparison of first or only episodes of severe and non-severe clinical pneumonia in vitamin D and placebo groups

Figure 15: Comparison of repeat episodes of severe and non-severe clinical pneumonia in vitamin D and placebo groups
Figure 16: Incidence of bronchiolitis by season in vitamin D and placebo groups

Figure 17: Mean serum vitamin D levels (nmol/L) in vitamin D and placebo over study period (Nov 2007 – July 2009) (N=636)
Figure 18: Local heating device (Chari & Bokhari) used during winter in Kabul city
Table 1: Estimates of incidence and number of new cases per year of clinical pneumonia in children aged less than 5 years, by WHO regions

<table>
<thead>
<tr>
<th>Country</th>
<th>Predicted no. of new cases (millions)</th>
<th>Estimated incidence (e/cy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>43.0</td>
<td>0.37</td>
</tr>
<tr>
<td>China</td>
<td>21.1</td>
<td>0.22</td>
</tr>
<tr>
<td>Pakistan</td>
<td>9.8</td>
<td>0.41</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>6.4</td>
<td>0.41</td>
</tr>
<tr>
<td>Nigeria</td>
<td>6.1</td>
<td>0.34</td>
</tr>
<tr>
<td>Indonesia</td>
<td>6.0</td>
<td>0.28</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>3.9</td>
<td>0.35</td>
</tr>
<tr>
<td>Democratic Republic of Congo</td>
<td>3.9</td>
<td>0.39</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>2.9</td>
<td>0.35</td>
</tr>
<tr>
<td>Philippines</td>
<td>2.7</td>
<td>0.27</td>
</tr>
<tr>
<td>Sudan</td>
<td>2.0</td>
<td>0.48</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>2.0</td>
<td>0.45</td>
</tr>
<tr>
<td>United Republic of Tanzania</td>
<td>1.9</td>
<td>0.33</td>
</tr>
<tr>
<td>Myanmar</td>
<td>1.8</td>
<td>0.43</td>
</tr>
<tr>
<td>Brazil</td>
<td>1.8</td>
<td>0.11</td>
</tr>
</tbody>
</table>

e/cy, episodes per child-year.


Table 2: Risk factors related to the host and the environment that affects incidence of childhood pneumonia in the communities in developing countries

**Definite risk factors**
- Malnutrition (weight for age z-score < -2)
- Low birth weight (≤ 2500 g)
- Non-exclusive breastfeeding during the first 4 months of life
- Lack of measles immunization (within the first 12 months of life)
- Indoor air pollution
- Crowding

**Likely risk factors**
- Parental smoking
- Zinc deficiency
- Mother's experience as a caregiver
- Concomitant diseases (e.g. diarrhea, heart disease, asthma)

**Possible risk factors**
- Mother's education
- Day-care attendance
- Rainfall (humidity)
- High altitude (cold air)
- Vitamin A deficiency
- Birth order
- Outdoor air pollution

Table 3: Trials evaluated the role of vitamin D in treatment or prevention of infections

<table>
<thead>
<tr>
<th>Age group</th>
<th>Vitamin D dose</th>
<th>Main end point</th>
<th>Outcome</th>
<th>Reference and study country</th>
</tr>
</thead>
<tbody>
<tr>
<td>453 children 1-36 months old</td>
<td>Single dose of 100,000 IU D3 along with antibiotic treatment for pneumonia</td>
<td>Risk of repeat episodes of pneumonia</td>
<td>Vitamin D significantly reduced the risk of repeat episodes of pneumonia (IMCI criteria) ($P=0.01$)</td>
<td>Manaseki-Holland et al (87), 2010 Kabul, Afghanistan</td>
</tr>
<tr>
<td>146 adults with sputum smear positive TB</td>
<td>100,000 IU D3 on days 7, 14, 28 and 42 along with anti TB treatment</td>
<td>Sputum culture conversion</td>
<td>Vitamin D significantly hastened sputum culture conversion in patients with Tt genotype of the Talq vitamin D receptor polymorphism (HR=8.09, $P=0.02$)</td>
<td>Martineau et al (81), 2011 London, UK</td>
</tr>
<tr>
<td>192 healthy adult TB contacts</td>
<td>Single dose of 100,000 IU D3 followed for 6 weeks</td>
<td>Ability of whole blood count to restrict luminescence, and hence, restrict growth of mycobacterium in vitro</td>
<td>Vitamin D significantly enhanced ability of participants’ whole blood count to restrict BCG-hux luminescence ($P=0.03$)</td>
<td>Martineau et al (82), 2007 London, UK</td>
</tr>
<tr>
<td>365 adults with pulmonary TB</td>
<td>100,000 IU D3 or placebo given at baseline, 5 mo, and 8 months of TB therapy</td>
<td>Sputum conversion rates over time</td>
<td>No difference in sputum conversion, radiographic treatment improvement in vitamin D group versus placebo</td>
<td>Wejse (120), 2009 Guinea-Buissau</td>
</tr>
<tr>
<td>67 adults with smear positive pulmonary TB</td>
<td>10,000 IU/d vitamin D or placebo given for first 6 wk of TB treatment</td>
<td>Sputum smear conversion at 6 wk</td>
<td>23% greater sputum conversion rate at 6 wk in vitamin D group versus placebo ($P = .002$) 22.5% greater rate of radiographic improvement in vitamin D group versus placebo</td>
<td>Nursyam et al (121), 2006 Indonesia</td>
</tr>
</tbody>
</table>
Table 3: Trials evaluated the role of vitamin D in treatment or prevention of bacterial and viral infections (Cont.)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Vitamin D dose</th>
<th>Main end point</th>
<th>Outcome</th>
<th>Reference and study country</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 children (1.5–13 y) with pulmonary and extra-pulmonary TB</td>
<td>1,000 IU/d vitamin D given in combination with standard TB therapy, or TB therapy alone</td>
<td>Clinical improvement in TB-related signs and symptoms</td>
<td>16% higher rate of TB symptom resolution in vitamin D group</td>
<td>Morcos et al (122), 1998 Egypt</td>
</tr>
<tr>
<td>27 children (3–12 y) with ≥6 respiratory or antibiotic requiring illnesses in prior 6 months and 20 children (3–12 y) with ≤1 respiratory or antibiotic-requireing illness in prior 6 months</td>
<td>60,000 IU vitamin D weekly × 6 wk or no supplement in control group</td>
<td>Frequency of respiratory infection in 6 mo after intervention</td>
<td>Difference in infection rates between groups no longer significant in 6 mo after intervention</td>
<td>Rehman (123), 1994 India</td>
</tr>
<tr>
<td>334 school children aged 6-15 years</td>
<td>1200 IU/day D3 for 4 months</td>
<td>Risk of influenza type A infection</td>
<td>Vitamin D significantly reduced the risk of influenza type A infection</td>
<td>Urashima et al (86), 2010 Japan</td>
</tr>
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</table>

Table 4: Total Population in Districts 2, 3 and 8 with Their Categories

<table>
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<tr>
<th>District</th>
<th>Total population</th>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td>D2</td>
<td>80,200</td>
<td>41,600</td>
<td>38,600</td>
</tr>
<tr>
<td>D3</td>
<td>96,900</td>
<td>50,400</td>
<td>46,500</td>
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<tr>
<td>D8</td>
<td>210,300</td>
<td>109,200</td>
<td>101,100</td>
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</table>
Table 5: Study timeline

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<td></td>
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<td>X</td>
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</tbody>
</table>

Table 6: Indoor air-pollution score matrix

<table>
<thead>
<tr>
<th>Length of time each device was used daily</th>
<th>Type of heating device and fuel used</th>
<th>Stove using wood or coal</th>
<th>Stove Using Smashed wood (Bori Ara)/or stove using Diesel</th>
<th>Stove using Gas/or Sandali using wood/cool</th>
<th>Taba Khana /No thing</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-24 hrs</td>
<td></td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>5-14 hrs</td>
<td></td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1-4 hrs</td>
<td></td>
<td>1.5</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>0 hr</td>
<td></td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
</tbody>
</table>

120
Table 7: Baseline socio-demographic characteristics of children, mothers, and fathers

<table>
<thead>
<tr>
<th></th>
<th>Vitamin D (n=1524)</th>
<th>Placebo (n=1522)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>811 (53.2)</td>
<td>780 (51.2)</td>
</tr>
<tr>
<td>Female</td>
<td>713 (46.8)</td>
<td>742 (48.8)</td>
</tr>
<tr>
<td><strong>Age in months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>6 (3.9)</td>
<td>6 (4.9)</td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>6.2 (6.02 - 6.34)</td>
<td>6.2 (6.04 - 6.35)</td>
</tr>
<tr>
<td>&lt; 2 months</td>
<td>132 (8.7)</td>
<td>111 (7.3)</td>
</tr>
<tr>
<td>2 to &lt;6</td>
<td>510 (33.5)</td>
<td>537 (35.3)</td>
</tr>
<tr>
<td>6 to 12</td>
<td>882 (57.8)</td>
<td>874 (57.4)</td>
</tr>
<tr>
<td><strong>Mothers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age in years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>98 (6.4)</td>
<td>111 (7.3)</td>
</tr>
<tr>
<td>20-39</td>
<td>1381 (90.7)</td>
<td>1352 (88.9)</td>
</tr>
<tr>
<td>40+</td>
<td>44 (2.9)</td>
<td>58 (3.8)</td>
</tr>
<tr>
<td><strong>Any formal education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>573 (37.6)</td>
<td>529 (34.8)</td>
</tr>
<tr>
<td>No</td>
<td>951 (62.4)</td>
<td>993 (65.2)</td>
</tr>
<tr>
<td><strong>Level of education in years</strong></td>
<td></td>
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</tr>
<tr>
<td>None</td>
<td>951 (62.4)</td>
<td>993 (65.2)</td>
</tr>
<tr>
<td>1-6</td>
<td>272 (17.8)</td>
<td>256 (16.8)</td>
</tr>
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<td>7-9</td>
<td>140 (9.2)</td>
<td>119 (7.8)</td>
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<tr>
<td>10-12</td>
<td>114 (7.5)</td>
<td>111 (7.3)</td>
</tr>
<tr>
<td>University or college</td>
<td>47 (3.1)</td>
<td>42 (2.8)</td>
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<tr>
<td><strong>Marital status</strong></td>
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<td></td>
</tr>
<tr>
<td>Married, only wife</td>
<td>1469 (96.4)</td>
<td>1477 (97.0)</td>
</tr>
<tr>
<td>Married, more wives</td>
<td>52 (3.4)</td>
<td>42 (2.8)</td>
</tr>
<tr>
<td>Widowed</td>
<td>2 (0.1)</td>
<td>2 (0.1)</td>
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<tr>
<td>Separated</td>
<td>0 (-)</td>
<td>1 (0.07)</td>
</tr>
<tr>
<td>Divorced</td>
<td>1 (0.07)</td>
<td>0 (-)</td>
</tr>
</tbody>
</table>
Table 7: Baseline socio-demographic characteristics of children, mothers and fathers (cont.)

<table>
<thead>
<tr>
<th>Mothers</th>
<th>Vitamin D (N=1524)</th>
<th>Placebo (N=1522)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
</tr>
<tr>
<td>Mother currently working if ever worked*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>50</td>
<td>(47.2)</td>
</tr>
<tr>
<td>No</td>
<td>56</td>
<td>(52.8)</td>
</tr>
<tr>
<td>Fathers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>4</td>
<td>(0.3)</td>
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<tr>
<td>20-39</td>
<td>1185</td>
<td>(77.8)</td>
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<td>40+</td>
<td>335</td>
<td>(21.9)</td>
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<tr>
<td>Missing</td>
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<td>(-)</td>
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<tr>
<td>Any formal education</td>
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<td>Yes</td>
<td>1.085</td>
<td>(71.2)</td>
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<td>(-)</td>
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<tr>
<td>Level of education in years</td>
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<td>(28.8)</td>
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<td>1-6</td>
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<td>(18.3)</td>
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<td>7-9</td>
<td>250</td>
<td>(16.4)</td>
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<tr>
<td>10-12</td>
<td>377</td>
<td>(24.7)</td>
</tr>
<tr>
<td>Semi-formal studies</td>
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<td>(0.6)</td>
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<tr>
<td>University or college</td>
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<td>(11.2)</td>
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<td>Father's ethnicity</td>
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<td>Tajik</td>
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<td>(69.7)</td>
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<td>Pashto</td>
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<td>(23.1)</td>
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<td>Uzbek</td>
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<td>(1.8)</td>
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<td>Hazara</td>
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<td>(4.1)</td>
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<td>Other</td>
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<td>(1.2)</td>
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<tr>
<td>Do not know</td>
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<td>(0.1)</td>
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<td>Fathers currently working</td>
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<td>Yes</td>
<td>1442</td>
<td>(94.6)</td>
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<tr>
<td>No</td>
<td>82</td>
<td>(5.4)</td>
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* Only asked if mother had ever worked
Table 8: Pneumonia risk factors in vitamin D and placebo groups

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Vitamin D (N=1524)</th>
<th>Placebo (N=1522)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Economic status</td>
<td>n</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Better Off</td>
<td>164</td>
<td>10.8</td>
<td>159</td>
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<tr>
<td>Less Poor</td>
<td>262</td>
<td>17.2</td>
<td>266</td>
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<tr>
<td>Poor</td>
<td>226</td>
<td>14.8</td>
<td>247</td>
</tr>
<tr>
<td>Very Poor</td>
<td>226</td>
<td>14.8</td>
<td>227</td>
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<td>Poorest</td>
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<td>16.7</td>
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<td>Malnutrition (weight for age z score)</td>
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<td></td>
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<tr>
<td>z-score ≥ -1</td>
<td>812</td>
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<td>832</td>
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<td>415</td>
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<td>399</td>
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<td>19</td>
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<td>Indoor smokers inside the child’s room</td>
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<tr>
<td>No one</td>
<td>900</td>
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<td>889</td>
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<tr>
<td>1 person</td>
<td>420</td>
<td>27.6</td>
<td>442</td>
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<tr>
<td>2-3 persons</td>
<td>39</td>
<td>2.6</td>
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<tr>
<td>Missing</td>
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<td>10.8</td>
<td>157</td>
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<td>Exposure to number of cigarettes smoked indoor</td>
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<td>1-9 cigarettes</td>
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<td>367</td>
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<td>57</td>
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<td>≥ 20 cigarettes</td>
<td>72</td>
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<td>74</td>
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<td>Missing</td>
<td>165</td>
<td>10.8</td>
<td>157</td>
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<td>People sleeping in child’s bedroom</td>
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<td>≤ 2 people</td>
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<td>238</td>
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<td>3-4 people</td>
<td>508</td>
<td>33.3</td>
<td>519</td>
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<tr>
<td>≥ 5 people</td>
<td>627</td>
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<td>601</td>
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<td>Missing</td>
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<td>164</td>
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Table 8: Pneumonia risk factors in vitamin D and placebo groups (cont.)

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<th>Placebo (N=1522)</th>
<th>P-value</th>
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<td>Yes</td>
<td>1463 96.0</td>
<td>1457 95.7</td>
<td>0.67</td>
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<td>22 1.4</td>
<td>28 1.8</td>
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<td>Missing</td>
<td>39 2.6</td>
<td>37 2.5</td>
<td></td>
</tr>
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<td>Currently breastfed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>894 58.7</td>
<td>902 59.3</td>
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<tr>
<td>No</td>
<td>589 38.6</td>
<td>580 38.1</td>
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<td>Missing</td>
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<td>38 2.5</td>
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</tr>
<tr>
<td>Exposure to indoor air pollution</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Low /No pollution</td>
<td>360 26.5</td>
<td>365 26.8</td>
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<td>Medium Pollution</td>
<td>350 25.7</td>
<td>332 24.3</td>
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<tr>
<td>High Pollution</td>
<td>649 47.8</td>
<td>668 48.9</td>
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<tr>
<td>Number of children from same mother</td>
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<td></td>
<td></td>
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<tr>
<td>≤3</td>
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<td>468 30.7</td>
<td>0.63</td>
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<td>4-7</td>
<td>493 32.3</td>
<td>467 30.7</td>
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<tr>
<td>≥8</td>
<td>85 5.6</td>
<td>93 6.1</td>
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<td>Missing</td>
<td>479 31.4</td>
<td>494 32.5</td>
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<td>Child’s sex</td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>811 53.2</td>
<td>780 51.2</td>
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<tr>
<td>Female</td>
<td>713 46.8</td>
<td>742 48.8</td>
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<tr>
<td>Child’s age in months</td>
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<td></td>
<td></td>
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<tr>
<td>&lt; 2 months</td>
<td>132 8.7</td>
<td>111 7.3</td>
<td>0.28</td>
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<tr>
<td>2 till &lt;6</td>
<td>510 33.5</td>
<td>537 35.3</td>
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<tr>
<td>6 till 12</td>
<td>882 57.8</td>
<td>874 57.4</td>
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<td>Mother’s any formal education</td>
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<td></td>
<td></td>
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<td>Yes</td>
<td>573 37.6</td>
<td>529 34.8</td>
<td>0.10</td>
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<td>951 62.4</td>
<td>993 65.2</td>
<td></td>
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<tr>
<td>Fathers any formal education</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>1085 71.2</td>
<td>1072 70.4</td>
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<tr>
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<td>449 29.5</td>
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<tr>
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<td>1 0.1</td>
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Table 9: Background characteristics of children with number of x-ray confirmed severe and non severe pneumonia episodes

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Categories</th>
<th>No pneumonia (N=2496)</th>
<th>Pneumonia (only one episode) (N=395)</th>
<th>Pneumonia (≥ 2 episodes) (N=155)</th>
<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>&lt; 3 months</td>
<td></td>
<td>434</td>
<td>17.4</td>
<td>60</td>
<td>15.2</td>
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<tr>
<td>Child's age at recruitment in months</td>
<td>3 to &lt;6</td>
<td>670</td>
<td>26.8</td>
<td>85</td>
<td>21.5</td>
</tr>
<tr>
<td></td>
<td>6 to &lt;9</td>
<td>719</td>
<td>28.8</td>
<td>143</td>
<td>36.2</td>
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<tr>
<td></td>
<td>9 to 12</td>
<td>673</td>
<td>27.0</td>
<td>107</td>
<td>27.1</td>
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<tr>
<td>Better Off</td>
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<td>274</td>
<td>11.0</td>
<td>36</td>
<td>9.1</td>
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<td>Less Poor</td>
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<td>433</td>
<td>17.3</td>
<td>74</td>
<td>18.7</td>
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<td>64</td>
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<td>79</td>
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<td>1</td>
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<td>64</td>
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<td>41</td>
<td>10.4</td>
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Table 9: Background characteristics of children with number of x-ray confirmed severe and non severe pneumonia episodes (cont.)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Categories</th>
<th>No pneumonia N=2496</th>
<th>Pneumonia (only one episode) N=395</th>
<th>Pneumonia (≥ 2 episodes) N=155</th>
<th>p-value</th>
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<tbody>
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<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
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<td>26.2</td>
<td>112</td>
<td>28.4</td>
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<tr>
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<td>-3 ≤ z-score &lt;-2</td>
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<td>12.3</td>
<td>45</td>
<td>11.4</td>
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<tr>
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<td>27</td>
<td>6.8</td>
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<td>Missing</td>
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<td>1.5</td>
<td>7</td>
<td>1.8</td>
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<td>Malnutrition</td>
<td>z-score ≥ -1</td>
<td>1370</td>
<td>54.9</td>
<td>204</td>
<td>51.6</td>
</tr>
<tr>
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<td>-2 ≤ z-score &lt;-1</td>
<td>655</td>
<td>26.2</td>
<td>112</td>
<td>28.4</td>
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<td>-3 ≤ z-score &lt;-2</td>
<td>308</td>
<td>12.3</td>
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<td>11.4</td>
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<td>z-score &lt;-3</td>
<td>126</td>
<td>5.1</td>
<td>27</td>
<td>6.8</td>
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<td>Missing</td>
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<td>1.5</td>
<td>7</td>
<td>1.8</td>
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<td>14</td>
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<td>41</td>
<td>10.4</td>
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Table 9: Background characteristics of children with number of x-ray confirmed severe and non severe pneumonia episodes (cont.)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Categories</th>
<th>No pneumonia N=2496</th>
<th>Pneumonia (only one episode) N=395</th>
<th>Pneumonia( ≥ 2 episodes) N=155</th>
<th>p-value</th>
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<tbody>
<tr>
<td></td>
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<td>%</td>
<td>n</td>
<td>%</td>
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<td>203</td>
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<td>0</td>
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Table 10: Predictors of single and multiple episodes of x-ray confirmed severe and non severe pneumonia

