PNEUMONIA IN CHILDREN LIVING AT HIGH ALTITUDES IN PAKISTAN

by

Aamir Javed Khan, MBBS

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Abstract

Pneumonia is responsible for an estimated 44% of deaths in children under 5 years of age in the Himalayan communities of the Northern Areas, Pakistan. The objectives of the three papers included in this thesis were to 1) determine the incidence of pneumonia in children using the World Health Organization Integrated Management of Childhood Illness (IMCI) criteria; 2) evaluate the impact of intensive follow-up training for Community Health Workers (CHWs) on pneumonia recognition and referral; and 3) compare health center staff classification of pneumonia based on IMCI criteria with evaluation by pediatricians.

Children 2-35 months were followed at home every two weeks by CHWs and surveillance was simultaneously established at 15 health centers for pneumonia. CHW performance was evaluated at six-weekly intervals using pre- and post-tests, by measuring the proportion of children with severe disease they referred correctly to health centers, and by comparing the incidence rates for pneumonia among children in their coverage area. Misclassification of disease was measured by determining overall agreement between health center staff classification of disease with a pediatrician's evaluation at a referral hospital in Gilgit.

The incidence rate was 29.9 per 100 child years of observation (CYO) for pneumonia and 8.1 per 100 CYO for severe pneumonia. The proportion of children that were correctly referred for severe disease by CHWs increased from zero at baseline to above 80% over one year. Significant improvements were reported between the pre- and post-test results of CHW in all 10 tests conducted (paired sample t-test p-value <0.001). Using the pediatrician's diagnosis as reference, health center staff correctly classified 125

(74.9%) of the children with severe pneumonia, and failed to identify 42 (25.1%) of children with the disease. Staff incorrectly labeled 328 (72.4%) children from the 453 they classified as children with severe pneumonia. Fewer children with pneumonia were missed (11.5%) or labeled incorrectly (2.8%).

The pneumonia incidence rates in this Himalayan region are among the highest reported, even after adjustments for over-diagnosis of severe pneumonia. Sustained improvements in pneumonia referral were achieved following intensive training for CHWs. These findings warrant consideration of new intervention strategies in this region.

Advisor:	Neal Halsey
Committee of Final Readers:	Jonathan Weiner (Chair), Lawrence Moulton
	William Greenough, George Comstock

Preface

This dissertation is the culmination of six years of work I have coordinated and conducted with a dedicated team of researchers in Baltimore, Gilgit and Karachi. The study was initially conceptualized over a lunch discussion with my advisor in the spring of 1999 and it took two years of preparation before we finally opened our office in Gilgit. Much of that time was spent writing the protocol, visiting Gilgit and Karachi many times to lay the groundwork for collaboration and expanding the core research team. All of this, of course, required funding.

In early 2000, we successfully procured funding for protocol development and site visits from Smith Kline Beecham, a company that was developing a new pneumococcal vaccine. Pasteur Mèrieux Foundation provided additional funds later that same year, allowing us to establish the field site, enroll children and begin disease surveillance in 2001. Aventis Pasteur awarded funds in early 2002 to plan for a pneumococcal vaccine trial at an expanded site in the Northern Areas and an urban site in Karachi. By June of 2002, however, the security situation had deteriorated in neighboring Afghanistan and spilled over to Pakistan. Both vaccine manufacturers elected to withdraw support and focus on other areas for field studies that appeared to be more secure for foreign personnel. Lack of continuing financial support resulted in stopping enrollment and follow-up on December 31, 2002, although the core coordination and data management team continued working until August 2003. Data analysis, dissertation writing and the development of a new urban site for cohort studies in Karachi have consumed the past two years. In 2005, the Global Alliance for Vaccines and Immunization (GAVI) Accelerated Development and Introduction Plan for

pneumococcal vaccines (PneumoADIP) selected the Karachi urban site for development for potential multi-country vaccine trials in Asia. Whatever the outcome of the current effort may be, a career spent researching new vaccines and figuring out ways to speed up their introduction to countries like Pakistan will continue to remain both challenging and rewarding.

Acknowledgments

I would like to acknowledge the support and mentorship of my advisor, Neal Halsey. His commitment to improving the lives of children around the world with safe and effective vaccines and his personal integrity, generosity, patience, and good humor, have all set standards that I sincerely hope to emulate. I will always remain grateful to him for introducing me to the life of birds, and the Chesapeake Bay.

I also acknowledge the faculty at the school for all that I have learned here. By working for and studying at Johns Hopkins, I have had the privilege of participating in the American scientific enterprise. If there were only one lesson that I could take back with me from here, it would be that cultivating the culture of science is an investment that societies like my own must make if we are to achieve our full potential.

I am indebted to my previous teachers at the Aga Khan University, including Jack Bryant, Kamal Islam, Steve Luby and Joe McCormick, each of whom was instrumental in guiding me towards the science and practice of public health.

Many thanks are due to the professionals from different organizations who helped us navigate through the many challenges and processes inherent in a collaboration of this size. I am grateful for the time and support provided by Dr. Imam Yar Baig, Mr. Nazim Somani and Mr. Sarfaraz Ali from AKHSP Gilgit and Dr. Rozina Mistry and Peter Hatcher from AKHSP Karachi; Dr. Franklin White, Dr. Arshad Altaf, Dr. Zeba Rasmussen, Dr. Masood Kadir, Mr. Nasiruddin Muhammad Ali and Ms. Ghazala Humayun from the Aga Khan University; Dr. Wazir Khan, the District Health Officer for Ghizer District and Mr. Mehboob Khan, the district logistics coordinator for the National Health Worker Program; Dr. Mohammed Rafi, Dr. Agha Jan, Dr. Mansoor Khan and Dr.

Abdul Latif from the Gilgit DHQ Hospital; Dr. Zahid Larik from the Primary Health Care Cell at the Ministry of Health; and Dr. Syed Jaffar Hussain from the WHO IMCI team in Islamabad.

I am obliged to the extraordinary group of colleagues who have worked with me on this study, including members of our site coordination team; Tai Bibi, Nahida Shah, Tai Saleem, Himmat Zareen, Akbar Khan, Adil Khan, Azizullah Baig, Amir Hayat, Zayed Yasin, Imran Khan, Sajid Ali, Agha Ajmal and Zafar Fatmi. It is not possible for me to name all the 99 Community Health Workers or the 51 health center staff, physicians and program managers who worked with us, but without their support, this study was simply not possible.

My sincerest gratitude to Hamidah Hussain, Saad Omer and Syed Mahmood Ali Shah - colleagues, friends and compatriots at Johns Hopkins. Their conviction, perseverance and hard work have been a source of inspiration. We make a great team.

The friendship and encouragement of Shehzad Noorani and Hamidah Hussain through these years have been key elements in the completion of this dissertation. Their hospitality will always remain hard to match, as will Shehzad's photography.

The friendship and support of Shahid and Naureen Mahmud have been a wonderful reward for the small trouble of waiting to catch flights to Gilgit, weather permitting. Their kindness and guidance will always be remembered.

I could not have imagined when I began this work how much I would come to depend upon the support of my parents-in-law, Samad Shera and Noorjehan Samad.

Their dedication to teaching and the practice of medicine have earned them a well-deserved reputation, one that has opened many doors and has served me well in my work.

Much gratitude is deserved by my sister, Sheerin Javed, for her selfless support during my sojourns to America, and who, along with her family, gives me every reason to keep coming back.

I am indebted to my parents, Abdur Razzaque Khan and Kishwar Javed, for instilling in me a very high regard for education and public duty, especially given their own humble origins in India. My privilege