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<th>P-value</th>
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<th>P-value</th>
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<td>95% CI</td>
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<td>95% CI</td>
<td>P-value</td>
<td>Adjusted OR</td>
<td>95% CI</td>
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<td>0.03</td>
<td>0.36</td>
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<td>&lt; 3 months</td>
<td>1.0</td>
<td>-</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>3 to &lt;6</td>
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<td>0.7 – 1.9</td>
<td>2.0</td>
<td>0.8 – 5.1</td>
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<td>6 to &lt;9</td>
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<td>0.8 – 2.1</td>
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<td>0.9 – 5.3</td>
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<td></td>
<td>9 to 12</td>
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<td>0.9 – 2.4</td>
<td>3.4</td>
<td>1.4 – 7.9</td>
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<td>1.0</td>
<td>-</td>
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<td>Poor</td>
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<td>0.8 – 1.5</td>
<td>1.2</td>
<td>0.8 – 2.0</td>
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<td>-</td>
<td>1.0</td>
<td>-</td>
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<tr>
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<td>No</td>
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<td>0.8</td>
<td>0.5 – 1.3</td>
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<td>1.0</td>
<td>-</td>
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<td>0.1 – 0.5</td>
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<td>0.3 – 0.8</td>
</tr>
<tr>
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<td>1.0</td>
<td>-</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td>Children from same mother</td>
<td>4-7</td>
<td>1.2</td>
<td>0.8 – 1.9</td>
<td>0.9</td>
<td>0.5 – 1.8</td>
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<tr>
<td></td>
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<td>1.9</td>
<td>1.0 – 3.4</td>
<td>0.8</td>
<td>0.3 – 2.3</td>
</tr>
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<td>Characteristics</td>
<td>Categories</td>
<td>Pneumonia (only one episode)</td>
<td>P-value</td>
<td>Pneumonia (≥ 2 episodes)</td>
<td>P-value</td>
</tr>
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<td>-----------------------------</td>
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<td>---------</td>
<td>-------------------------</td>
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<tr>
<td></td>
<td></td>
<td>Adjusted OR*</td>
<td>95%CI</td>
<td>Adjusted OR</td>
<td>95%CI</td>
</tr>
<tr>
<td>People sleeping in child’s bedroom</td>
<td>≤ 2 people</td>
<td>1.0</td>
<td>-</td>
<td>0.49</td>
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<td>3 -4 people</td>
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<td>0.6</td>
<td>0.3 - 1.3</td>
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<td>0.7</td>
<td>0.4 - 1.3</td>
<td>0.9</td>
<td>0.4 - 2.0</td>
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<td>Father’s any formal education</td>
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<td>-</td>
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<td>No</td>
<td>1.3</td>
<td>0.9 - 1.8</td>
<td>1.1</td>
<td>0.6 - 1.7</td>
</tr>
<tr>
<td>Vitamin D status</td>
<td>Placebo</td>
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<td>-</td>
<td>0.71</td>
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<td></td>
<td>Vitamin D</td>
<td>1.1</td>
<td>0.8 - 1.4</td>
<td>1.7</td>
<td>1.1 - 2.8</td>
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</tbody>
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* Odds Ratio(OR) adjusted for the effect of other variables listed in the table
Table 11: Comparison of first/only episode of severe and non-severe pneumonia in vitamin D and placebo groups (intention to treat analysis)

<table>
<thead>
<tr>
<th>Type of Pneumonia</th>
<th>Vitamin D</th>
<th>Placebo</th>
<th>Incidence rate ratio</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Episode</td>
<td>Person years at risk</td>
<td>Incidence Rate</td>
<td>95% CI</td>
<td>Episode</td>
</tr>
<tr>
<td>x-ray confirmed</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>All Pneumonia</td>
<td>260</td>
<td>1782</td>
<td>0.145</td>
<td>0.129 - 0.164</td>
<td>245</td>
</tr>
<tr>
<td>Simple Pneumonia</td>
<td>230</td>
<td>1812</td>
<td>0.126</td>
<td>0.111 - 0.144</td>
<td>219</td>
</tr>
<tr>
<td>Severe Pneumonia</td>
<td>45</td>
<td>1989</td>
<td>0.022</td>
<td>0.016 - 0.030</td>
<td>40</td>
</tr>
<tr>
<td>Very Severe diseases</td>
<td>13</td>
<td>2021</td>
<td>0.006</td>
<td>0.003 - 0.011</td>
<td>9</td>
</tr>
<tr>
<td>x-ray confirmed</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>All Pneumonia</td>
<td>1023</td>
<td>740</td>
<td>1.38</td>
<td>1.30 - 1.47</td>
<td>1030</td>
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<td>817</td>
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<td>1.16 - 1.31</td>
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<td>1847</td>
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<td>0.074 - 0.101</td>
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<td>1899</td>
<td>0.079</td>
<td>0.067 - 0.093</td>
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Table 12: Comparison of Repeat Episodes of severe and non-severe pneumonia in vitamin D and placebo groups (intention to treat analysis)

<table>
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<tr>
<th>Type of Pneumonia</th>
<th>Vitamin D</th>
<th>Placebo</th>
<th>Incidence Rate ratio</th>
<th>95% CI</th>
<th>P-Value</th>
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<tbody>
<tr>
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<td>Episode</td>
<td>Person years at risk</td>
<td>Incidence</td>
<td>95% CI</td>
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<td></td>
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<td>All Pneumonia</td>
<td>138</td>
<td>2031</td>
<td>0.07</td>
<td>0.06 - 0.08</td>
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<tr>
<td>Simple Pneumonia</td>
<td>96</td>
<td>2031</td>
<td>0.04</td>
<td>0.04 - 0.06</td>
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<td>Severe Pneumonia</td>
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<td>2031</td>
<td>0.004</td>
<td>0.002 - 0.009</td>
<td></td>
</tr>
<tr>
<td>Very Severe diseases</td>
<td>0</td>
<td>2031</td>
<td>0</td>
<td>n/a</td>
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</tr>
<tr>
<td>x-ray confirmed and non-confirmed</td>
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<td>All Pneumonia</td>
<td>2338</td>
<td>2029</td>
<td>1.15</td>
<td>1.11 - 1.19</td>
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<tr>
<td>Simple Pneumonia</td>
<td>1945</td>
<td>2029</td>
<td>0.95</td>
<td>0.91 - 1.00</td>
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<td>Severe Pneumonia</td>
<td>50</td>
<td>2029</td>
<td>0.02</td>
<td>0.01 - 0.03</td>
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<tr>
<td>Very Severe diseases</td>
<td>43</td>
<td>2029</td>
<td>0.02</td>
<td>0.01 - 0.03</td>
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Table 13: Comparison of all episodes of severe and non-severe pneumonia in vitamin D and placebo groups (intention to treat analysis)

<table>
<thead>
<tr>
<th>Type of Pneumonia</th>
<th>Episode</th>
<th>Person years at risk</th>
<th>Incidence Rate</th>
<th>95% CI</th>
<th>Episode</th>
<th>Person years at risk</th>
<th>Incidence Rate</th>
<th>95% CI</th>
<th>Incidence rate ratio</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
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<tbody>
<tr>
<td>x-ray confirmed</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>All Pneumonia</td>
<td>398</td>
<td>2031</td>
<td>0.195</td>
<td>0.177 - 0.216</td>
<td>327</td>
<td>2027</td>
<td>0.161</td>
<td>0.144 - 0.179</td>
<td>1.22</td>
<td>1.05 – 1.41</td>
<td>0.008</td>
</tr>
<tr>
<td>Simple Pneumonia</td>
<td>329</td>
<td>2031</td>
<td>0.162</td>
<td>0.145 - 0.180</td>
<td>270</td>
<td>2027</td>
<td>0.133</td>
<td>0.118 - 0.150</td>
<td>1.22</td>
<td>1.03 – 1.43</td>
<td>0.01</td>
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<tr>
<td>Severe Pneumonia</td>
<td>56</td>
<td>2031</td>
<td>0.027</td>
<td>0.021 - 0.036</td>
<td>48</td>
<td>2027</td>
<td>0.023</td>
<td>0.017 - 0.031</td>
<td>1.17</td>
<td>0.79 – 1.72</td>
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<td>2031</td>
<td>0.006</td>
<td>0.003 - 0.011</td>
<td>9</td>
<td>2027</td>
<td>0.004</td>
<td>0.002 - 0.008</td>
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<td>0.61 – 3.39</td>
<td>0.39</td>
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<td>All Pneumonia</td>
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<td>2029</td>
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<td>1.601 - 1.713</td>
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<td>2025</td>
<td>1.594</td>
<td>1.540 - 1.650</td>
<td>1.04</td>
<td>0.99 – 1.09</td>
<td>0.11</td>
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<tr>
<td>Simple Pneumonia</td>
<td>2957</td>
<td>2029</td>
<td>1.475</td>
<td>1.405 - 1.510</td>
<td>2822</td>
<td>2025</td>
<td>1.393</td>
<td>1.343 - 1.445</td>
<td>1.05</td>
<td>0.99 – 1.10</td>
<td>0.08</td>
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<tr>
<td>Severe Pneumonia</td>
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<td>2029</td>
<td>0.103</td>
<td>0.090 - 0.118</td>
<td>203</td>
<td>2025</td>
<td>0.100</td>
<td>0.087 - 0.115</td>
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<td>0.85 – 1.25</td>
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<tr>
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<td>2029</td>
<td>0.095</td>
<td>0.083 - 0.110</td>
<td>205</td>
<td>2025</td>
<td>0.101</td>
<td>0.088 - 0.116</td>
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<td>0.77 – 1.15</td>
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Table 14: Time to repeat episodes of x-ray confirmed severe and non-severe pneumonia after latest vitamin D/Placebo dose

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<tr>
<th>Time to episode in day</th>
<th>Vitamin D N=81</th>
<th>Placebo N=56</th>
<th>P-value</th>
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<tr>
<td>Mean (95% CI)</td>
<td>63.5 (47.2 – 79.8)</td>
<td>67.1 (44.5 – 89.7)</td>
<td>0.39</td>
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Table 15: Comparison of first/only episode of severe and non-severe pneumonia in vitamin D and placebo groups (intention-to-treat analysis 15 days gap for new episode)

<table>
<thead>
<tr>
<th>Type of Pneumonia</th>
<th>Episode</th>
<th>Person years at risk</th>
<th>Incidence Rate</th>
<th>95% CI</th>
<th>Episode</th>
<th>Person years at risk</th>
<th>Incidence Rate</th>
<th>95% CI</th>
<th>Incidence rate ratio</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>x-ray confirmed</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Pneumonia</td>
<td>260</td>
<td>1782</td>
<td>0.14</td>
<td>0.13 - 0.16</td>
<td>245</td>
<td>1782</td>
<td>0.14</td>
<td>0.12 - 0.15</td>
<td>1.06</td>
<td>0.89 - 1.27</td>
<td>0.48</td>
</tr>
<tr>
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<td>1812</td>
<td>0.13</td>
<td>0.11 - 0.14</td>
<td>219</td>
<td>1814</td>
<td>0.12</td>
<td>0.10 - 0.14</td>
<td>1.05</td>
<td>0.87 - 1.27</td>
<td>0.57</td>
</tr>
<tr>
<td>Severe Pneumonia</td>
<td>45</td>
<td>1989</td>
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<td>0.02 - 0.03</td>
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<td>1990</td>
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<td>0.01 - 0.03</td>
<td>1.13</td>
<td>0.73 - 1.72</td>
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<tr>
<td>Very Severe diseases</td>
<td>13</td>
<td>2021</td>
<td>0.006</td>
<td>0.003 - 0.011</td>
<td>9</td>
<td>2018</td>
<td>0.004</td>
<td>0.002 - 0.008</td>
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<td>0.62 - 3.39</td>
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<tr>
<td>x-ray confirmed &amp; non-confirmed</td>
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</tr>
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<td>All Pneumonia</td>
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<td>740</td>
<td>1.38</td>
<td>1.30 - 1.46</td>
<td>1031</td>
<td>704</td>
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<td>1.38 - 1.55</td>
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<td>0.87 - 1.04</td>
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<td>1.16 - 1.31</td>
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<td>786</td>
<td>1.27</td>
<td>1.19 - 1.35</td>
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<td>0.89 - 1.07</td>
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<td>1854</td>
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<td>0.07 - 0.09</td>
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<td>0.87 - 1.35</td>
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<tr>
<td>Very Severe diseases</td>
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<td>1899</td>
<td>0.08</td>
<td>0.07 - 0.09</td>
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<td>1894</td>
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<td>0.08 - 0.10</td>
<td>0.90</td>
<td>0.72 - 1.12</td>
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</tbody>
</table>
Table 16: Comparison of repeat episodes of severe and non-severe pneumonia in vitamin D and placebo groups (intention-to-treat analysis 15 days gap for new episode)

<table>
<thead>
<tr>
<th>Type of Pneumonia</th>
<th>Vitamin D</th>
<th>Placebo</th>
<th>Incidence rate ratio</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Episode</td>
<td>Person years at risk</td>
<td>Incidence Rate</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>x-ray confirmed</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>All Pneumonia</td>
<td>138</td>
<td>2031</td>
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<td>0.06 - 0.08</td>
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<td>0.04 - 0.06</td>
<td>1.94</td>
</tr>
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<td>0.002 - 0.009</td>
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<tr>
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<td>n/a</td>
<td>n/a</td>
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<td>x-ray confirmed &amp; non-confirmed</td>
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</tr>
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<td>All Pneumonia</td>
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<td>1.18 - 1.28</td>
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<td>2030</td>
<td>1.03</td>
<td>0.99 - 1.07</td>
<td>1.06</td>
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<td>Severe Pneumonia</td>
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<td>2030</td>
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<td>0.02 - 0.03</td>
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<tr>
<td>Very Severe diseases</td>
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<td>0.02 - 0.03</td>
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<td>Died at</td>
<td>Verbal autopsy code</td>
<td>Verbal Autopsy Title</td>
<td>ICD code</td>
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<tr>
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<td>Meningitis</td>
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<td>Prematurely including respiratory diseases)</td>
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<td>VA-01.13 (immediate cause)</td>
<td>Acute lower respiratory infections including pneumonia and acute bronchitis</td>
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<td>Severe malnutrition</td>
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<td>Unspecific causes of death</td>
<td>R99</td>
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<tr>
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<td>VA-01.11</td>
<td>Meningitis</td>
<td>G009</td>
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<td>14 March 2008</td>
<td>Home</td>
<td>VA-01.13 (immediate cause)</td>
<td>Acute lower respiratory infections including pneumonia and acute bronchitis</td>
<td>J189</td>
</tr>
</tbody>
</table>
Table 17: Distribution and causes of deaths according to WHO IDD-10 codes between Vitamin D and Placebo groups (cont.)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Date of death</th>
<th>Died at</th>
<th>Verbal autopsy code</th>
<th>Verbal Autopsy Title</th>
<th>ICD code</th>
<th>ICD Title</th>
<th>Additional problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D</td>
<td>12 April 2008</td>
<td>Home</td>
<td>VA-11.03</td>
<td>Accidental fall</td>
<td></td>
<td></td>
<td>TV fallen over the child</td>
</tr>
<tr>
<td></td>
<td>21 April 2008</td>
<td>Home</td>
<td>VA-04.99</td>
<td>Diseases of circulatory system, unspecified</td>
<td>J99</td>
<td>Other and unspecified disorders of circulatory system</td>
<td>Probably congenital heart diseases</td>
</tr>
<tr>
<td></td>
<td>24 June 2008</td>
<td>Home</td>
<td>VA-12</td>
<td>Misadventure to patient during surgical and medical care</td>
<td></td>
<td></td>
<td>The child was choked by pill</td>
</tr>
<tr>
<td>Placebo</td>
<td>4 Dec 2007</td>
<td>Hospital</td>
<td>VA-01.99</td>
<td>Infectious diseases, unspecified</td>
<td>B99</td>
<td>Other and unspecified infectious diseases</td>
<td>Septic Shock, unknown</td>
</tr>
<tr>
<td></td>
<td>20 Dec 2007</td>
<td>Hospital</td>
<td>VA-01.13</td>
<td>Acute lower respiratory infections including pneumonia and acute bronchitis</td>
<td>J189</td>
<td>Pneumonia, unspecified</td>
<td>Pneumonia and Septicemia</td>
</tr>
<tr>
<td></td>
<td>10 April 2008</td>
<td>Home</td>
<td>VA-02.98</td>
<td>Other specified carcinoma</td>
<td></td>
<td></td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td></td>
<td>3 July 2008</td>
<td>Home</td>
<td>VA-11.03</td>
<td>Accidental fall</td>
<td></td>
<td></td>
<td>TV fallen over the child</td>
</tr>
<tr>
<td></td>
<td>17 Aug 2008</td>
<td>Other hospital</td>
<td>VA-01.13</td>
<td>Acute lower respiratory infections including pneumonia and acute bronchitis</td>
<td>J189</td>
<td>Pneumonia, unspecified</td>
<td>Pneumonia and Septicemia</td>
</tr>
<tr>
<td></td>
<td>6 Sep 2008</td>
<td>Hospital</td>
<td>VA-01.99</td>
<td>Infectious diseases, unspecified</td>
<td>B99</td>
<td>Other and unspecified infectious diseases</td>
<td>Septicemia post operational</td>
</tr>
<tr>
<td></td>
<td>3rd Feb 2009</td>
<td>Home</td>
<td>VA-01.99</td>
<td>Infectious diseases, unspecified</td>
<td>B99</td>
<td>Other and unspecified infectious diseases</td>
<td>Possibility of Bacterial Meningitis</td>
</tr>
</tbody>
</table>
### Table 18: Comparison of hospital admissions in vitamin & placebo groups

<table>
<thead>
<tr>
<th>Hospital Admissions</th>
<th>Vitamin D</th>
<th>Placebo</th>
<th>Incidence rate ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Episode</td>
<td>Person years at risk</td>
<td>Incidence Rate</td>
<td>95% CI</td>
<td>Episode</td>
</tr>
<tr>
<td>First/ only Admission</td>
<td>134</td>
<td>1918</td>
<td>0.07</td>
<td>0.06 - 0.08</td>
<td>134</td>
</tr>
<tr>
<td>Repeat Admissions</td>
<td>42</td>
<td>2030</td>
<td>0.02</td>
<td>0.01 - 0.03</td>
<td>53</td>
</tr>
</tbody>
</table>

### Table 19: Common causes and length of hospital admissions between vitamin D and placebo groups

<table>
<thead>
<tr>
<th>Causes (determined by study clinicians)</th>
<th>Vitamin D n= 1524</th>
<th>Placebo n= 1522</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Severe pneumonia</td>
<td>64</td>
<td>4.2</td>
</tr>
<tr>
<td>Watery diarrhea and Moderate dehydration</td>
<td>22</td>
<td>1.4</td>
</tr>
<tr>
<td>Febrile convulsion</td>
<td>28</td>
<td>1.8</td>
</tr>
<tr>
<td>Asthma</td>
<td>10</td>
<td>0.7</td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>15</td>
<td>1.0</td>
</tr>
<tr>
<td>UTI</td>
<td>17</td>
<td>1.1</td>
</tr>
</tbody>
</table>

**Length of stay at hospital in days**

<table>
<thead>
<tr>
<th>N= 132</th>
<th>N= 146</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (95%CI)</td>
<td>0.7 (0.4 - 1.0)</td>
</tr>
<tr>
<td>Type of Pneumonia</td>
<td>Episode</td>
</tr>
<tr>
<td>------------------</td>
<td>---------</td>
</tr>
<tr>
<td>All Pneumonia</td>
<td>230</td>
</tr>
<tr>
<td>Simple Pneumonia</td>
<td>201</td>
</tr>
<tr>
<td>Severe Pneumonia</td>
<td>44</td>
</tr>
<tr>
<td>Very Severe diseases</td>
<td>12</td>
</tr>
<tr>
<td>All Pneumonia</td>
<td>915</td>
</tr>
<tr>
<td>Simple Pneumonia</td>
<td>902</td>
</tr>
<tr>
<td>Severe Pneumonia</td>
<td>148</td>
</tr>
<tr>
<td>Very Severe diseases</td>
<td>135</td>
</tr>
</tbody>
</table>
Table 21: Comparison of Repeat Episodes of severe and non-severe pneumonia in vitamin D and placebo groups (per-protocol analysis)

<table>
<thead>
<tr>
<th>Type of Pneumonia</th>
<th>Incidence</th>
<th>Person years at risk</th>
<th>Incidence Rate</th>
<th>95% CI</th>
<th>Episode</th>
<th>Person years at risk</th>
<th>Incidence Rate</th>
<th>95% CI</th>
<th>Incidence rate ratio</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vitamin D</td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Episode</td>
<td>Person years at risk</td>
<td>Incidence Rate</td>
<td>95% CI</td>
<td></td>
<td>Episode</td>
<td>Person years at risk</td>
<td>Incidence Rate</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>x-ray confirmed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Pneumonia</td>
<td>125</td>
<td>1828</td>
<td>0.07</td>
<td>0.06 - 0.08</td>
<td>74</td>
<td>1824</td>
<td>0.04</td>
<td>0.03 - 0.05</td>
<td>1.69</td>
<td>1.27 - 2.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Simple Pneumonia</td>
<td>88</td>
<td>1828</td>
<td>0.05</td>
<td>0.04 - 0.06</td>
<td>47</td>
<td>1824</td>
<td>0.03</td>
<td>0.02 - 0.04</td>
<td>1.87</td>
<td>1.31 - 2.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe Pneumonia</td>
<td>10</td>
<td>1828</td>
<td>0.005</td>
<td>0.003 - 0.010</td>
<td>6</td>
<td>1824</td>
<td>0.003</td>
<td>0.001 - 0.007</td>
<td>1.67</td>
<td>0.61 - 4.59</td>
<td>0.31</td>
</tr>
<tr>
<td>Very Severe diseases</td>
<td>0</td>
<td>1828</td>
<td>0</td>
<td>n/a</td>
<td>0</td>
<td>1824</td>
<td>0</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>x-ray confirmed and non-confirmed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Pneumonia</td>
<td>2134</td>
<td>1826</td>
<td>1.17</td>
<td>1.12 - 1.22</td>
<td>1977</td>
<td>1822</td>
<td>1.08</td>
<td>1.04 - 1.13</td>
<td>1.08</td>
<td>1.01 - 1.14</td>
<td>0.02</td>
</tr>
<tr>
<td>Simple Pneumonia</td>
<td>1779</td>
<td>1826</td>
<td>0.97</td>
<td>0.93 - 1.02</td>
<td>1645</td>
<td>1822</td>
<td>0.90</td>
<td>0.86 - 0.94</td>
<td>1.08</td>
<td>1.01 - 1.15</td>
<td>0.02</td>
</tr>
<tr>
<td>Severe Pneumonia</td>
<td>44</td>
<td>1826</td>
<td>0.024</td>
<td>0.017 - 0.032</td>
<td>42</td>
<td>1822</td>
<td>0.023</td>
<td>0.017 - 0.031</td>
<td>1.04</td>
<td>0.68 - 1.59</td>
<td>0.84</td>
</tr>
<tr>
<td>Very Severe diseases</td>
<td>41</td>
<td>1826</td>
<td>0.022</td>
<td>0.016 - 0.030</td>
<td>37</td>
<td>1822</td>
<td>0.020</td>
<td>0.014 - 0.028</td>
<td>1.10</td>
<td>0.71 - 1.72</td>
<td>0.66</td>
</tr>
</tbody>
</table>
Table 22: Comparison of first/only episode of severe and non-severe pneumonia in vitamin D and placebo groups (Per-protocol analysis with at least 4 consecutive doses of vitamin D/placebo)

<table>
<thead>
<tr>
<th>Type of Pneumonia</th>
<th>Vitamin D</th>
<th></th>
<th>Placebo</th>
<th></th>
<th>Incidence Rate ratio</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Episode</td>
<td>Person years at risk</td>
<td>Incidence Rate</td>
<td>95% CI</td>
<td>Episode</td>
<td>Person years at risk</td>
<td>Incidence Rate</td>
</tr>
<tr>
<td>x-ray confirmed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Pneumonia</td>
<td>194</td>
<td>1332</td>
<td>0.14</td>
<td>0.13 - 0.18</td>
<td>172</td>
<td>1322</td>
<td>0.13</td>
</tr>
<tr>
<td>Simple Pneumonia</td>
<td>171</td>
<td>1356</td>
<td>0.13</td>
<td>0.11 - 0.15</td>
<td>152</td>
<td>1349</td>
<td>0.11</td>
</tr>
<tr>
<td>Severe Pneumonia</td>
<td>38</td>
<td>1491</td>
<td>0.025</td>
<td>0.018 - 0.035</td>
<td>29</td>
<td>1479</td>
<td>0.019</td>
</tr>
<tr>
<td>Very Severe diseases</td>
<td>10</td>
<td>1519</td>
<td>0.006</td>
<td>0.003 - 0.122</td>
<td>8</td>
<td>1499</td>
<td>0.005</td>
</tr>
<tr>
<td>x-ray confirmed and non-confirmed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Pneumonia</td>
<td>754</td>
<td>541</td>
<td>1.39</td>
<td>1.29 - 1.49</td>
<td>755</td>
<td>500</td>
<td>1.51</td>
</tr>
<tr>
<td>Simple Pneumonia</td>
<td>746</td>
<td>599</td>
<td>1.24</td>
<td>1.16 - 1.34</td>
<td>722</td>
<td>566</td>
<td>1.27</td>
</tr>
<tr>
<td>Severe Pneumonia</td>
<td>126</td>
<td>1379</td>
<td>0.09</td>
<td>0.08 - 0.11</td>
<td>97</td>
<td>1398</td>
<td>0.07</td>
</tr>
<tr>
<td>Very Severe diseases</td>
<td>101</td>
<td>1438</td>
<td>0.07</td>
<td>0.05 - 0.08</td>
<td>133</td>
<td>1397</td>
<td>0.09</td>
</tr>
</tbody>
</table>
Table 23: Comparison of Repeat Episodes of severe and non-severe pneumonia in vitamin D and placebo groups (Per-protocol analysis with at least 4 consecutive doses of vitamin D/placebo)

<table>
<thead>
<tr>
<th>Type of Pneumonia</th>
<th>Vitamin D</th>
<th>Placebo</th>
<th>Incidence rate ratio</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Episode</td>
<td>Person years at risk</td>
<td>Incidence Rate</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>x-ray confirmed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Pneumonia</td>
<td>110</td>
<td>1526</td>
<td>0.07</td>
<td>0.06 – 0.09</td>
<td></td>
</tr>
<tr>
<td>Simple Pneumonia</td>
<td>75</td>
<td>1526</td>
<td>0.05</td>
<td>0.04 – 0.06</td>
<td></td>
</tr>
<tr>
<td>Severe Pneumonia</td>
<td>10</td>
<td>1526</td>
<td>0.006</td>
<td>0.003 – 0.012</td>
<td></td>
</tr>
<tr>
<td>Very Severe diseases</td>
<td>0</td>
<td>1526</td>
<td>0</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>x-ray confirmed and non-confirmed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Pneumonia</td>
<td>1796</td>
<td>1525</td>
<td>1.18</td>
<td>1.12 – 1.23</td>
<td></td>
</tr>
<tr>
<td>Simple Pneumonia</td>
<td>1502</td>
<td>1525</td>
<td>0.98</td>
<td>0.94 – 1.03</td>
<td></td>
</tr>
<tr>
<td>Severe Pneumonia</td>
<td>41</td>
<td>1525</td>
<td>0.03</td>
<td>0.02 – 0.04</td>
<td></td>
</tr>
<tr>
<td>Very Severe diseases</td>
<td>34</td>
<td>1525</td>
<td>0.022</td>
<td>0.016 – 0.031</td>
<td></td>
</tr>
</tbody>
</table>
Table 24: Comparison of first/only episode of severe and non-severe pneumonia in vitamin D and placebo groups (Per-protocol analysis with at least 5 consecutive doses of vitamin D/placebo)

<table>
<thead>
<tr>
<th>Type of Pneumonia</th>
<th>Vitamin D</th>
<th>Placebo</th>
<th>Incidence Rate ratio</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Episode Person years at risk Incidence Rate 95% CI</td>
<td>Episode Person years at risk Incidence Rate 95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>x-ray confirmed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Pneumonia</td>
<td>176 1253 0.14 0.12 - 0.16</td>
<td>166 1242 0.13 0.11 - 0.15</td>
<td>1.06 0.85 - 1.31 0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple Pneumonia</td>
<td>155 1275 0.12 0.10 - 0.14</td>
<td>146 1264 0.11 0.09 - 0.13</td>
<td>1.06 0.85 - 1.32 0.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe Pneumonia</td>
<td>37 1395 0.03 0.02 - 0.04</td>
<td>28 1394 0.02 0.01 - 0.04</td>
<td>1.32 0.81 - 2.16 0.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Severe diseases</td>
<td>7 1242 0.005 0.002 - 0.010</td>
<td>8 1410 0.006 0.003 - 0.011</td>
<td>0.87 0.31 - 2.39 0.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>x-ray confirmed and non-confirmed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Pneumonia</td>
<td>704 506 1.39 1.29 - 1.49</td>
<td>710 468 1.51 1.41 - 1.63</td>
<td>0.93 0.84 - 1.03 0.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple Pneumonia</td>
<td>696 561 1.24 1.15 - 1.33</td>
<td>677 531 1.27 1.18 - 1.37</td>
<td>0.97 0.88 - 1.08 0.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe Pneumonia</td>
<td>121 1289 0.09 0.08 - 0.11</td>
<td>93 1319 0.07 0.05 - 0.09</td>
<td>1.32 1.01 - 1.74 0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Severe diseases</td>
<td>90 1349 0.07 0.05 - 0.08</td>
<td>124 1314 0.09 0.08 - 0.11</td>
<td>0.70 0.54 - 0.93 0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 25: Comparison of Repeat Episodes of severe and non-severe pneumonia in vitamin D and placebo groups (Per-protocol analysis with at least 5 consecutive doses of vitamin D/placebo)

<table>
<thead>
<tr>
<th>Type of Pneumonia</th>
<th>Person years at risk</th>
<th>Incidence Rate</th>
<th>95% CI</th>
<th>Person years at risk</th>
<th>Incidence Rate</th>
<th>95% CI</th>
<th>Incidence rate ratio</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>x-ray confirmed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Pneumonia</td>
<td>103</td>
<td>1429</td>
<td>0.07</td>
<td>0.06 – 0.09</td>
<td>59</td>
<td>1419</td>
<td>0.04</td>
<td>0.03 – 0.05</td>
<td>1.75</td>
</tr>
<tr>
<td>Simple Pneumonia</td>
<td>70</td>
<td>1429</td>
<td>0.05</td>
<td>0.04 – 0.06</td>
<td>40</td>
<td>1419</td>
<td>0.03</td>
<td>0.02 – 0.04</td>
<td>1.74</td>
</tr>
<tr>
<td>Severe Pneumonia</td>
<td>10</td>
<td>1429</td>
<td>0.007</td>
<td>0.004 – 0.013</td>
<td>3</td>
<td>1419</td>
<td>0.002</td>
<td>0.001 – 0.006</td>
<td>3.31</td>
</tr>
<tr>
<td>Very Severe diseases</td>
<td>0</td>
<td>1429</td>
<td>0</td>
<td>n/a</td>
<td>0</td>
<td>1419</td>
<td>0</td>
<td>n/a</td>
<td>n/a</td>
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<td><strong>x-ray confirmed and non-confirmed</strong></td>
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<td>All Pneumonia</td>
<td>1668</td>
<td>1428</td>
<td>1.17</td>
<td>1.11 – 1.22</td>
<td>1564</td>
<td>1418</td>
<td>1.10</td>
<td>1.05 – 1.16</td>
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<td>1428</td>
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<td>0.93 – 1.03</td>
<td>1318</td>
<td>1418</td>
<td>0.93</td>
<td>0.88 – 0.98</td>
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<tr>
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<td>0.024</td>
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Table 26: Effect of different risk factors on the incidence rate of first or only episode of x-ray confirmed severe and non-severe pneumonia

<table>
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<th>Risk factors</th>
<th>Categories</th>
<th>Cases</th>
<th>Person years at risk</th>
<th>Unadjusted IRR</th>
<th>95% CI</th>
<th>p-value</th>
<th>Adjusted IRR</th>
<th>95% CI</th>
<th>p-value</th>
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<td>Child's age in months</td>
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<td>1.00</td>
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<td>1.38</td>
<td>0.81 - 2.36</td>
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</tr>
<tr>
<td></td>
<td>6 to 12</td>
<td>333</td>
<td>2001</td>
<td>1.54</td>
<td>1.07 - 2.22</td>
<td>1.73</td>
<td>1.04 - 2.89</td>
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</tr>
<tr>
<td>Economic status</td>
<td>better Off</td>
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<td>419</td>
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<td>0.70 - 1.53</td>
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<td>1.04 - 2.89</td>
<td>0.81 - 2.36</td>
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</tr>
<tr>
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<td>84</td>
<td>670</td>
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<td>1.04 - 2.89</td>
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<td>595</td>
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<td>0.95 - 1.93</td>
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<td>1.04 - 2.89</td>
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<td>564</td>
<td>1.38</td>
<td>0.97 - 1.97</td>
<td>1.73</td>
<td>1.04 - 2.89</td>
<td>0.81 - 2.36</td>
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<td>Poorest</td>
<td>99</td>
<td>601</td>
<td>1.45</td>
<td>1.03 - 2.06</td>
<td>1.73</td>
<td>1.04 - 2.89</td>
<td>0.81 - 2.36</td>
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<tr>
<td>Currently breastfed</td>
<td>Yes</td>
<td>298</td>
<td>2082</td>
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<td>0.99</td>
<td>0.83 - 1.19</td>
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<td>0.83 - 1.19</td>
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<td>Low/No Pollution</td>
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<td>827</td>
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<td>0.003</td>
<td>1.00</td>
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<tr>
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<td>medium pollution</td>
<td>81</td>
<td>852</td>
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<td>0.38 - 0.66</td>
<td>0.55</td>
<td>0.39 - 0.77</td>
<td>0.39 - 0.77</td>
<td>0.39</td>
</tr>
<tr>
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<td>217</td>
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<td>0.72</td>
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<tr>
<td>Malnutrition (weight for age z-score)</td>
<td>z-score ≥ -1</td>
<td>254</td>
<td>1947</td>
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<td>0.10</td>
<td>1.00</td>
<td>0.10</td>
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<td>0.10</td>
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<tr>
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<td>-2 ≤ z-score &lt; -1</td>
<td>145</td>
<td>942</td>
<td>1.17</td>
<td>0.96 - 1.44</td>
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<td>0.81 - 1.42</td>
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<td>440</td>
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<td>0.81 - 1.42</td>
<td>1.49</td>
<td>1.05 - 2.12</td>
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<tr>
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<td>z-score &lt; -3</td>
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<td>183</td>
<td>1.49</td>
<td>1.05 - 2.12</td>
<td>1.08</td>
<td>0.81 - 1.42</td>
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10 Incidence rate ratio
Table 26: Effect of different risk factors on the incidence rate of first or only episode of x-ray confirmed severe and non-severe pneumonia (cont.)

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<tr>
<th>Risk factors</th>
<th>Categories</th>
<th>Cases</th>
<th>Person years at risk</th>
<th>Unadjusted IRR</th>
<th>95% CI</th>
<th>p-value</th>
<th>Adjusted IRR</th>
<th>95% CI</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Exposure to indoor cigarette smoke</td>
<td>No Exposure</td>
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<td>2114</td>
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<td>0.59</td>
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<tr>
<td></td>
<td>1-9 cigarettes</td>
<td>132</td>
<td>850</td>
<td>1.15</td>
<td>0.94 – 1.42</td>
<td>0.94</td>
<td>1.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10-19 cigarettes</td>
<td>20</td>
<td>136</td>
<td>1.11</td>
<td>0.70 – 1.75</td>
<td>1.11</td>
<td>1.75</td>
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</tr>
<tr>
<td></td>
<td>≥ 20 cigarettes</td>
<td>24</td>
<td>172</td>
<td>1.05</td>
<td>0.69 – 1.59</td>
<td>1.05</td>
<td>1.59</td>
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<tr>
<td>Children from same mother</td>
<td>≤3</td>
<td>138</td>
<td>1145</td>
<td>1.00</td>
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<td>1.00</td>
<td>0.70</td>
<td>0.36</td>
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<td>4-7</td>
<td>178</td>
<td>1164</td>
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<td>1.01 – 1.58</td>
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<td>1.16 – 2.31</td>
<td>1.35</td>
<td>2.10</td>
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<tr>
<td>People sleeping in child’s bedroom</td>
<td>≤2 people</td>
<td>71</td>
<td>545</td>
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<td>0.54</td>
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<tr>
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<td>3-4 people</td>
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<td>1194</td>
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<td>0.70 – 1.24</td>
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<td>≥ 5 people</td>
<td>234</td>
<td>1477</td>
<td>1.22</td>
<td>0.94 – 1.59</td>
<td>0.88</td>
<td>1.32</td>
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<td>female</td>
<td>230</td>
<td>29</td>
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<td>0.96 – 1.37</td>
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<td>0.25</td>
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<td>No</td>
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<td>982</td>
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<td>1.18 – 1.69</td>
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<td>Person years at risk</td>
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<td>95% CI</td>
<td>p-value</td>
<td>Adjusted IRR</td>
<td>95% CI</td>
<td>p-value</td>
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<tr>
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<td>321</td>
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<td>&lt;0.001</td>
<td>1.00</td>
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<tr>
<td></td>
<td>2 to &lt;6</td>
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<td>1405</td>
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<td>0.43 - 1.56</td>
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<td>6 to 12</td>
<td>160</td>
<td>2332</td>
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<td>0.69 - 2.35</td>
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<tr>
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<td>18</td>
<td>465</td>
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<td>0.14</td>
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<tr>
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<td>759</td>
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<td>0.59 - 2.03</td>
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<tr>
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<tr>
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<td>0.43</td>
<td>0.27 - 0.68</td>
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<td>high pollution</td>
<td>88</td>
<td>1798</td>
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<td>0.69</td>
<td>0.49 - 0.97</td>
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<td>z-score ≥ -1</td>
<td>97</td>
<td>2185</td>
<td>1.00</td>
<td>0.02</td>
<td>1.00</td>
<td>0.19</td>
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<td>1091</td>
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<td>1.03</td>
<td>0.71 - 1.49</td>
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<td>-3 ≤ z-score &lt; -2</td>
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<td>507</td>
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<td>1.01 - 2.93</td>
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Table 27: Effect of different risk factors on the incidence rate of repeat episode of x-ray confirmed severe and non-severe pneumonia (cont.)

<table>
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<th>Risk factors</th>
<th>Categories</th>
<th>Cases</th>
<th>Person years at risk</th>
<th>Unadjusted IRR</th>
<th>95% CI</th>
<th>p-value</th>
<th>Adjusted IRR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
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<td><strong>Exposure to cigarette smoke</strong></td>
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<td></td>
<td></td>
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<td></td>
</tr>
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<td>0.23</td>
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<tr>
<td>1-9 cigarettes</td>
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<td>982</td>
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<td>0.59 - 1.14</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-19 cigarettes</td>
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<td>154</td>
<td>1.33</td>
<td>0.74 - 2.40</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 20 cigarettes</td>
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<td>0.28 - 1.30</td>
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</tr>
<tr>
<td><strong>Children from same mother</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>≤ 3</td>
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<td>0.37</td>
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<td></td>
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<tr>
<td>4-7</td>
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<td>1340</td>
<td>1.22</td>
<td>0.88 - 1.69</td>
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<td>≥ 8</td>
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<td>254</td>
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<td>0.80 - 2.34</td>
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Table 28: Effect of different risk factors on the incidence rate of first or only episode of x-ray confirmed severe pneumonia

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<tr>
<th>Risk factors</th>
<th>Categories</th>
<th>Cases</th>
<th>Person years at risk</th>
<th>Unadjusted IRR</th>
<th>95% CI</th>
<th>p-value</th>
<th>Adjusted IRR</th>
<th>95% CI</th>
<th>p-value</th>
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<td>0.26</td>
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<td>less Poor</td>
<td>9</td>
<td>749</td>
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<td>0.18 - 0.73</td>
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<td>0.14 - 0.60</td>
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<td>0.07 - 0.61</td>
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<td>0.18 - 0.73</td>
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<td>-3 ≤ z-score &lt;-2</td>
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<td>z-score &lt;-3</td>
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<td>1-9 cigarettes</td>
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<td>960</td>
<td>1.01</td>
<td>0.60 - 1.71</td>
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<td>0.97 - 4.35</td>
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Table 28: Effect of different risk factors on the incidence rate of first or only episode of x-ray confirmed severe pneumonia (cont.)

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<tr>
<th>Risk factors</th>
<th>Categories</th>
<th>Cases</th>
<th>Person years at risk</th>
<th>Unadjusted IRR</th>
<th>95% CI</th>
<th>p-value</th>
<th>Adjusted IRR</th>
<th>95% CI</th>
<th>p-value</th>
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<td>1.06-3.24</td>
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<td>≥8</td>
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<td>0.80-4.55</td>
<td>0.85</td>
<td>0.20-3.49</td>
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<tr>
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<td>0.01</td>
<td>1.00</td>
<td>0.96</td>
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<td>3 -4 people</td>
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<td>34</td>
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</table>
Table 29: Effect of different risk factors on the incidence rate of first or only episode of x-ray confirmed simple pneumonia

<table>
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<tr>
<th>Risk factors</th>
<th>Categories</th>
<th>Case</th>
<th>Person years at risk</th>
<th>Unadjusted IRR</th>
<th>95% CI</th>
<th>p-value</th>
<th>Adjusted IRR</th>
<th>95% CI</th>
<th>p-value</th>
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<td>0.79 – 2.48</td>
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<td>1.21 – 3.57</td>
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<td>2.09</td>
<td>1.21 – 3.57</td>
<td>1.21 – 3.57</td>
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</table>
Table 29: Effect of different risk factors on the incidence rate of first or only episode of x-ray confirmed simple pneumonia (cont.)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Categories</th>
<th>Case</th>
<th>Person years at risk</th>
<th>Unadjusted IRR</th>
<th>95% CI</th>
<th>p-value</th>
<th>Adjusted IRR</th>
<th>95% CI</th>
<th>p-value</th>
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<tbody>
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<td>0.56-1.44</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Children from same mother</td>
<td>≤3</td>
<td>125</td>
<td>1161</td>
<td>1.00</td>
<td></td>
<td>0.02</td>
<td>1.00</td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>4-7</td>
<td>156</td>
<td>1193</td>
<td>1.21</td>
<td>0.96-1.53</td>
<td>1.10</td>
<td>0.86-1.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥8</td>
<td>39</td>
<td>220</td>
<td>1.65</td>
<td>1.15-2.37</td>
<td>1.52</td>
<td>1.05-2.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>People sleeping in child’s bedroom</td>
<td>≤ 2 people</td>
<td>64</td>
<td>551</td>
<td>1.00</td>
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<td></td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>3-4 people</td>
<td>131</td>
<td>1209</td>
<td>0.93</td>
<td>0.69-1.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 5 people</td>
<td>204</td>
<td>1512</td>
<td>1.16</td>
<td>0.88-1.54</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Child sex</td>
<td>Male</td>
<td>243</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>female</td>
<td>206</td>
<td>30</td>
<td>1.15</td>
<td>0.96-1.39</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mother’s any formal education</td>
<td>Yes</td>
<td>147</td>
<td>1334</td>
<td>1.00</td>
<td></td>
<td>0.07</td>
<td>1.00</td>
<td></td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>302</td>
<td>2293</td>
<td>1.19</td>
<td>0.97-1.45</td>
<td>1.09</td>
<td>0.84-1.43</td>
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</tr>
<tr>
<td>Father’s any formal education</td>
<td>Yes</td>
<td>291</td>
<td>2619</td>
<td>1.00</td>
<td>&lt;0.001</td>
<td></td>
<td>1.00</td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>158</td>
<td>1008</td>
<td>1.39</td>
<td>1.15-1.69</td>
<td>1.17</td>
<td>0.91-1.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D status</td>
<td>placebo</td>
<td>219</td>
<td>1814</td>
<td>1.00</td>
<td></td>
<td>0.56</td>
<td>1.00</td>
<td></td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>Vitamin D</td>
<td>230</td>
<td>1812</td>
<td>1.05</td>
<td>0.88-1.27</td>
<td>1.09</td>
<td>0.86-1.37</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

151
Table 30: Effect of different risk factors on the incidence rate of first or only episode of x-ray confirmed very severe diseases

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Categories</th>
<th>Cases</th>
<th>Person years at risk</th>
<th>Unadjusted IRR</th>
<th>95% CI</th>
<th>p-value</th>
<th>Adjusted IRR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child’s age in months</td>
<td>&lt; 2 months</td>
<td>4</td>
<td>319</td>
<td>1.00</td>
<td></td>
<td>0.30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 to &lt;6)</td>
<td>7</td>
<td>1397</td>
<td>0.40</td>
<td>0.11 – 1.37</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 to 12</td>
<td>11</td>
<td>2324</td>
<td>0.37</td>
<td>0.12 – 1.18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Economic status</td>
<td>better Off</td>
<td>2</td>
<td>462</td>
<td>1.00</td>
<td></td>
<td>0.75</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>less Poor</td>
<td>4</td>
<td>754</td>
<td>1.22</td>
<td>0.22 – 6.69</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>poor</td>
<td>2</td>
<td>684</td>
<td>0.68</td>
<td>0.09 – 4.83</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>very poor</td>
<td>5</td>
<td>649</td>
<td>1.78</td>
<td>0.34 – 9.20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poorest</td>
<td>5</td>
<td>701</td>
<td>1.65</td>
<td>0.32 – 8.50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently breastfed</td>
<td>Yes</td>
<td>10</td>
<td>2361</td>
<td>1.00</td>
<td></td>
<td>0.19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>12</td>
<td>1652</td>
<td>1.73</td>
<td>0.75 – 4.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indoor air pollution status</td>
<td>Low/No Pollution</td>
<td>8</td>
<td>990</td>
<td>1.00</td>
<td></td>
<td>0.17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>medium pollution</td>
<td>2</td>
<td>927</td>
<td>0.26</td>
<td>0.05 – 1.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>high pollution</td>
<td>10</td>
<td>1789</td>
<td>0.68</td>
<td>0.27 – 1.74</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malnutrition (weight for age z-score)</td>
<td>z-score ≥ -1</td>
<td>11</td>
<td>2175</td>
<td>1.00</td>
<td></td>
<td>0.63</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-2 ≤ z-score &lt; -1</td>
<td>5</td>
<td>1086</td>
<td>0.91</td>
<td>0.31 – 2.62</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-3 ≤ z-score &lt; 2</td>
<td>5</td>
<td>504</td>
<td>1.96</td>
<td>0.68 – 5.64</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>z-score &lt; -3</td>
<td>1</td>
<td>214</td>
<td>0.92</td>
<td>0.11 – 7.16</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Table 30: Effect of different risk factors on the incidence rate of first or only episode of x-ray confirmed very severe diseases (cont.)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Categories</th>
<th>Cases</th>
<th>Person years at risk</th>
<th>Unadjusted IRR</th>
<th>95% CI</th>
<th>p-value</th>
<th>Adjusted IRR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Exposure</td>
<td></td>
<td>11</td>
<td>2380</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure to indoor cigarette smoke</td>
<td>1-9 cigarettes</td>
<td>7</td>
<td>976</td>
<td>1.54</td>
<td>0.59 - 3.98</td>
<td>0.59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10-19 cigarettes</td>
<td>1</td>
<td>154</td>
<td>1.39</td>
<td>0.17 - 10.78</td>
<td>0.39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 20 cigarettes</td>
<td>1</td>
<td>196</td>
<td>1.10</td>
<td>0.14 - 8.52</td>
<td>0.14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children from same mother</td>
<td>≤3</td>
<td>6</td>
<td>1283</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>4-7</td>
<td>8</td>
<td>1333</td>
<td>1.28</td>
<td>0.44 - 3.71</td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥8</td>
<td>2</td>
<td>251</td>
<td>1.72</td>
<td>0.34 - 8.52</td>
<td>0.24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>People sleeping in child’s bedroom</td>
<td>≤2 people</td>
<td>3</td>
<td>609</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td>3 - 4 people</td>
<td>6</td>
<td>1334</td>
<td>0.91</td>
<td>0.22 - 3.65</td>
<td>0.22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥5 people</td>
<td>11</td>
<td>1695</td>
<td>1.33</td>
<td>0.37 - 4.76</td>
<td>0.37</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child sex</td>
<td>Male</td>
<td>15</td>
<td>47</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>female</td>
<td>7</td>
<td>35</td>
<td>0.57</td>
<td>0.23 - 1.44</td>
<td>0.23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother’s any formal education</td>
<td>Yes</td>
<td>4</td>
<td>1467</td>
<td>1.00</td>
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<td></td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
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<td></td>
<td>No</td>
<td>18</td>
<td>2573</td>
<td>2.57</td>
<td>0.87 - 7.59</td>
<td>0.68</td>
<td></td>
<td></td>
<td>0.20</td>
</tr>
<tr>
<td>Father’s any formal education</td>
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<td>11</td>
<td>2885</td>
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<td></td>
<td></td>
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<tr>
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<td>No</td>
<td>11</td>
<td>1155</td>
<td>2.49</td>
<td>1.08 - 5.76</td>
<td>0.88</td>
<td></td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>Vitamin D status</td>
<td>Placebo</td>
<td>9</td>
<td>2018</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>Vitamin D</td>
<td>13</td>
<td>2021</td>
<td>1.45</td>
<td>0.62 - 3.39</td>
<td>1.47</td>
<td></td>
<td></td>
<td>0.37</td>
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</tbody>
</table>

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Table 31: Level of agreement between two readers for chest x-rays

<table>
<thead>
<tr>
<th>Reader 1</th>
<th>Reader 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pneumonia n (%)</td>
<td>No pneumonia n (%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>763 (85)</td>
<td>62 (2.3)</td>
</tr>
<tr>
<td>No pneumonia</td>
<td>134 (15)</td>
<td>2657 (97.7)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>897 (100)</strong></td>
<td><strong>2719 (100)</strong></td>
</tr>
</tbody>
</table>

Table 32: Comparison of all bronchiolitis episodes in vitamin D and placebo groups (intention to treat analysis)

<table>
<thead>
<tr>
<th>Bronchiolitis</th>
<th>Vitamin D</th>
<th>Placebo</th>
<th>Incidence Rate ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Episode</td>
<td>Person years at risk</td>
<td>Incidence Rate</td>
<td>95% CI</td>
<td>Episode</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>859</td>
<td>0.116</td>
<td>0.095 - 0.141</td>
<td>75</td>
</tr>
</tbody>
</table>
Table 33: Vitamin D level in blood samples of intervention and non-intervention groups after each 3-monthly dose administration

<table>
<thead>
<tr>
<th>Timing of sample to supplementation</th>
<th>Intervention (25 OH)D serum Concentration n (%)</th>
<th>Control (25 OH)D serum Concentration n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;5 ng/ml</td>
<td>5-15 ng/ml</td>
</tr>
<tr>
<td>1st sample</td>
<td>0 (-)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Nov 2007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 week after 1st dose) n=139</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd Sample</td>
<td>0 (-)</td>
<td>10 (15.9)</td>
</tr>
<tr>
<td>Jan 2008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 months after dose 1) n=133</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd sample</td>
<td>1 (1.6)</td>
<td>15 (24.2)</td>
</tr>
<tr>
<td>Feb 2008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months after dose 1 and just before dose 2) n=122</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4th Sample</td>
<td>0 (-)</td>
<td>0 (-)</td>
</tr>
<tr>
<td>May 2008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 weeks after 3rd dose) n=141</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5th Sample</td>
<td>0 (-)</td>
<td>3 (5.5)</td>
</tr>
<tr>
<td>July 2009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 months after 6th dose) n=101</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 34: Vitamin D serum levels measured at different stages in samples of study children

<table>
<thead>
<tr>
<th>Timing of sample to supplementation</th>
<th>Month of sample</th>
<th>Intervention serum 25(OH)D concentrations</th>
<th>Control serum 25(OH)D concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean nmol/L</td>
<td>CI nmol/L</td>
</tr>
<tr>
<td>1 week after first dose (n=140)</td>
<td>Nov (2007)</td>
<td>129.5</td>
<td>(111.1 - 147.9)</td>
</tr>
<tr>
<td>2 months after first dose (n=133)</td>
<td>Jan (2008)</td>
<td>76.3</td>
<td>(64.5 - 88.2)</td>
</tr>
<tr>
<td>3 months after dose 1 and just before dose 2 (n=122)</td>
<td>Feb (2008)</td>
<td>55.5</td>
<td>(46.0 - 65.0)</td>
</tr>
<tr>
<td>2 weeks after 3rd dose (n=141)</td>
<td>May (2008)</td>
<td>104.9</td>
<td>(89.8 - 120.0)</td>
</tr>
<tr>
<td>4 months after dose 6 (n=101)</td>
<td>July (2009)</td>
<td>51.9</td>
<td>(49.0 - 54.9)</td>
</tr>
</tbody>
</table>
ANNEXES

Annex 1: ERB application for Ethics Committee of MoPH, Afghanistan

Introductory Questionnaire

Title of protocol: Double-blind randomised controlled trial investigating the effect of vitamin D supplementation on the incidence of pneumonia

Principle Investigator: Daniel Chandramohan
Department of Infectious and Tropical
London School of Hygiene & Tropical Medicine
0044-2079272322
0044-2075809075
Daniel.chandramohan@ishtm.ac.uk

1. Project involves the use of check all pertinent ones

   a. [] Experimental drugs(s)
   b. [] Radioactive agents
   c. [] Non-therapeutic research
   d. [] Non-approved use or non-approved dose for approved drugs
   e. [] Experimental surgical procedure
   f. [] Fetal research
   g. [] Behavioral research
   h. [] Genetic research
   i. [] Other (please specify):

2. What is the purpose of the study?

Pneumonia is the prime killer of infants in developing countries globally accounting for 19% of the 10.6 million deaths that occur each year. ALRI rates are not available for Kabul or at the national level for Afghanistan. However, under-5 mortality rates are reported as 176-250 and infant mortality as 128-170 per 1000 live births. As with other developing countries, ALRIs are likely to be the leading cause of death and in the winter time one of the main causes of death of young children. Prevalence of acute respiratory infections (for upper and lower respiratory infection rates) for under 5 year old infants in the 2 weeks before a summer survey was reported at 18.5% in Kabul.

Two case-control and other observational studies have linked immunological functions of vitamin D with an increased risk of pneumonia in <5-year olds (adjusted odds ratios: 13.4 and 11.1). In the recent years, numerous other immunological studies have highlighted the important role of vitamin D in regulating and enhancing immune functions during infection.
Vitamin D is commonly deficient in many developing countries with rates ranging from 5-45%, even where abundant sun-shine is available – Afghanistan is one such country with >73% of high-risk <5-year olds below severe deficiency levels (8 ng/dl) in Chindawal area of Kabul (see appendix 1 in protocol document). Therefore, there is a possibility that giving vitamin D in such high risk populations be protective by reducing further cases of pneumonia (or even other infective illnesses). If this proves to be the case it is likely that child deaths due to pneumonia will be reduced.

A single oral dose of 100,000iu (2.5 mg) of vitamin D has been shown to be safe and effective in preventing vitamin D deficiency for a period of 3 months in infants as young as 1 week of age and for under 5 year olds. It is cheap and possible to use routinely during vaccination programmes. This makes the application of this supplementation practical and the use of our intervention sustainable at large scale nationally if proven to be effective.

Study Purpose

With the above considerations, the purpose of our study is as follows:

1. To investigate whether vitamin D supplementation will reduce the incidence of pneumonia in children.

3. To provide recommendations to clinicians and policy makers on the role of vitamin D in improving incidence of young children with pneumonia in Afghanistan, where pneumonia is one of the commonest causes of child death.

4. To provide similar recommendations for international adaptation.

5. Enumerate the objective(s) of the study.

The specific objectives are to investigate the following study questions and then use these for policy making and clinical decision making:

Primary study questions:
Will 3-monthly supplementation of 100,000 IU of oral vitamin D reduce the incidence of pneumonia, among children aged 1 to 11 months living in a socio-economically deprived community of Kabul, Afghanistan?

Secondary questions:
Will 3-monthly supplementation of 100,000 IU of oral vitamin D to children aged 1 to 11 months reduce vitamin D deficiency in the population during the 18 months of follow-up?

Will 3-monthly supplementation of 100,000iu of oral vitamin D to children aged 1 to 11 months reduce the incidence of other infective illnesses during the period of supplementation (including diarrhea)?
6. Description of methods used in protocol.

Overall design

This will be an individually randomised double blind placebo controlled trial, involving 3000 children aged 1 to 11 months (the high risk age group for pneumonia), who will be randomised to receive six doses of either 100,000iu of vitamin D or placebo. Dosing will take place at home, and children will be visited two weekly for 18 months by a team of 45 Fieldworkers, each visiting up to 10 children per day, 6 days per week. Data on illnesses, particularly pneumonia, will be ascertained though the two weekly home visits and from attendances and admissions at the trial clinic in the nearby Maywand Teaching Hospital with paediatric in-patient and out-patient facilities and equipped/trained x-ray department.

Study Hospital and Population Base

The trial will be based in selected residential areas around the Maywand Teaching Hospital. The paediatric hospital that serves this area is the Maywand Teaching Hospital. These are all areas included in a 2006-7 winter vitamin D trial being based at the Maywand Hospital which means that our research team is familiar with the setting and the authorities. Furthermore, all but a few areas have been mapped by Aga Khan Trust for Culture (AKTC) as part of their renovation and development work. We can use this information for clustering and random sampling will be made easier and more cost effective.

The 2005 MOPH/UNICEF survey in Chindawal area of District 1 near the Maywand Hospital suggested a very high level of vitamin D deficiency amongst the under 5 year olds of Chindawal. District 1 is an old part of the city with narrow, shaded lanes, often with roofed tops, between high walled mud houses; the houses have small courtyards with high walls so that for much of the day sunshine does not reach the courtyard. Other areas we will cover share some of these building characteristics too.

Our winter 2006-7 study has confirmed that dietary intake of vitamin D by the child population is poor because fish and liver are hard to get, and breast milk is a poor source of vitamin D (especially when mothers are rarely exposed to the sun due to a low level of outdoor activity and covering of most of the skin). The population is mostly socio-economically deprived with large families and high rates of all illnesses.

The Maywand Teaching Hospital has a teaching unit for paediatrics and through previous collaborations we have established a close working relationship with the paediatric doctors. Since the population involved in the study is already part of the catchment area of the hospital, we will not be adding to the workload of the hospital.

The study being conducted during the winter of 2006-7 (still not concluded in February 2007) with these same populations and hospital involved, has so far progressed with satisfaction and the cooperation of the population and hospital staff. We expect the same level of success in the study being proposed here.
Community sensitization
Community sensitization will be ongoing, but will start at about 6 weeks before the subject recruitment in order to facilitate agreement and cooperation of elders and decision makers of the community. The elders approached will specially include the Vakils of Gozar through the District Rais Nahiya, and the religious leaders in the areas covered.

Recruitment

Area mapping: A complete household mapping of the households exists through the work of Aga Khan Trust for Culture (a collaborating agency). For the areas where this is not available, during the preparation phase a mapping exercise will be conducted.

Recruitment will proceed from randomly chosen streets and continue house to house along each of those streets until 3000 children are recruited; 45 female Fieldworkers, each accompanied by a chaperone to facilitate their entry into households, will recruit an average of 6 children per day over a 4-week period.

Informed consent: At recruitment the Fieldworker will explain to the family the purpose of the study, the benefits offered and the procedures involved. An information sheet with the details of the study objectives, procedures, risk and benefits will also be given to the parents. Informed consent will then be obtained from both the mother and father of the child: finger prints and signature (literacy rate estimated at <50%) will be obtained in the presence of two witnesses, one a friend or family member and one the chaperone accompanying the Fieldworker.

Initial Dosing: After consent the first dose of oil (placebo or vitamin D) will be given from a numbered syringe to the child. The number on the syringe will be recorded as that child’s unique study id number. If a child has diarrhea/vomiting/pneumonia at the time of supplementation, the Fieldworker will return the next week or the week after in order to dose after symptoms have subsided.

A study id card with study information (see sample of this id/information card) will be given to the child with this number on it for future reference by study staff and the recruitment questionnaire will be filled.

Supplementation dosing for children
One dose of 100,000iu of vitamin D (in olive oil base), or placebo (olive oil alone), will be given by the recruiting Fieldworker to each child after consent on the first visit and then quarterly (6 doses during the 18 months).

Randomisation and intervention/placebo packaging: The children will be individually randomized into intervention or placebo group. An independent statistician from the LSHTM will produce the randomization list allocating individual study numbers to vitamin D or placebo within variable blocks of study numbers. The placebo and vitamin D doses will be individually packaged into sealed 1ml syringes at LSHTM and labeled with one of the numbers generated by the central office at LSHTM. After consent, the recruiting Fieldworker will give the oral dose of oil in pre-packed syringes, with the next consecutive number, to the child. The number on the syringe will be the child’s
unique study number and will be recorded for each child. (we have tested this method of dosing successfully during our RCT of this winter at Maywand Hospital.

The placebo and vitamin D syringes will look the same and the taste of the fluid will be the same. Therefore, the families and all project personnel, including clinicians, will be blind to the children’s group allocations. Oil from the syringes will be dropped in the mouth of each child at dosing. During the dosing weeks, Fieldworkers will receive 10 syringes each day with consecutive study numbers to be used that day and checks will be conducted in the evening. Thus Fieldworkers will only ever have 10 single doses in their possession, minimizing the possibility of mis-dosing.

Follow-up for 18 months

Two weekly home visits (active case finding follow-up): For 18 months and two weekly, Fieldworkers will collect information on signs and symptoms of acute respiratory infections and diarrhoea in the last 14 days and current breastfeeding status.

1. After each visit, the Fieldworker will leave a graphic chart with the mother. This is simply to aid the mother’s memory for the next visit and will not act as an illness diary since many mothers will be illiterate. The mother will be asked to mark each picture if the child has one of the illnesses shown during the 2 weeks between Fieldworker visits. We have successfully used these diaries during our RCT in this winter at Maywand Hospital.

2. Every 2 week, Fieldworkers will visit the child’s residence and conduct a verbal recall interview from mother or primary caregiver (usually the mother) about illnesses in the last weeks, diet, sun-exposure and some other factors. They will also be trained to take the child’s temperature, count the respiratory rate twice using a stop watch, examine for sub-costal recession, and refer to the study clinic if appropriate.

3. The families will be given details of the research staff in Maywand Hospital and told to go to this clinic and see our study staff if their child becomes ill. If a study child (coming with study id card and other proof of identity) is diagnosed with pneumonia again in the Maywand Hospital outpatient clinic, first-line antibiotics will be given free by the project.

4. The families will also be told to call the Fieldworker or hospital clinic doctors if the child is diagnosed as having pneumonia by another doctor.

45 female Fieldworkers will be recruited. These will be divided into 4 teams each with a team leader in order to ensure that the visits are made on time and questionnaires collected daily. The team leaders will also check the quality of the questionnaires and will also make unscheduled visits to the homes of families visited by one other team in order to monitor the quality of the data collection by other Fieldworkers. These Fieldworkers and their team leaders will receive one month training on IMCI and clinical measurements and usage of study tools that they are required to do.
Outpatient clinic and hospital admissions of pneumonias (passive case finding follow-up):
For 18 months, the first port of call will be a trial outpatient clinic set up within the Maywand Teaching Hospital located in the study area and within easy reach for all recruited families.

This will be run by 4 paediatricians with at least 3 years experience, who will receive refresher training in the diagnosis of pneumonia (according to the WHO/UNICEF Integrated Management of Childhood Illness [IMCI] criteria); they will work a shift system covering 24 hours, 7 days a week. They will be supervised by 1 senior paediatricians working 8am to 3pm who will also examine children with signs of pneumonia and a random sample of other children seen at the clinic.

The paediatricians will fill out a detailed clinical assessment form for each child, conduct pulse oximetry, request X-rays and treat (according to standard IMCI) and/or refer for admission if there is severe pneumonia. In the Maywand Hospital, the protocol for admission is that, simple pneumonias will be sent home with treatment, while severe or very severe cases (pure IMCI criteria) will be admitted. Therefore, since we follow the same protocol, this study should not increase the inpatient load of the hospital excessively. The recovery criteria and additional in-patient data on the progress of children admitted will be collected by the duty clinic paediatricians. That is, the admitted patients will be visited every 12 hours daily by the study doctors, important clinical and management changes recorded and their respiratory rate (using a stop watch and 2 times count for 1 minutes each), subcostal recession, fever and danger signs for pneumonia (see definitions section in summary project proposal) will be examined and recorded.

The Fieldworkers and doctors will use a standardised patient diary questionnaire to collect data on all pneumonia criteria (cough, respiratory rate and the danger signs) as well as fever. Clinical management of pneumonia will follow standard WHO-recommended guidelines.

In order to encourage care-seeking for illness episodes, the trial will cover costs of all IMCI recommended or hospital inpatient related ALRI medications.

All these doctors will attend a 3 week theory and practical training on the ARI and a few other components of IMCI (this is a refresher course since all have already been trained) and on the study design, requirements and questionnaires and including practicing the questionnaire with patients.

Vitamin D blood measurement
In order to ensure that the vitamin D supplements have been effective, a random sample of the children will be selected at 5 strategic times in order to measure their blood vitamin D status. The sample will include half of the vitamin D and half of the placebo group, but the children will be selected by the independent statistical methods of LSHTM. In order to reduce the number of children giving multiple blood tests, for each round of testing a new group of children will be randomly selected. In analysis, the rate of pooled sufficient or insufficient vitamin D results will be compared. Consent will be sought at the start of the project (see consent form).
A trained paediatric phlebotomist will be retrained to visit to the homes and conduct the blood sampling. The same procedure will be followed as the prevalence study in Chindawal during January 2005. This will be as follows:

The blood samples will be carried between houses in a cooler containing ice packs and at the end of each working day or half a day (no longer than 5 hours) the blood samples will be taken to the German Diagnostic Clinic of Kabul where a trained and experienced lab technician, supervised by the senior staff of the German Clinic will centrifuge the clotted blood samples and extract the plasma. The samples will be immediately transferred in cool boxes to a nearby EPI centre where they will be frozen to below -20C. At the end of the survey the samples of plasma will be sent frozen to Aga Khan Laboratories in Karachi for analysis. High pressure liquid chromatography (HPLC) will be performed to establish vitamin D status in each child.

The measurement of plasma 25-hydroxyvitamin D can be variable between laboratories. The Aga Khan University Micronutrient Research Laboratory has established internal and external quality control protocols in collaboration with the Nutrition Biochemistry laboratories at the International Center for Diarrheal Diseases Research (Dhaka, Bangladesh) and Bio-Rad (EQAS, UK). For external quality control there is a regular (fortnightly) monitoring system established with Bio-Rad (EQAS) and the coefficient of variation (CV) of the analysis ranges from 2-4%.

Baseline, confounders and other data collection
At recruitment and the next visit the study staff will collect data on a range of socio-economic and demographic variables, as well as known risk factors for pneumonia or vitamin D deficiency, including exposure to cigarette smoke, type of fuel and heating used at home, vaccination, supplementation, diet, and sun exposure habits/practices. Some of this information will be collected again at appropriate intervals in the study.

Trial management and monitoring:
• The trial director will be based in Kabul responsible for overall aspects of the day to day conduct of the trial.
• The trial directors will be assisted in this by a trial manager, a data manager and 1 of the 3 senior paediatricians, meeting weekly as the Trial Management Team (TMT).
• She will be in regular email and telephone contact with the other international collaborators.
• An independent data monitoring and ethics committee (DMEC) will be set up in accordance with the UK Medical Research Council criteria; they will receive weekly reports concerning any deaths or hospitalisations among study children.
• They will be advisory to the Trial Steering Committee (TSC), which will comprise the TMT, representatives from the collaborating institutions in Kabul (MOPH, UNICEF, Save the Children US, Maywand Teaching Hospital, German Diagnostic Centre, and District 1 Municipality) and the applicants.
• The Trial Director will provide 3 monthly progress reports for the TSC that will meet at least quarterly; international applicants will participate by telephone.
Data issues

Data entry
12 data entry staff will be trained and will enter the questionnaires into an ACCESS database. A data manager will monitor their work and manage the quality of the database, conduct consistency checks weekly and interface with the computer programmer in order to ensure an optimal database.

Data analysis
The study groups will be compared for the range of baseline variables, and regression techniques will be used to control for their effect if any important differences are found. The main analysis will consist of a comparison of pneumonia incidence rates between the vitamin D and placebo groups on an intention to treat basis, using a multilevel regression model to account for repeated pneumonia episodes. All time series data will be analyzed using the Cox proportional hazards model, controlling for age and other covariates.

The impact of the intervention on vitamin D status in plasma will be confirmed using t-tests to compare mean serum concentrations, and chi-squared tests to compare the proportions severely deficient between the two treatment groups.

All time series data will be analyzed using the Cox proportional hazards model, controlling for age and other covariates, and will be plotted on Kaplan-Meier survival curves. Vitamin D and placebo groups will be compared for the range of baseline variables, and regression techniques used to control for their effect if any important differences are found.

There will not be an interim analysis since this a safe intervention study.

Data management and quality control:

High data quality will be achieved through several means:

1. All staff will be trained:
   - Clinical staff will all be retrained in technical skills such as IMCI criteria of pneumonia in order to standardize procedures and definitions – this will reduce examination/diagnostic bias.
   - We will minimize inter-observer variation through standardisation exercises for all clinical personnel prior to the study. This has been considerably successful in previous pneumonia studies.
   - With the details of how to fill the questionnaires in order to reduce recording errors and biases.

2. Questionnaires are translated into Dari, the main local language in the area of study, and pre-tested for appropriateness and quality. Most of the questionnaires are identical to the questionnaires used for the vitamin D trial in Maywand Hospital during the winter of 2006-7 and thus adapted for Kabul use.
3. The Fieldworkers will be organized into 4 teams of 10 Fieldworkers, each supervised by a team-leader who will collect and check all questionnaires daily before submitting them to the trial manager.

4. The clinical reports will similarly be checked and submitted on a daily basis by one of the senior paediatricians. The trial manager will make further checks before passing to the data manager.

5. Any unclear entries at the time of data entry will be checked with the field staff.

6. Double entry of all data within a week of collection and built-in range and consistency checks will minimise data entry and field errors.

7. Team-leaders will make unscheduled visits to Fieldworkers’ families to check on the quality of their data collection.

8. Senior Paediatricians will make unscheduled checks of the clinical assessment of patients by study doctors every 3 days, in order to check on the quality of their clinical assessment.

9. Patients are frequently absent during home follow-up in community-based studies. This is factored into the sample size calculations. The Fieldworker will try to minimise absenteeism by reminding families at the time of each visit about the following week when the Fieldworker would come for visit. The time of the next visit will be reminded to the families. Questions will be asked about possible move of the family to another address at the time of the next visit. Furthermore, several addresses and phone numbers of friends and relatives will be obtained to help locate a family if they move unexpectedly. This method was very successful during the 3 month follow-up of the winterwinter of 2006-7 study – only 5% of the families were lost to follow-up in 3 months.

10. Children will have more than one episode of pneumonia during the observation period. We are interested in these second episodes and will encourage families to tell the study about these episodes. However, in order not to enroll the same child more than once as having a first episode, we will give them study ID cards, and we will maintain patient records notes and a list of all participants (basic identification details only with study id number) on site in the outpatient and inpatient clinicss of Mayanwar Maywand Hospital. Those identified as coming in for a second episode will be excluded from being recruiting again.

Reporting

Interim reports for the steering committee (TSC) are described in the above section. Once the fieldwork is complete, the study manager and director, with the advice of statisticians at LSHTM will analyse the data and report upon it through the compilation of a final report and a paper for peer review publication.
It is hoped that some of the staff will be recruited from the university of Kabul students or staff in order to strengthen the rigorous epidemiological experience gained by these professionals.

At least 3 open lectures will be held about the scientific aspects of the study, one at the Maywand Hospital for the staff, and two at the Medical University for the lecturers and students. Other scientific lectures can be held on request.

7. Study duration
   a. Expected duration of study period to be completed: 20 months
   b. Expected duration of study on each individual subject: 18 Months

8. Description and justification of sample size.

Sample size for the rate and severity of pneumonia as the result of supplementation

We estimate that the incidence of pneumonia in the placebo group will be 0.008/child/month during the six month study period. This is calculated as follows:

In Rudan et al’s global estimates, for South-East Asia low or non-Malaria populations studies, the incidence of acute lower respiratory infections ranges from 0.18 - 0.75 episodes/child year(cy) (these are mostly rural studies). Since our population is socioeconomically deprived, crowded urban population, with known high prevalence of diseases and micronutrient deficiencies, we assume that conservatively, a mid-point of these rates would apply to our population, i.e. 0.65 episodes/child year. Rudan et al, found that globally 6 - 12% of these incidences were severe pneumonia (defined mostly by hospitalization). Given the circumstances of our population, harsh winters of Kabul, and that we would use clinical criteria for definition of severe pneumonia which may not lead to hospitalization in all cases, we took 12% as being applicable to our study. Assuming 25% of pneumonia will be repeat episodes during 18 months of follow up, we estimate that the incidence of pneumonia in the placebo group will be 0.0585 episodes/child (0.65 x0.12x0.75) during the 18 months study period.

We expect a 35% reduction in the incidence of pneumonia in the vitamin D group given that 73% of children have vitamin D deficiency in the study area and that the incidence of pneumonia is 10 times higher in vitamin D deficient children than in normal children. A study with 80% power and 95% significance to detect a 35% reduction in the incidence of pneumonia compared to the placebo group will require 22079 child months per group. Since each child will be followed for 18 months and assuming a 20% loss to follow up, the study will require 1472 child per group. In order to facilitate randomization and allocation of staff we have rounded this figure to 1500 child per group.

Therefore in total we aim to recruit 3000 1 to 11 month infants.

Sample size for vitamin D blood test as process measure:

50 children per group will give 80% power of detecting a 50% reduction in the proportion of children with \(1,25(OH)_{2}D <8\text{ng/ml}\) (50% being conservative compared to the published literature), assuming that this deficiency is about 70% in the placebo group (the level
observed in the prevalence study). The sub-samples of children for this outcome will be selected by the independent statistician.

All calculations assume the probability of a Type I error of 5% and a Type II error of 10% (power of 90%). Epi-Info sample size programme was used for sample calculations.

a. Subject information.
   i. Age range: 1-11 months infants
   ii. Sex: □ Male □ Female □ Both

9. If subjects are children, pregnant woman, people with disabilities or mental illness, prisoners, or if it includes fetal research, give brief explanation of need to use these particular individuals.

The subjects are children. This is important because we intend to investigate the effect of vitamin D supplementation on reducing infant and child pneumonia. The background that led to the plan of this project is based on children and pneumonia and therefore it is only by researching in children that this research question can be answered.

10. Criteria for inclusion and exclusion of study subjects (type separately)

Inclusion criteria
Any child, living in the study areas aged 1 to 11 months.

Exclusion criteria
Children will not be eligible if:
(1) The family is expecting to move within the next 6 months;
(2) The child has been diagnosed with rickets or known to have received a course of vitamin D treatment in the past 3 months.
(3) Child has Kwashiorkor or Marasmus. Delayed entry for those with diarrhea, vomiting, or pneumonia by up to 2 weeks until symptoms are minimized.
(4) Caretakers do not give consent.

11. Compensation/Incentives (to research subject):

   a. Monetary: □ No □ Yes Amount:
      Please describe rational for monetary amount:

   b. Other: □ No □ Yes
      Please describe compensation/incentive:

      Benefits and incentive for families and children
      1. Free antibiotics for pneumonia illness of the child for 18 months of follow-up;
2. Two weekly visit of a trained female research staff at home which could identify unreported illness;
3. Extended access to well trained paediatricians for 18 months in their own area;
4. Treatment with vitamin D for all (placebo group receiving at the end of 18 months);
5. Box of biscuits after each blood-taking visit.

c. Reimbursement of expenses: ☐ No ☑ Yes

Please describe types of expenses covered and amounts:

1. Medical reimbursement – For all episodes of respiratory infections will be given according to IMCI and protocol guidelines.
2. Easier access to pediatric assessment (especially for pneumonia) at Maywand hospital will be provided for the 18 months after recruitment. This is not for payment and the clinic is specially set up for the study with well trained, experienced and supervised pediatricians.

12. Adverse events

a. What adverse events are expected to the subjects involved in the investigation during the study and;

1. Participation is anticipated to cause NO HARM to the children; in fact children will benefit through the provision of free medication and vitamin supplementation.

2. Although vitamin D overload is a theoretical possibility, this is unlikely. 100,000iu of vitamin D has been shown to provide the best protection against vitamin D deficiency and no overload in high-risk 0-9 month infants with normal baseline ranges of vitamin D. There are no known noticeable side effects from this supplementation. Furthermore single intramuscular injection of 3 times this dose (300,000iu) was safe and effective in treating nutritional rickets in 6–30 month old children residing in lower socioeconomic regions of sunny Istanbul24. In addition higher than recommended doses of daily supplementation of vitamin D (500-1000iu/day, adding-up to 120,000iu over 3 months) plus additional vitamin D fortified milk, has been shown not to induce an overload; this was the case in infants starting with normal ranges of vitamin D, even when supplementation continued during the summer (in France) and mothers had antenatal vitamin D supplementation. Both in the published literature and in one of the collaborator’s clinical experience (ZM), clinical and biochemical features of vitamin D toxicity occur in plasma 25-hydroxyvitamin D concentrations >100ng/ml due to inadvertent vitamin D poisoning, e.g. 600,000iu administered orally several times a week or month. Thus the evidence suggests that the proposed dosing regime should be safe and effective. Nevertheless, close monitoring of any unusual symptoms will be established in the 10 days following dosing.
3. There is no routine screening for vitamin D deficiency in Kabul which the trial would interfere with; children known to have rickets, or prescribed vitamin D supplements by a doctor on clinical grounds, will be excluded. Due to the known high rate of deficiency in the area, the placebo group will be given one dose of 100,000iu vitamin D at the end of the trial.

b. What is the provision for managing these events?

N/A

c. Who will pay for them?

N/A

13. What are the actual potential benefits if any to be obtained by participating or society as a result of this study?

For benefits to families please see above question number 9.

Capacity building
One of the main objectives of this project will be epidemiological research capacity building in Afghanistan. All staff or collaborators of the project will benefit through formal training and involvement in the project. All staff will be trained in team work, research disciplines and data integrity. Furthermore, each will have training specific to their work which will be of benefit in their career development. A randomised controlled trial is the highest level of medical research which looks to prove hypothesis in an indisputable way by eliminating biases which can affect the results. Experienced gained through participation in such an academic study will be of value to those individuals and Afghanistan.

It is hoped that some of the staff will be recruited from the university of Kabul students or staff in order to strengthen the rigorous epidemiological experience gained by these professionals. It is also hoped that one or more Afghan staff can register and start a PhD based on their work in this study.

At least 3 open lectures will be held about the scientific aspects of the study, one at the Maywand Hospital for the staff, and two at the Medical University for the lecturers and students. Other scientific lectures can be held on request.

Benefits for MOPH
Evidence will be provided for policy development which may impact Millennium Development Goals of infant and child mortality: For Afghanistan this study can lead to policy applications with reduced deaths of pneumonia in young children. This is one of the 2 health MDGs which is high on MOPH’s priorities.

Furthermore, if incidence of pneumonia is improved, and less children get repeat pneumonias, the hospital/health service costs, will be reduced.
Publications and global profile for Afghanistan: Whatever the findings of this study, the results will be of interest internationally; WHO headquarters have already shown an interest in this study. The findings will no doubt be published in major peer reviewed medical journals (with Afghan collaborators as co-authors) and this will help to outline the capacity of Afghan professionals and the positive road to development taken here which can impact the lives of others globally.

Global benefits
At the present, the evidence available in support of an association between vitamin D and pneumonia is limited, but compelling. If indeed supplementation will reduce the incidence of pneumonia, lives may be saved. Global literature indicates that vitamin D deficiency is prevalent in many sun-rich developing countries. Whatever the cause of this, it is clear that given the high rates child death from pneumonia in these countries, if a relationship is found with this common illness and this common vitamin deficiency the results of this proposed study will be of major clinical importance in all such countries. The impact could potentially be as important as those resulting from the trials demonstrating that zinc given at the time of illness reduces treatment response and child mortality in developing countries, leading to its incorporation in WHO/UNICEF child survival strategies. If effective, oral vitamin D supplementation could feasibly be implemented in developing countries since it is cheap and easy to administer since a once only dose for 3 monthly administration is safe and effective.

14. How is confidentiality going to be maintained?

1. The staff will be trained about the principles of confidentiality in order to prevent use or communication of families’ information for other means. Their contracts will make them legally responsible in this regard.

2. Strict confidentiality and security of data will be maintained at all times through safe keeping of paper forms and coding of computer entries so that individual identity will not be apparent without access to the paper forms and decoding of the entries:

All participants will have a study ID number. For data entry, the computer programming in ACCESS will hide all personal details except this number after entry. Access to the data will be limited to the study number for each child by those staff with a code.

The paper copies of questionnaires will be kept in a safe and secure place (locked) in order to keep the information confidential and out of public access. Access to these will be by authorized staff only.

3. Address and family identification details of the participants and address of one friend/family member is needed so that after recruitment the children can be found again, visited at home, examined and questionnaires filled. Sometimes families move home and by having family member details we can find the family again (We have successfully used this method during this winter’s RCT at Maywand Hospital.) This will be explained at the time of consent and these details will be kept secure as above.
15. Location of study:
- Outpatient clinic
- Inpatient units
- Other (specify):
The subjects will be identified through household recruitment and followed up at home and during their clinic visits or inpatient treatment for 18 months.

16. Laboratory studies:

a. Will any test be performed which are not routinely included as part of the workup for these types of patients? b) Who or what agency will pay for these tests?

Yes – a blood test for vitamin D level in a sub-sample of the children. The project grant will pay and conduct these tests.

17. Explain any ETHICAL ISSUES or CONSIDERATIONS of this study. Discuss obtaining informed consent in this section.

1. Strict confidentiality and security of data will be maintained at all times through safe keeping of paper forms and coding of computer entries so that individual identity will not be apparent without access to the paper forms and decoding of the entries.
2. Address of the participants and one friend/family member is needed so that after recruitment the children can be visited at home, examined and questionnaires filled.
3. Participation is anticipated to cause no harm to the children; in fact children will benefit through the provision of free medication and vitamin supplementation.
4. Although vitamin D overload is a theoretical possibility, this is unlikely. 100,000iu of vitamin D has been shown to provide the best protection against vitamin D deficiency and no overload in high-risk 0-9 month infants with normal baseline ranges of vitamin D26. There are no known noticeable side effects from this supplementation. Furthermore single intramuscular injection of 3 times this dose (300,000iu) was safe and effective in treating nutritional rickets in 6-30 month old children residing in lower socioeconomic regions of sunny Istanbul24. In addition higher than recommended doses of daily supplementation of vitamin D (500-1000iu/day, adding-up to 120,000iu over 3 months) plus additional vitamin D fortified milk, has been shown not to induce an overload25; this was the case in infants starting with normal ranges of vitamin D, even when supplementation continued during the summer (in France) and mothers had antenatal vitamin D supplementation27. Both in the published literature40 and in one of the collaborator’s clinical experience (ZM), clinical and biochemical features of vitamin D toxicity occur in plasma 25-hydroxyvitamin D concentrations >100ng/ml due to inadvertent vitamin D poisoning, e.g. 600,000iu administered orally several times a week or month. Thus the evidence suggests that the proposed dosing regime should be safe and effective. Nevertheless, close monitoring of any unusual symptoms will be established in the 10 days following dosing.
5. There is no routine screening or supplementation for vitamin D deficiency which the trial would interfere with; children known to have rickets, or prescribed vitamin D supplements by a doctor on clinical grounds, will be excluded.
6. Due to the known high rate of deficiency, the placebo group will be given one dose of 100,000iu vitamin D at the end of the trial.
7. Some discomfort will be experienced by the children selected for the vitamin D blood sub-samples; the small volume of venous blood will be taken by carefully trained and experienced staff.
Other considerations: Calcium deficiency is a possibility in these deprived populations and may speed vitamin D metabolism. This population has access to dairy products, eggs and nuts. To reduce calcium deficiency, all families will be given dietary advice to improve the child or breastfeeding mother’s calcium intake. Introduction of calcium supplements will divert from the programmatic approach of this trial: that is testing 3 monthly supplementation of vitamin D which for programmatic approaches will be much more useful than daily supplementation. Furthermore, there is no evidence that the immunological function of vitamin D is related to calcium.

Informed consent: At recruitment the Fieldworker will explain to the family the purpose of the study, the benefits offered and the procedures involved. An information sheet with the details of the study objectives, procedures, risk and benefits will also be given to the parents. Informed consent will then be obtained from both the mother and father of the child: finger prints and signature (literacy rate estimated at <50%) will be obtained in the presence of two witnesses, one a friend or family member and one the chaperone accompanying the Fieldworker. (See consent form)

18. Any other information relevant to the study in the context to Afghanistan?

Feasibility of the study and pilot performed in 2005
During the pilot study mentioned above, as well as investigating the prevalence of vitamin D deficiency in the proposed study population, several caretakers of infants who were visited for sampling were informally interviewed. The aim was to investigate their possible acceptance to take part in a larger study with the set-up described in this proposal. All but one said that they would agree to participate. Even 4 out of 5 caretakers who did not consent to have blood taken from their infants (all mothers with children less than 1 year of age) declared that they would consent to be involvement in a larger study if consent was obtained from the father, and if there seemed to be a direct benefit to their infant from giving blood (such as free treatment or free visit to trained doctors).

The population proposed for study live near the Maywand Hospital and it is practical that the staff can visit up to 6 families per day with the help of project transport. Community sensitisation will be conducted at the start of the project where the Area Hakim and District Governor and authorities and Mullahs and other known representatives of the community will be informed of the project.

Given the range of health problems facing the children of Afghanistan, vitamin D’s effects upon skeletal development is not important enough for a national priority. However, should clinical management of a common disease such as pneumonia be improved through supplementation, this may have major implications for children’s health and public health in Afghanistan.

19. Has this type of study been conducted elsewhere earlier? If yes please give details.
Similar study designs were used to show the effectiveness of zinc and vitamin A for improving the rate and severity of infections and pneumonias. This particular study involving vitamin D has not been done before – for this reason the findings of this study will be of great international interest.

20. Who is the funding agency for this study?
We have applied to the Wellcome Trust for funding and will know in May.
21. What is the total budget of the study?  
   US$300,000 although this may change depending on donor limits or requirements.

Email Note:

To the Chairman  
Ethics Review Board of the Ministry of Public Health  
Ministry of Public Health of the Islamic Republic of Afghanistan  
Kabul

Dear Esteemed Chairman and Members of the Ethics Review Board

I am writing to request that you would kindly review the submitted Check-list with attached summary protocol (which contains pertinent technical appendixes), consent form (English and Dari), and questionnaires A to F (English and Dari). The questionnaires are very similar to those used during our 2006-2007 vitamin D study at Maywand Hospital approved by your committee in November. Therefore they have been pre-tested and piloted for that study and improved.

You will know from your records, that this project follows a vitamin D survey that was conducted by this same investigating team together with the MOPH (Nutrition Dpt) and UNICEF in 2005 (appendix 1 of the protocol document) and the present 2006-2007 vitamin D study at Maywand Hospital which was approved by your Ethics Board. This present proposal was discussed at the Board meetings as early as in 2005. We can continue this important line of work still in collaboration with the MOPH, Kabul University Medical School and its Teaching Hospital, Maywand Hospital.

We would be grateful if you could kindly review this proposal in the October meeting.

We look forward to your comments.  
Yours sincerely
Annex 2 Study approval letter by Ethic Committee, MoPH, Afghanistan

To,

Dr. Semira Manaseki Holland
AKDN, Central Asia

Subject: Approval for proposal entitled "Double-blind randomized controlled trial investigating the effect of vitamin D supplementation on the incidence and/or severity of pneumonia."

Dear Madam,

The Institutional Review Board, Ministry of Public Health, Islamic Republic of Afghanistan has examined and reviewed your proposal entitled "Double-blind randomized controlled trial investigating the effect of vitamin D supplementation on the incidence and/or severity of pneumonia."

We are pleased to approve your proposal. However, we reserve the right to monitor and audit your research, and any violation of ethical norms shall lead to withdrawal of approval.

The approval is subject to submission of result of your study to IRB prior any dissemination plan.

With Best regards,

Associate Prof. Dr. Bashir Noormal
Acting Chairman Institutional Review Board
Ministry of Public Health
Annex 3 Study approval letter by Ethics Committee, LSHTM

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE
ETHICS COMMITTEE

APPROVAL FORM
Application number: 5117

Name of Principal investigator Daniel Chandramohan
Department Infectious and Tropical Diseases
Head of Department Professor Simon Croft

Title: The effect of Vitamin D supplementation on the incidence of pneumonia in Afghanistan: a randomized controlled trial

Amendments to this application have been approved by the Ethics Committee.

Chair Professor Tom Meade

Date 29 July 2008

Approval is dependent on local ethical approval having been received.

Any subsequent changes to the application must be re-submitted to the Committee.
Annex 4 Consent form

Ministry of Public Health of Afghanistan

Vitamin D supplementation trail in children in Afghanistan

1. Who is doing the study? What is the aim of the study?

The Ministry of Public Health, Maywand Hospital, Kabul Medical School, London University and the Aga Khan Health Services are doing a study in children in your area of Kabul. We want to find out whether giving vitamin D to children will help to reduce chest infection (pneumonia), diarrhea and other microbial diseases.

2. Why are we doing this study?

We already know that (1) Vitamin D helps to make bones and teeth of children and to keep them healthy; (2) Vitamin D may help our body’s ability to fight infections; (3) children who have pneumonia may have less vitamin D than children who did not have pneumonia (4) Supplementation dose of vitamin D is safe in children. But we do not know whether vitamin D can prevent or reduce the severity of pneumonia in children.

In Afghanistan many children have less vitamin D in their blood and pneumonia is a common cause of illness and death in young children. If we find out that giving vitamin D can prevent incidence of pneumonia and diarrhea or can reduce the severity of these diseases, we can help many children.

3. What will happen to your child if you agree to take part in the study?

1. Our Survey is for 18 months.
2. First we will examine your child to find out whether he/she has any illness that will disqualify from the study.
3. We will ask you questions about your child’s health, and your living conditions.
4. At the start of our project, and every 3 months during 18 months (totally 6 doses), the children will receive a few drops of olive oil in their mouth. With these drops of oil, by chance, half of the children will get vitamin D at the beginning and 3 month basis, and the other half will get vitamin D at the end of the survey.
5. Our female health worker will visit and examine your child at home for chest infection, diarrheal disease and other microbial diseases every two week for 18 months.
6. During each house visit if our staff suspect that you child has a chest infection or other mentioned diseases they will request you to bring your child to the Maywand hospital.

7. We will also request you to bring your child to the Maywand hospital if your child has any illness during the 18 months of the survey.

8. If they suspect pneumonia, the doctors at the Maywand hospital will do a X-Ray examination and other testes needed to confirm and treat pneumonia.

9. All treatment, tests and visit to Maywand hospital by our doctors for your will be free.

10. All you and your child’s information will remain confidential and safe in our store place. We will never tell anyone about your information and only use this information grouped together with other children’s information (for example we will not tell anyone that Ali was 13 months old, but we will count that 10% of study children were 13 months old).

4. Will we collect blood from your child?
Totally we are selecting 3000 children and only 600 of these will be selected by lottery for taking one teaspoon full of blood. The reason for this is that we need to know the amount of vitamin D in the blood after we have given this vitamin. If your child is selected, you will be told later and can discuss this separately with our staff. Your child can still be part of this study if you do not want blood to be taken and this will not make any difference to your child’s participation in the study.

This means that by lottery we will select only 120 children at the start of the survey, 120 children 1 month after the start of the survey, 120 children 3 months after, another 120 children in the summer, and 120 in the spring next year (2009).

We will not collect blood from any child more than once.

Blood collection will be carried out by an experienced phlebotomist (nurse) and we will follow strict safety procedures.

5. What are the benefits for your child?

1. Your child will get free vitamin D,

2. In the next 18 months you can get good free advice from specialist doctors if your child gets ill and get free medicine for your child if he/she gets a chest infection and diarrhoea.

6. What if you refuse to take part in the study?

There are no penalties if you refuse to take part in the study. Your child will continue to receive all routine health services. Taking part in the study is entirely your choice.
7. Can you withdraw your child after agreeing to take part in the study?
Yes. You can withdraw your child from the study at anytime. If you decide to withdraw from the study your child will continue to receive the routine health care.

8. Who has approved the study?

The Head of your District (Rais Nahiyah) and the trustee of your street (Vakils of Gozar) agree with our work and support us. The ethical research committees of the Ministry of Public Health of Afghanistan and London School of Hygiene and Tropical Medicine, London have approved this study.

9. Whom should you contact if there is any problem or question?

If during the study you have any questions or worries or your address changes you can talk to the lady health worker who visits your home, to the Maywand Hospital doctors listed below or contact Dr ------------------ on the phone number ------------------.

If God forbid, your child gets ill in the next 18 months, you should come to the Paediatric Department of the Maywand Hospital, bring the child’s study card, and see our well trained doctors for treatment. The name of our doctors are: -----------,----------------------,--------------------,-----------

11. Do you have any questions?

12. If you agree that your child participates in this study, please sign this form:
Full name of the child-------------------------------sex----------------------------study number of the child--------
Birth date of the child (or if not exactly known the rough age) -----------------------------------------------
Month __________________ Year __________________
Full name of the consenting person---------------------------------------------------------------
The relation of the consenting person to the child (please specify your relationship with the child)  
-----------------------------------------------------------------------------------------------
Address of the consenting person (district, street, number of house, etc)  -----------------------------
I have read the above information (or was read to me), I understood it and asked my questions from
the visiting staff (name)---------------------------and I am happy with all the explanations.
I agree that my child has the drops of oil, that my child be examined at home weekly for 18 months
by a female health worker and examine the child and ask me questions for the survey. I understand
that at anytime I can stop taking part in this study without giving a reason and without any effect on
medical care or treatment to my child.
I understand that if my child is selected, one teaspoon full of blood will be taken from the arm of
my child to measure the amount of vitamin D in the blood and I agree with that.
I am happy to take part in this survey
Yes __________ No __________
Signature (or thumb print) from parents or legal carer---------------------------------------------
Witness’ name-------------------------------------- signature/thumb print-------------------------------------
Witness’ relation to the child------------------------
Name of the interviewing staff---------------------- signature -----------------------------------
Name of the interviewer’s mahram--------------------------- signature -----------------------------------
Date-------dd----- mm -----  yy
Time (24 hour clock) ------hr------min
We are very grateful for your cooperation.
Annex 5 Recruitment questionnaires (Form A and F)

Questions about family members

Questions about the mother

10. First and middle name of the mother [ ] Surname/Family name of the mother [ ]

12. What is your date of birth? Day [ ] Month [ ] Year [ ] Do not know [ ]

13. What is your age in complete years (please choose one)?
   - 0 - 15 and below
   - 16 - 19 (2)
   - 20 - 24 (3)
   - 25 - 29 (4)
   - 30 - 34 (5)
   - 35 - 39 (6)
   - 40 - 44 (7)
   - 45 - 49 (8)
   - 50 - 54 (9)
   - 55 - 59 (10)
   - 60 - 64 (11)
   - 65 or older

14. What is your current marital status (please choose one)?
   - 1) Only Wife of the husband
   - 2) Husband has other wives
   - 3) Widow
   - 4) Separated not divorced
   - 5) Divorced
   - 99) Do not know

15. Do you attend any formal education (if not, then refer to question number 17)?
   - 1- Yes
   - 2- No
   - 99- Don't know

16. What was the highest level of education you attended (please choose one)?
   - Primary completed 1-6 years
   - Secondary completed 7-9 years
   - High school 10-12 years
   - Vocational education completed
   - College or university completed (please specify)

17. What other education did you attend? (please choose one or more)
   - 1) Not attended school or Madrasa, but can read and write
   - 2) Religious study at Madrasa
   - 3) Religious study at home or Mosque
   - 4) Can not read and write
   - 5) Can read, but can not write
   - 6) Vital education

18. Have you ever worked? (please choose one or more)
   - 1- Yes
   - 2- No (If No, refer to question number 22)
   - 99- Don't know

19. Official
   - 2- Non-official
19a. Do you work now?  
19b. If yes please specify:  
   ○ 6) Farmer  ○ 5) Huckster  ○ 4) Servant  ○ 3) Government employee  ○ 2) Tailor  ○ 1) Teacher  
   ○ 99) Don't know  ○ 10) Other (please specify)  
20. What was your previous job?  
   ○ 6) Farmer  ○ 5) Huckster  ○ 4) Servant  ○ 3) Government employee  ○ 2) Tailor  
   ○ 99) Don't know  ○ 10) Other (please specify)  
21. Who takes care of your child (study child) if you go to work? (Please choose 1 or maximum 3)  
   1) Husband  
   2) Brother or Sister of the child  
   3) Child's Grandparents  
   4) Uncle or aunt (maternal or paternal)  
   5) Other family members of the child  
   6) Friend/Neighbor  
   7) Private child caregiver  
   8) Kindergarten  
   9) Other (Please specify)  
22. Questions asked from:  ○ 2- Mother  ○ 1- Father  ○ Others specify  
23. First and middle name of father  ______________  Surname/Family name  ______________  24. Nickname of Father  ______________  
25. Age of father in complete years (please choose one)  ○ 2- Estimated  ○ 1- Confirmed  
   ○ 40 - 44 (7)  ○ 35 - 39 (6)  ○ 30 - 34 (5)  ○ 25 - 29 (4)  ○ 20 - 24 (3)  ○ 16 - 19 (2)  ○ 15 or below (1)  
   ○ 99) Don't know  ○ 12) 65 or older  ○ 60 - 64 (11)  ○ 55 - 59 (10)  ○ 50 - 54 (9)  ○ 45 - 49 (8)  
   ○ 99) Don't know  ○ 5) Other (Please specify)  ○ 4) Hazara  ○ 3) Uzbek  ○ 2) Pashtoon  ○ 1) Tajik  
26. Did you attend any formal education?  ○ 1- Yes  ○ 2- No  ○ 99- Don't know
28. What was the highest level of education you attended (please choose one)?

- Primary education 1-6 years
- Secondary education 7-9 years
- High school 10-12 years
- Vocational education completed
- College or University completed (please specify)

29. What other education you completed (please choose one or more)

1) Not attended school or Madrasa, but can read and write.
2) Religious study in Madrasa
3) Religious study at home or Mosque
4) Can not read and write
5) Can read, but can not write
6) Vital education

30. Are you working now?

1) Yes
2) No

31. What was your previous job?

1) Teacher
2) Doctor
3) Nurse
4) Engineer
5) Carpenter
6) Mason
7) Military officer
8) Other (please specify)
9) None
99) Don’t know

32. What was your main current occupation?

1) Teacher
2) Shopkeeper
3) Businessman
4) Servant
5) Huckster
6) Farmer
7) Freighter
8) Rug Maker
9) Don’t know
10) Labour
11) Driver
12) Tailor
13) Other (please specify)

33. Field workers observation:

1) Respiratory rate per minute First Respiratory rate per minute Second Respiratory rate per minute
2) At the time of taking the respiratory rate was the child awake or sleep?

1) Awake
2) Sleep
99) Don’t know

3) Sub costal recession (chest in drawing)
Questionnaire for Recruitment to Program (Form A)

1. Date of filling the questionnaire in solar (Shamsi) day __ month __ year __ time according 12 hour Hour __ minute __ AM __ PM

2. Name of the field worker who filled the questionnaire

3. Code of the study Child ___

4. Complete name and last name of the child ___

6. Gender ____________ ○ 1-male ○ 2-Female

5. F/name of the child ___

Details about sickness of today and yesterday

7. Does your child have the following sickness today or yesterday?

Field worker please read the following symptom and sickness. (Please tick one of the option what mother says below)

1. Cough ____________ ○ 1-yes ○ 2-No ○ 99-D-Know

2. Difficulty in breathing ____________ ○ 1-yes ○ 2-No ○ 99-D-Know

3. Fever ____________ ○ 1-yes ○ 2-No ○ 99-D-Know

4. Nasal construction and flu ____________ ○ 1-yes ○ 2-No ○ 99-D-Know

5. Sore throat and Rooph Sounds ____________ ○ 1-yes ○ 2-No ○ 99-D-Know

6. Ear discharge and ear pain ____________ ○ 1-yes ○ 2-No ○ 99-D-Know

7. Child irritation and more crying ____________ ○ 1-yes ○ 2-No ○ 99-D-Know

8. Unconscious ____________ ○ 1-yes ○ 2-No ○ 99-D-Know

9. No breast sucking ____________ ○ 1-yes ○ 2-No ○ 99-D-Know

10. No eating and drinking ____________ ○ 1-yes ○ 2-No ○ 99-D-Know

11. Eye problems ____________ ○ 1-yes ○ 2-No ○ 99-D-Know

12. Skin problems ____________ ○ 1-yes ○ 2-No ○ 99-D-Know

13. Diarrhea ____________ ○ 1-yes ○ 2-No ○ 99-D-Know

14. Vomiting ____________ ○ 1-yes ○ 2-No ○ 99-D-Know

15. Convulsion ____________ ○ 1-yes ○ 2-No ○ 99-D-Know

16. Other clinical signs and symptoms (Please clear it) ____________ ○ 1-yes ○ 2-No ○ 99-D-Know

17. None of signs and symptoms (If yes follow question 11) ____________ ○ 1-yes ○ 2-No ○ 99-D-Know
8. If you have visited the doctor what was the main sickness of the child. (please select one of the following, if multiple select the last one)

Have visit the doctor(if No follow question 9)

1. Pneumonia
2. Cold and flu
3. Bone trauma and skin burns
4. Sore throat and difficult sound
5. Meningitis
6. Other sicknesses (please clear it)
7. Measles
8. Diarrhea and vomiting disease
9. Anemia
10. Rickets
11. Skin disease
12. Others (please clear it)

When it started? Please select only one

Day: [ ] month [ ] year

1. I don’t know precisely- more than a week and less than a month
2. I don’t know precisely- more than a month and less than three months
3. I don’t know precisely- from new born more than three months
4. I don’t know precisely- from new born till now
10. During i~it4a~hour if child have given some pills, syrop or injection (ask from mother to bring the drugs and its covers) please read each of them for mother and select one or more

<table>
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<tr>
<th>1. ethical treatment (Please clarify it)</th>
<th>1- yes</th>
<th>2- No</th>
<th>99- DkNow</th>
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<tr>
<td>2. Some pills or syrop like drug (name it if possible)</td>
<td>1- yes</td>
<td>2- No</td>
<td>99- DkNow</td>
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<td>3. injection - (name it if possible)</td>
<td>1- yes</td>
<td>2- No</td>
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<td>4.) other actions out of above (name it if possible)</td>
<td>1- yes</td>
<td>2- No</td>
<td>99- DkNow</td>
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<td>5. )No Drugs)</td>
<td>1- yes</td>
<td>2- No</td>
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**Chronic heart diseases**

11. Does your child during last three months has given any serious or chronic diseases (special medical past story)

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<tr>
<th>1. Heart diseases (name it if possible)</th>
<th>1- yes</th>
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<td>2. Measals</td>
<td>1- yes</td>
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<td>3. Pneumonia</td>
<td>1- yes</td>
<td>2- No</td>
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<td>4. Chronic diheria (more than 14 days) or vomitive diseases</td>
<td>1- yes</td>
<td>2- No</td>
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<td>5. Animia</td>
<td>1- yes</td>
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<td>6. Rikets</td>
<td>1- yes</td>
<td>2- No</td>
<td>99- DkNow</td>
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<td>7. others (name it if possible)</td>
<td>1- yes</td>
<td>2- No</td>
<td>99- DkNow</td>
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12. Child weight/Kg :first [ ] second [ ]

12.a. Did child wore anything else During child's weighting out of thin underwear (if no follow Q13-2)

12.b. If yes how much was the weight this dothes [ ] mother didn't take out the clothes [ ]

12.c. If she didn't what clothes remained [ ]

13. Child's height/CM :first [ ] second [ ]

14. head circumference - Cm :first [ ] second [ ]

**Address**

15. Is this house your own properties

If yes have you planned to sell or rent this house in coming 18 mont (Months before) 1- yes 2- No 99- DkNow

When will your house Agreement complete? month [ ] year [ ] Don't know [ ]

Do you live in the same area of kabul when your agreement complete 1- yes 2- No 99- DkNow
Study of the effect of vitamin D supplementation upon incidence of pneumonia in children

(Note - this form was first made in Dari and translated to English - therefore, some of the phrases make better sense in Dari)

The Ministry of Public Health, Maywand Hospital, Kabul Medical University, London University and the Aga Khan Health Services are doing an 18-months survey of children in some parts of Kabul.

Vitamin D helps to make bones and teeth of children and to keep them healthy. Some doctors think that as well as strengthening bones and teeth, giving vitamin D may help reduce chest infection. This study will help the Ministry of Public Health and doctors decide if for reducing chest infection, they should give all children vitamin D or not.

The Head of your District (Rais Nahiyah) and the trustee of your street (Vakils of Gozar) are aware of our work and support us. The ethical research committees of the Ministry of Public Health and London University have approved this project too.

In addition to your support, please keep in mind the following benefit of the project to you and your child during the study period:

1. **Free Vitamin D**: At the start, and every 3 months during 18 months of the project your child will receive a few drops of olive oil in their mouth (totally 6 doses of Vitamin D). With these drops of oil, by chance, half of the children will get vitamin D at the beginning and middles and the other half will get vitamin D at the end of the survey. This way we can compare if giving vitamin D at the start or the end of the cold seasons as well as warm seasons is better for chest infections and diarrhoeal disease or not. The vitamin D has no side effects and tastes like the oil itself.

2. **Experienced doctors and easy access to them in Maiwand Hospital**: If God forbid, your child gets ill in the next 18 months, you should come to the Paediatric Department of the Maywand Hospital, bring this child’s study card, and see our well-trained doctors for treatment. The names of our doctors are: Rashid, Wali, Mujahid, and Khesraw.
3. **Free good quality medicine**: If your child needs medicines for chest infection and diarrhoea, our doctors will give you this medicine for free.

4. **Free Chest X-Rays**:

5. **Free examination of the child at home**: Our female health worker will visit and examine your child at home for chest infection and diarrhoea every two weeks for 18 months. She will also ask some questions from you and all your information will remain confidential and safe in our store place. We will never tell anyone about your information and only use this information grouped together with other children’s information (for example we will not tell anyone that Ali was 13 months old, but we will count that 10% of study children were 13 months old.)

6. **Measuring Weight and Height**:

7. Please give your children aged less than 6 months old foods rich in calcium for better growth and better absorption of vitamin D. These foods are: Dairy such as milk, butter, yoghurt, cheese, beans, peas, lentils, vegetables such as spinach, clover, cabbage, lettuce etc.

With all mentioned services, please contact our doctors whenever you child get any diseases and use our free and quality medicines.

We hope you and your child may get benefited. If you face any problem, please contact our field workers, our clinical doctors whose names are mentioned above or contact the project.

*We are very happy that your child is part of this study. Thanks for your cooperation*
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This table is for clinicians to record the dates if a child comes to the hospital frequently.

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Annex 7 Pictorial signs and symptoms card

Pictorial Signs and Symptoms Card for Mothers

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<th>Days after Field worker’s home visit</th>
<th>Date (Day and Month)</th>
<th>Well</th>
<th>Diarrhea</th>
<th>Fever</th>
<th>Cough or difficult breathing</th>
<th>Vomit</th>
<th>Not eat anything</th>
<th>Rash</th>
<th>Other</th>
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</tbody>
</table>

Child’s name: ___________________________  Study number: _____________  Date given to Family: _____ / _____ / _____
Annex 8 Standard Operating Procedure (SOP) for vitamin D administration

Standard Operating Procedure 5:
Vitamin D/Placebo Administration; and
Observing and Managing Serious Adverse Events administration of Vitamin D/placebo

1. Once you have obtained consent from the mother and father of the child ask if the child has vomiting on that day. **If the child HAS vomiting on the day,** ask for a clean spoon and water and test by giving a spoon of water. If this is vomited after 10 minutes tell the mother that you will return in a week and try to give the drug and complete recruitment then. Arrange with the mother to be home when you think you will be back.

2. **If child has NO vomiting on the day** give the contents of the syringe (containing Vitamin D/placebo) you choose for this child.

3. To give the syringe contents, remove the syringe cap. Lay the baby almost flat in the mother’s arms, put the syringe in the child’s mouth and slowly push the plunger so that the fluid goes in and is swallowed by the child.

4. Do not do this in a rush. If the baby seems to have spitted the oil or it has dribbles out of the mouth – try to estimate how much is spitted out and record on the Drug administration form.

5. After administration of Vitamin D/Placebo, ask that they keep the baby in the same room as you. Watch the child during the next few activities and for at least 30 minutes to see if he/she vomits or develops any new symptoms.

6. Fill the drug administration form immediately and make sure you put the syringe number in the space for study number for the child.

7. Put the study number written on the syringe on questionnaire A, the child study tag and ID card.
8. Proceed to fill Questionnaire A, ID form and anthropometric measures, and during this time ask that the child be kept in the same room as you. Observe the child to make sure he/she does not vomit the syringe oil.

9. If the child develops other symptoms before you leave the house make a note of this on the Drug Administration form and tell your supervisor at the end of the day.

10. Ask the mother (or main caretakers of the child) to watch out for any unusual/new symptoms in the child and write them in the "Pictorial symptoms card for mothers".

11. There is very little likelihood of a drug reaction, but what to do if there is an apparent drug reaction will depend on the nature of the reaction. You should inform your supervisor urgently and the action to be taken will be decided by the management team and you will be informed about this.

12. Submit the drug admin form to your supervisor at the end of the day (Form M).
### Questionnaire for administration of VitD/Placebo

1. **Date of filling the questionnaire:**
   - Day [ ]
   - Month [ ]
   - Year [ ]
   - Time (12 Hours): [Hour] [Min] [ ] AM [ ] PM

2. **Name of the fieldworker filling the questionnaire:**

3. **Child’s study number:**

4. **First, middle and last name of the child:**

5. **First and middle name of the child’s father:**

6. **Sex of the study child:**
   - [ ] 2- Female
   - [ ] 1- Male

7. **Code number of syringe containing VitD/Placebo administered to the child:**

8. **Did the child vomit the oil within 20 minutes after administration?**
   - [ ] 1- Yes
   - [ ] 2- No

9. **If Yes, how many minutes after the administration of the oil the child vomited?**
   - [ ] 1) 10 - 15 minutes after dose
   - [ ] 2) 16 - 20 minutes after dose
   - [ ] 3) 21 - 25 minutes after dose
   - [ ] 4) Others (please specify R)

10. **Did the child have any other symptom within 20 minutes after administration of oil?**
    - [ ] 1) Rash
    - [ ] 2) Difficulty in breathing
    - [ ] 3) Swelling of the body
    - [ ] 4) Other (please specify)
    - [ ] 99- Don't know
    - [ ] 2- No
    - [ ] 1- Yes
Annex 10 Two-weekly home visit form

Two-weekly Home visit Questionnaire

1. Date of filing the questionnaire
   (according to 12 hours)
   Time
   Year
   Month
   Day

2. Name of the field worker filling the questionnaire

3. Visit Number

4. Child's study number

5. First, middle and surname of the child

6. Complete name of child's father

7. Sex of the child
   - 2. Female
   - 1. Male

8. Who were the main caretaker of your child in the last 2 weeks (14 days)? Ask three main caretaker
   1) Child's mother
   2) Child's father
   3) Brother or Sister
   4) Grand father or mother of the child
   5) Uncle or Aunt of the Child
   6) Uncle or Aunt of the Child
   7) Other relatives
   8) Friends or neighboors
   9) Child Caretaker
   10) Kindergarten
   11) Others (please specify)

   Ask remaining from one of three main people

9. Relation of person to the child?
   - 1- Mother
   - 2- Father
   - 3- Brother or sister of the child
   - 4- Grand father or Grand mother of the child
   - 5- Others (please specify)
13. From which of the following did you get advice about any of the above symptoms in the last 2 weeks (including last 24 hours)?

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14. Which of the following treatments did you give for any of the above symptoms in the last 2 weeks (including last 24 hours)?

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<td>Gave some medicine tablets or syrup (please specify ________________ )</td>
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<td>Gave some injection (please specify ________________ )</td>
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<td>Bandage/cool with cloth/cold compress (please specify ________________ )</td>
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<td>5)</td>
<td>Other extra fluid treatment (water, tea milk, herbal drinks etc)</td>
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<td>Other (please specify ________________ )</td>
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195
### Field worker observation

1) Respiratory rate per min

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2. Sleep (1) Awake

3) At the time of taking respiratory rate was the child awake or sleep (W or S)?

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</table>

4) Fever

5) Nasal flaring

6) Not eating or drinking (observe by giving some drink or breastfeed)

7) Loose motion

8) Vomits everything (Observe by giving some drink or breastfeed)

9) Lost skin turgor (Observe by pinching)

10) Lethargic

11) Others (please specify)

---

16. Do you know if you will stay at this same address for my next 2 weekly visit?
## Absent Form for Recording Illness When Child is Absent

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<table>
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<th>Name and surname of Father</th>
<th>Name of the field worker who fill this form</th>
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1. When did the field worker visit you for the last time? (Before you moved or if she could not find you)

   - Day [ ]
   - Month [ ]
   - Year [ ]

   Name of field worker visited you last time:

2. Date family was visited again (After return or if the lost family was found again)?

   - Day [ ]
   - Month [ ]
   - Year [ ]

   Period family has not been visited (Absence period till before past two weeks):

3. Where was the child in the period where has was not visited by field worker?

   - A) in the city or other provinces (Specify it)
     [ ]
   - B) in other parts of Kabul (Specify it)
     [ ]
   - C) in other cities (Specify it)
     [ ]

4. During absence, did your child have any of the following conditions?

   - [ ] 01- Yes
   - [ ] 02- No
   - [ ] 99- D Know

   If yes how many times admited Due to Different health Problems:

   - Due to Pneumonia
   - Due to Diarrhea
   - Due to other diseases (Specify it)

---

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Outpatient Questionnaire (OPD Form)

1. Date of filling the questionnaire
   Year       Month       Day       Time (12 hour clock)
   Hour       Minute      PM        AM

2. Name of doctor filling the questionnaire

3. Child’s study number

4. Child’s full name and surname

5. Name of Child’s father

6. Sex of the child  
   0-2· Girl  0-1· Boy

7. Age of child in months

8. First visit for this disease
   Second visit for this disease
   - More than 48 hours and less than 14 days
   - 48 hours
   - 24 hours
   - Less than 24 hours

Illness Detail
Clinical notes from Mother

8. Signs and symptoms that mother says about this disease

   1) Fever
   2) Getting cold
   3) Skin rash
   4) Cough
   5) Difficulty breathing
   6) Wheeze
   7) Blocked or runny nose
   8) Sore throat / hoarse voice
   9) Ear ache / pussy
   10) Loose motion
       0-99· Don’t know  0-2· No  0-1· Yes
   11) Dysentry
   12) Mucous diarrhea
       0-99· Don’t know  0-2· No  0-1· Yes
   13) Vomiting
       0-99· Don’t know  0-2· No  0-1· Yes
   14) Projectile vomiting
   15) Drinking eagerly / thirsty
   16) Not able to drink or eat food / not take breast
   17) Excessive crying / restless
   18) Sunken eyes
   19) Eye problem / eye discharge
   20) Severe Palmar pallor
   21) Unconscious
   22) Convulsion in last 24 hours
   23) Other clinical signs or symptoms (Specify it ___________________________)

How many times in how many hours
   - More than 48 hours and less than 14 days
   - 48 hours
   - 24 hours
   - Less than 24 hours

   How many times in how many hours
   - More than 48 hours and less than 14 days
   - 48 hours
   - 24 hours
   - Less than 24 hours
9. For this illness or symptoms of your child that you said about, did you or other family members do anything or get advice from anyone?

☐ 99 - Don't know ○ 2 - No ○ 1 - Yes

10. From which of the following did you get advice about any of the above symptoms?

1) Mother's own experience
2) Grandparents of the child/child's other family members
3) Friends/neighbours
4) Study Hospital doctor/Clinic
5) Doctor from another hospital/other doctors
6) Nurse
7) Pharmacist
8) Dai or old ladies/Fortune seller/Hakim shops/Greek Herbs doctor
9) Mullahs
10) Others (please specify ________________________ )

11. Which of the following treatments did you give for any of the symptoms in question # 8?

1) Traditional medicine or treatment (please specify ________________________ )
2) Gave some medicine tablets or syrup (please specify ________________________ )
3) Gave some injection (please specify ________________________ )
4) Bandage/cool with cloth/cold compress (please specify ________________________ )
5) O.R.S ______________________________
6) Other extra fluid treatment (water, tea milk, herbal drinks etc)
7) Brought to Hospital or doctor
8) Advice from another
9) Did nothing
10) Other (please specify ________________________ )

12. Did you see the doctor in this Maywand Study clinic for this illness of your child?

☐ 2 - No ○ 1 - Yes

13. If yes, why did you come back to the clinic today?

1) Symptoms did not improve
2) Symptoms got worse
3) Another illness seems to have appeared
4) Other (please specify ________________________ )
Other points about mother's/caretaker's visit to the clinic

**Signs and symptoms that the doctor observed through examination**

14. After examination, are the following signs and symptoms present in child?

1) Strider

2) Sub-costal recession (chest in drawing)

3) Raised Respiratory rate according to the age of child

   - 2nd Sleep
   - 1st Awake

4) Fever

5) Diarrhea with signs of mild, moderate, or severe dehydration

6) Other reasons for admission to hospital (Please specify ________)

15. Is one or more of the above present in child?

16. Write your diagnosis and go to the end to question number 26.

1) Common cold and cough

2) Viral URTI

3) Mild watery diarrhea with no dehydration

4) Mild Ear Infection

5) Mild Eye Infection

6) Others (please specify)

17. Further clinical notes from doctor observed through examination.

   1) Cough

   2) Sore throat / hoarse voice

   3) Strider

   4) Wheeze

   5) Grunting

   6) Sub-costal recession (chest drawing)

   7) Blocked or runny nose

   8) Convulsion

   9) Sunken Eye

   10) Ear ache or pussy

   11) Neck rigidity

   12) Watery Diarrhea

   13) Drinks eagerly (by offering some water)

   14) Vomits all drinks
15) Projectile vomiting
   - 2- >2 sec
   - 1- <2 sec

16) Not taking Breast/Food/Drinks
   - No

17) Lost skin turgor (Be skin pinching)
   - 2- No
   - 1- Yes

18) Abdominal distension
   - No

19) Coated tongue
   - No

20) Thrush in Mouth
   - No

21) Sever Palmer pallor
   - No

22) Moderate Palmer pallor
   - No

23) Irritable / Restless
   - No

24) Labthargy
   - No

25) Unconsciousness
   - No

26) Convulsion
   - No

27) Other things and symptoms (please specify)

18. Doctor's clinical diagnosis

1) Pneumonia
2) Sever Pneumonia
3) Very sever Pneumonia
4) Congestive heart failure
5) Septicemia
6) Laryngitis or sore throat
7) Acute Watery Diarrhea with some dehydration
8) Acute Watery Diarrhea with moderate dehydration
9) Acute Watery Diarrhea with sever dehydration
10) Persisent Diarrhea
11) Sever persisent Diarrhea
12) Otitis media
13) Measles
14) Typhoid fever
15) Malaria
16) Simple Ferbile Convulsion
17) Meningitis
18) Sever anemia
19) Sever malnutrition
20) Hepatitis
21) Tuberculosis
22) Other please specify
19. Have you sent his child for chest X-Ray?

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20. Doctor admitted the child for hospitalization?

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21. Is the child already on antibiotic?

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22. If yes, what antibiotic is the child taking now?

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23. Did you (Doctor) give treatment to the child that was same or different from before?

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24. If yes, is the antibiotic a continuation of previous one?

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25. If No, What is the new antibiotic's name?

<table>
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<tbody>
<tr>
<td>Second antibiotic name</td>
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26. Name of the advised medicine: (Choose one or more)

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</tbody>
</table>

1) Drug for cough

2) Pain killer and antipyretic

3) ORS

4) Other medicine (please specify)
Clinical Protocol (1)

DEFINITIONS

Pneumonia: Is defined as age specific rapid breathing and cough associated with fever or not without wheezing.

Rapid breathing is defined as respiratory rate 60 or more in children < 2 months, 50 or more in children 2 months up to < 1 year, and 40 or more in children one year to 3 years old.

Severe Pneumonia: Is defined as rapid breathing with cough and chest in-drawing.

Very Severe pneumonia: Is defined as having signs and symptoms of severe pneumonia plus danger sings (central cyanosis, severe respiratory distress, nasal flaring, grunting, convulsion, vomiting and not being able to drink)

Fever: Axillary temperature > 37.5 °C (age 1 week – 3 months) and >38 °C (age 2-24 months)

- Rectal Temperature of ≥ 38 °C (definition of fever in childhood by American College of Emergency Physicians)

Wheezing: Long high- pitched whistling or musical sound on expiration that can be heard from mouth.

Recovery criteria for in-patients (severe or very severe pneumonia) - 3 following criteria have to be met for two successive days:

1) Normal respiratory rate of <60/minute in children <2 months, <50 breaths/minute in children aged <12 months and <40/minute in those aged 12 months or more.

2) No danger signs or sub-costal recession (chest in drawing).

3) No fever (axillary temperature <37.5°C in <2 month-olds and <38°C in 2-24 months age children).

* Discharge after one day or more in presence of above criteria

11 Not drinking/breastfeeding, convulsion, vomiting everything, lethargic/unconscious, stridor in a calm child
**Failure to respond to treatment:** Failure to improve refers to no change in the resting respiratory rate over the respiratory rate detected at baseline during diagnosis in clinic (or fever if present) over a 72-hour period. This will allow for a rate of ± 5 breaths/minute of the baseline value. For example, if the baseline rate was 55 breaths/minute, the condition would be viewed as failure to improve if the sustained rate at 72 hours ranged between 50 – 60 breaths/minute at rest.

**Worsening condition:**

1. Worsening condition refers to a sustained increase of greater than 5 breaths/minute over baseline in respiratory rate.
2. The new emergence of sub-costal recession (chest in drawing) or one of the danger signs suggestive of severe pneumonia. In this case there may be a progression of severity definition, which will either be from ‘pneumonia’ to ‘severe pneumonia’ or ‘very severe pneumonia’.

**Relapse:** Diagnosis of pneumonia again within 14 days after the last day of illness of the previous episode of pneumonia.

**Duration of illness:** Date of clinical diagnosis and treatment onset to the last date of illness with any of the following criteria:

1. Normal respiratory rate according to age
2. No danger signs or sub-costal recession (chest in drawing)
3. No fever (temperature < 38.0°C or < 37.5 °C if < 2 months old)

**Episode:** A minimum of 14 days\(^{10, 124}\) (equal to 2 home visits) free of raised respiratory rate or sub-costal recession will be required to define a new (rather than continuing) episode of pneumonia.

**Respiratory rate measurement:** To be reported using a stop watch and after 2 repeated counts for 1 minute and while infant/child is calm.
### DIAGNOSIS AND TREATMENT GUIDELINES:

Children aged 2 months to 5 years:

<table>
<thead>
<tr>
<th>Sign and symptoms</th>
<th>Classification</th>
<th>Treatment</th>
<th>Where to treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR/min:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ≥60 (&lt;2 months age)</td>
<td>Pneumonia</td>
<td>Oral Amoxicillin&lt;sup&gt;12&lt;/sup&gt;. After second referral oral Cephalexine&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Home</td>
</tr>
<tr>
<td>- ≥50 (2-12 months age)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ≥40 (12-59 months age)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest in drawing</td>
<td>Severe Pneumonia</td>
<td>IV / IM Penicillin crystal&lt;sup&gt;14&lt;/sup&gt; If not improving add Gentamicin&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Hospital</td>
</tr>
<tr>
<td>Cyanosis, Inability to feed</td>
<td>Very severe pneumonia</td>
<td>IV / IM Penicillin crystal + gentamicin or Ceftriaxon&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Hospital</td>
</tr>
</tbody>
</table>

Children aged 7 days to 2 months:

<table>
<thead>
<tr>
<th>Sign &amp; symptoms</th>
<th>Classification</th>
<th>Therapy</th>
<th>Where to treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR ≥ 60/min</td>
<td>Sever pneumonia</td>
<td>IM / IV Ampicillin&lt;sup&gt;17&lt;/sup&gt; + gentamicin</td>
<td>Hospital</td>
</tr>
<tr>
<td>Sever chest in drawing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR ≥ 60/min</td>
<td>Very severe pneumonia</td>
<td>IM or IV Ampicillin + gentamicin or Ceftriaxon + Amikacin&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Hospital</td>
</tr>
<tr>
<td>Sever chest in drawing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyanosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inability to feed</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Respiratory distress ( grunting, nasal flaring)</td>
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</tbody>
</table>

<sup>12</sup> Amoxicillin: 25-50 mg/kg/day thrice daily for 5 days
<sup>13</sup> Cephalexine: 25-50 mg/kg four times daily for 5 days
<sup>14</sup> Penicillin Crystal: 50,000-100,000 IU/Kg /day every 6 hours for 5 days
<sup>15</sup> Gentamicin: 5-7mg/kg/day every 8 hours for 5 days
<sup>16</sup> Ceftriaxon: 50-75mg/kg/day 12 hourly for 5 days
<sup>17</sup> Ampicillin: 100-200mg/kg/day 6 hourly for 5 days
<sup>18</sup> Amikacin: 15-20mg/kg/day 12 hourly for 5 days
Inpatient Questionnaire (IPD Form)

1. Date of filling the form in Hejri Shamsi
   Day   month  year  hour  minute
   According to 12 hour  hour  minute
   AM  PM

2. Name of the doctor who admit the child

3. Code of the study child

4. Complete Name, surname of the child

5. Complete F/name of the child

6. Gender
   1- Male  2- Female

7. Age of child

Dear Doctors: Please record the admission information from question 19!

This section should be filled when the child gets discharged by doctor

8. Date of Admission

9. Date of Discharge

10. Name of the doctor who discharge the Child

11. Final diagnosis (Underlying Cause)
   1. Idiopathic
   2. Severe pneumonia
   3. acute Watery diarrhea
   4. Dysentry
   5. Severe Persistent Diarrhea
   6. Urinary Track infection
   7. Very severe malnutrition
   8. Measles
   9. Severe Animia
   10. Congestive heart failure
   11. Congenital heart diseases (Please clear it)
   12. Other congenital disorders

Others (please describe it)

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12. Final diagnosis (Immediate Cause) Select more than one

1. Severe numonia
2. Very severe pneumonia
3. Watery diarrhea with severe Dehydration
4. Disentry without Dehydration
5. Disentry with Dehydration
6. (Server Persistent Diarrhea)
7. Diarrhea with moderate Dehydration but treatment with ORS Failed
8. Severe Malnutrition
9. Measles
10. Severe anemia
11. Congestive heart failure
12. Convulsion due to fever
13. Asthma
14. Branchialitis
15. U.T.I.
16. Others (Please describe it)

admission result of patient
1. Child is completely cured and return home
2. Some sympumt remained but the child could be follow up it at home
3. The child was sick but due to some reasons, discharge from hospital (Clear it) _______ 
4. He referred to other hospital
5. The patient with no notice to the doctor, left the hospital _______ 
6. Deid

Whether all the treatment with its answer noted or not?
1- yes 2- No

Treatment recommended during discharge
15. Dear Doctor: Have you recommended any equal or different treatment to the previous one to the child that could continue at home?
1- Yes 2- No

What is the name of Antibiotic that the child could take it at home?

Name of first Antibiotic __________________________ 1- Oral 2- IV 3- IM
Name of second Antibiotic __________________________ 1- Oral 2- IV 3- IM

4- Antipyric 5- ORS 6- Other drags
7. If any special comment in regard to Admission and Discharge of the Child please note that?

8. Please ask mother incase they shift or change their address in coming two weeks so that the field worker don't face any problem for searching the child. Will your address change or not?

Details of the child diseases during Admission:

Clinical signs and symptoms that mother says for her child during the Admission:

9. Clinical signs and symptoms that mother states (Please note all the signs and symptoms what mother says?)

1. Fever
2. Cold
3. Skin Problem
4. Cough
5. Difficulty in Breathing
6. Extra sound during breathing
7. Nazal Discharge
8. Soar throat (Not other sounds)
9. Ear Discharge
10. Wattery Diarrhea
11. Bloody Diarrhea
12. Mucous Diarrhea
13. Vomatting
14. Projectile vomiting
15. Very thirsty
16. Not eating, drinking, or taking mother's breast and weakly drinking
17. Crying
18. Sunken Eye
19. Eye problem
20. Litargic
21. Unconscious
22. Convulsion in last 24 house
23. Other clinical signs and symptoms (Describe it)
1. For the same sign and symptoms that you said, Has you or any member of your family (before now have you taken any treatment from anyone for your child?  

22. Which kind of the following treatment have given for the child for the above signs and symptoms (Question 19)  

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Don't know</th>
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<tbody>
<tr>
<td>1. Traditional treatment (Please clear it)</td>
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<tr>
<td>2. Some drags like syrop and pills (If possible name it)</td>
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<tr>
<td>3. Injection (If possible name it)</td>
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<tr>
<td>4. Cold compress</td>
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<td>5. Using other examination for treatment (using ORS water instead of boiled Milk)</td>
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<tr>
<td>6. We brought the child to the doctor or Hospital</td>
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<td>7. We took suggestion from other people</td>
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<td>8. We did nothing</td>
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<tr>
<td>9. other action taken (clear it)</td>
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</table>
Clinical findings of the doctor

Cough
soar throat and difficulties in sound
Stridor in breathing
Wising in breathing
granting during breathing
chest in drawing
Flue or nazel contruction
Nazal flaring
sunken eye
ear pain or ear discharge
neck regedity
wattery diarrheria
drinking with interesete (please give water for the child)
(the child vomating everything) please give the child breast milk, water or ORS
projectal vomating
No sacking, eating and drinking
losing of skin torgar (test Skin pinching)
(1- less than two second  2- more than two second
1. Abdomenal distintion
1. loaded tongue
2. Mouth trush
1. severe palmer pale
2. moderate palmer pale
3. Irritation
4. litergic (sleepy)
5. Unconscious
6. Convulsion
ther symptoms and signs (please clear it)

1. breathing rate first time  breathing/min  1- awake  2- sleep second time  breathing/min  1- awake  2- sleep
Fever first time  silses degrees second time  silses degrees

4. Discription for treatment Givne to the child
25. Table of signs and symptoms to be filled 2 times (12 hourly) daily if the child is admitted in hospital
Please fill this form for routine morning and evening assessments (8:00 AM and 8:00 PM)

<table>
<thead>
<tr>
<th>Day/mon/yy</th>
<th>Time</th>
<th>Name of Doctor</th>
<th>Chest in drawing</th>
<th>fever in °C</th>
<th>Nasal flaring</th>
<th>the child was asleep or awake</th>
<th>breathing rate 1st</th>
<th>Total convulsion in last 12 hours</th>
<th>not drinking, eating</th>
<th>Cyanosis 2nd</th>
<th>oxygen saturation 1st</th>
<th>number of watery diarrhea in last 6 hours</th>
<th>the child vomits everything</th>
<th>Skin turgor</th>
<th>Conscious status</th>
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- 1·yes
- 2·No
- 0·1·yes
- 0·2·no
- 0·1·awake
- 0·2·sleep
- 0·1·yes
- 0·1·yes
- 0·2·No
- 0·2·No
- 0·1·yes
- 0·2·No
- 0·Normal
- 0·1·Alert
- 0·Slowly
- 0·2·Early
- 0·very
- 0·Slowly
- 0·3·Regic
- 0·4·unconscious
Annex 15: X-ray form

Radiographer Questionnaire

1. Date of filling the checklist  Year [ ] Mor [ ] Day
   Time [ ] Min [ ] Hour (12 Hours): [ ] PM [ ] AM
   2. Name of the Radiographer filling the checklist
   3. Child’s study number
   4. First, middle and last name of the child
   5. First and middle name of the child’s mother
   6. First and middle name of the child’s father
   7. Sex of the study child
   8. Name of the doctor who referred the child for X-Ray
   9. Type of advised X-ray
      - 1- Chest x-ray
      - 2: Bone x-ray (Please specify it)
   10. Number of the films eliminated, because of their bad quality: (X-rays taken)
      - 0- Five
      - 1- Four
      - 2- Three
      - 3- Two
      - 4- One
      - 5- Non
   11. Child’s ID and date of taken X-ray is written on the film:
      - 0- No
      - 1- Yes
   12. The film(s) was sent/given to:
      - 1- Ward Doctor
      - 2- OPD Doctor
      - 3- Parents
      - 4- kept in X-ray department
   13. Date received back the film(s) after use by doctors and stored for project in X-ray department
      - Year [ ] Month [ ] Day

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Annex 16 Breastfeeding and living status form

Information about Breastfeeding and Living Status

1. Date of filling the Questionnaire
   Year ______ Month ______ Day ______ Time ______ AM ______ PM ______ Minute ______ Hour (12 hours clock)

2. Name of fieldworker filling the questionnaire

3. Visit Number
   ______

4. Child's study number
   ______

5. First, middle and surname of child
   ______

6. Name of Child's father
   1- Male 0 2- Female 0

Questions about breastfeeding the child

8. Have you ever breastfed your child? (If yes, go to question 10) 1- Yes 0 2- No 0 99- Don't know 0
9. If you never breastfed your baby, please explain why?
   1) Baby ill/weak/doesn't take breast 0 1- Yes 0 2- No 0 99- Don't know
   2) Mother ill/weak 0 1- Yes 0 2- No 0 99- Don't know
   3) Breast disease or cracked nipples 0 1- Yes 0 2- No 0 99- Don't know
   4) Mother didn't have milk at all 0 1- Yes 0 2- No 0 99- Don't know
   5) Baby doesn't take breast
   0 1- Yes 0 2- No 0 99- Don't know
   6) Mother needed to work
   0 1- Yes 0 2- No 0 99- Don't know
   7) Mother used contraceptive drugs
   0 1- Yes 0 2- No 0 99- Don't know
   8) Mother became pregnant
   0 1- Yes 0 2- No 0 99- Don't know
   9) Other (please specify ______) 0 1- Yes 0 2- No 0 99- Don't know

10. when did you first breastfeed your baby after delivery?
    0 1- Within few minutes (in first half an hour) 0 2 - Within first 3 hours (after first half an hour) 0 3- During 24 hours
    0 4- During 2 or more days 0 99- Don't know
11. Are you still breastfeeding? (If yes go to question number 14) 0 1- Yes 0 2- No 0 99- Don't know
12. If No, When did you stop breastfeeding? (if stopped from last month, then write days, if not then months)
    Days ______ Month ______ 0 99- Don't know
13. Why did you stop breastfeeding? Please choose one or more of following:

1) Child ill/weak
2) Mother ill/weak
3) Breast disease or cracked nipples
4) No milk
5) Child does not take breast
6) Mother needed to work
7) Mother used contraceptive drugs
8) Mother became pregnant
9) Child reached age of supplementary feeding
10) Child was elder to be breastfed
11) Other reasons (Please specify)

<table>
<thead>
<tr>
<th>Reason</th>
<th>Yes</th>
<th>No</th>
<th>Don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child ill/weak</td>
<td>0</td>
<td>99</td>
<td>1</td>
</tr>
<tr>
<td>Mother ill/weak</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Breast disease or cracked nipples</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>No milk</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Child does not take breast</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Mother needed to work</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Mother used contraceptive drugs</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Mother became pregnant</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Child reached age of supplementary feeding</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Child was elder to be breastfed</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Other reasons (Please specify)</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
</tbody>
</table>

14. At any time since yesterday morning till this morning (24 hrs) was your child given any food or drink other than breast milk? (Please choose one or more)

<table>
<thead>
<tr>
<th>Food</th>
<th>Yes</th>
<th>No</th>
<th>Don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lentil soap</td>
<td>0</td>
<td>99</td>
<td>1</td>
</tr>
<tr>
<td>Vegetable soap</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Boiled usual herbs</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Vegetable oil</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Honey</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Fruit</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Fruit juice</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Sweet tea</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Simple tea</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Plain water</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Medicine in tablet or syrup</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Other food (please specify)</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Meat</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Milk products like butter</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Yogurt</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Cheese</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Cow's milk</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Dried milk</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Egg</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Seriluck</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Mashed/porridge/litti or halwa (Please specify)</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Potato</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Rice</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>Meat soap</td>
<td>0</td>
<td>99</td>
<td>0</td>
</tr>
</tbody>
</table>
In other days during last week except yesterday, was your child given any other food or drink other than milk? (Please choose one or more) (Please read to mother)

<table>
<thead>
<tr>
<th>Food</th>
<th>1) Yes</th>
<th>2) No</th>
<th>3) Don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cereal soap</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vegetable Soap</td>
<td>99</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Boiled usual herbs (Please specify)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vegetable Oil</td>
<td>99</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Honey</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruit Juice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweet tea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple tea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plain water</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicine in tablets or syrup</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other food (Please specify)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What type of house is the family of child living in? (Please fill in this question based on your observation of the family's house)

1) Modern house with proper water and sanitation system
2) House with enough number of rooms but not having proper water and sanitation system
3) Crowded house, lacking proper doors and windows
4) Others (Specify it)

How many rooms do the family of the child live in? (Do not count the child)

1) No. of children 0 - 5 yrs 2) No. of people 6 - 15 yrs 3) No. of people more than 15 yrs or above

How many people usually sleep with the baby in one bedding? (Do not count the child)

1) No. of children 0 - 5 yrs 2) No. of people 6 - 15 yrs 3) No. of people more than 15 yrs and above
Annex 17 Sun-exposure and Indoor air pollution form

Sun Exposure and Indoor Air Pollution

1. Date of filling the questionnaire
   Year __  Month __  Day __  Minute __  Hour __  Time (12 hours clock)

2. Name of the field worker filling the questionnaire

3. Visit Number

4. Child's study number:

5. First, middle and surname of the child:

6. Full name of child's father

7. Sex
   ○ 2- Female
   ○ 1- Male

Questions about Child's Sun Exposure

8. Ask the following questions for the child's sun exposure
   Please ask all the below questions
   1) Was the child playing in the house yard/on the roof (on average during last two weeks time, during the day?
      ○ 99- Don't know
      ○ 3- Rarely
      ○ 2- At least twice in a week
      ○ 1- Everyday

2) Is the yard exposed to enough daily sun shine?
   ○ 99- Don't know
   ○ 3- No
   ○ 2- Yes (Less)
   ○ 1- Yes (more)

3) Was the child going out with his/her parents to hazar or when parents went out for working (on average during last 2 weeks)?
   ○ 99- Don't know
   ○ 3- Rarely
   ○ 2- At least twice in a week
   ○ 1- Everyday

4) If yes go to question 1 and 3, has the child's body been bare for sun exposure?
   ○ 1- No, the child has been either swaddled or had many clothes, even his/her face was covered
   ○ 2- Yes, only hands and face
   ○ 3- Yes, hands including arms, face, head and legs including thighs
   ○ 4- Yes, parts of the body in addition to hands feet, face arms and thighs
   ○ 5- Don't know

5) Has the child been exposed to sun from 11am - 3pm (on average in the last two weeks)?
   ○ 99- Don't know
   ○ 3- Rarely
   ○ 2- At least twice in a week
   ○ 1- Everyday

6) Has the child been exposed to sun at least 2 - 3 hours (on average in the last two weeks)?
   ○ 99- Don't know
   ○ 3- Rarely
   ○ 2- At least twice in a week
   ○ 1- Everyday

9. Take the answers of question 8 into consideration and write your estimation regarding child's sun exposure
   (Fieldworker)
   ○ 3- Often
   ○ 2- Sometimes
   ○ 1- Never
**Questions about Indoor Air Pollution**

10. Does anybody in your home smoke cigarettes or chalam (bubblies)?
   - 0 99= Don't know
   - 0 2- No
   - 1- Yes

11. If yes, how many people smoke cigarettes or chalam (bubblies)?

12. Among them, how many people smoke cigarettes or chalam (bubblies) inside the room the child lives?

13. On average how many cigarettes/chalam do all these people smoke in a day?

14. What do you use to cook your food?
   1) Degdan (using wood)
   - 0 99= Don't know
   - 0 2- No
   - 1- Yes
   2) Degdan (using coal)
   - 0 99= Don't know
   - 0 2- No
   - 1- Yes
   3) Picnic (Gas)
   - 0 99= Don't know
   - 0 2- No
   - 1- Yes
   4) Diesel Bokhari
   - 0 99= Don't know
   - 0 2- No
   - 1- Yes
   5) Others (please specify)
   - 0 99= Don't know
   - 0 2- No
   - 1- Yes

15. What kind of heating did you use in your main living area during last 2 week? (Choose one or more)

<table>
<thead>
<tr>
<th>Types of heating</th>
<th>Do you use?</th>
<th>How many hours in 24 hours is the heater on (on average in the last week)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nothing</td>
<td>(A)</td>
<td>0 2- No 1- Yes</td>
</tr>
<tr>
<td>Diesel Bokhari</td>
<td>(B)</td>
<td>0 2- No 1- Yes</td>
</tr>
<tr>
<td>Wood Bokhari</td>
<td>(C)</td>
<td>0 2- No 1- Yes</td>
</tr>
<tr>
<td>Gas Bokhari</td>
<td>(D)</td>
<td>0 2- No 1- Yes</td>
</tr>
<tr>
<td>Electric Bokhari</td>
<td>(E)</td>
<td>0 2- No 1- Yes</td>
</tr>
<tr>
<td>Bori Aara Bokhari</td>
<td>(F)</td>
<td>0 2- No 1- Yes</td>
</tr>
<tr>
<td>Sandalii</td>
<td>(G)</td>
<td>0 2- No 1- Yes</td>
</tr>
<tr>
<td>Chaari</td>
<td>(H)</td>
<td>0 2- No 1- Yes</td>
</tr>
<tr>
<td>Taba Khana</td>
<td>(I)</td>
<td>0 2- No 1- Yes</td>
</tr>
</tbody>
</table>
Annex 18 Vaccination, economic status, and total birth form

Questionnaire About Child Vaccination, Economic Status and Total Births in a Family

1. Date of filling the form (Solar/Shamsi)
   :year:month :Day time :Hour :minute AM PM According to 24 hour

2. Name of Field worker of study child

3. Number of visit

4. Code of the study child

5. Complete name and surname of child

6. F/name of the study child

7. Gender

   ◯ 2-Girl ◯ 1-Boy

B. Information about Vaccination Status

   ◯ 1) He or she has the card and all the vaccines are recorded, it must be entered in the following table
   ◯ 2) He or she has the card but some of the vaccines are not recorded (it must be entered in the following table)
   ◯ 3) Doesn't have card and hasn't vaccinated
   ◯ 4) Doesn't have the card but has vaccinated

<table>
<thead>
<tr>
<th>No</th>
<th>Vaccination</th>
<th>Date of Vaccination</th>
<th>Usual timing for implement of vaccination</th>
<th>Note/Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BCG</td>
<td></td>
<td>as soon as after born</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>DPT1/HepB1</td>
<td></td>
<td>sixth weekly</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Polio1</td>
<td></td>
<td>sixth weekly</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>DPT2/HepB2</td>
<td></td>
<td>tenth weekly</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Polio2</td>
<td></td>
<td>tenth weekly</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>DPT3/HepB3</td>
<td></td>
<td>forth weekly</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Polio3</td>
<td></td>
<td>forth weekly</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Measles</td>
<td></td>
<td>nine monthly</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Economic Status

9. Does your family own the following assets?

1. sewing machine
2. wall clock
3. cooking pressure
4. Radio.
5. TV.
6. Bicycle
7. Motor cycle
8. Generator
9. Car
10. Trucktor

12. How much is the average income of your family?
(Husband, wife, Children, Charity help who are eating from the same table) This will be a secret

11. Estimation of Field worker about economic status of the family (from the current condition of the house that you can estimate)

- 4: Very good
- 3: Good
- 2: Medium
- 1: Poor

Total number of the child you have given born to (Live and dead children) With the current child

<table>
<thead>
<tr>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live births still aren't alive</td>
<td>still alive</td>
</tr>
</tbody>
</table>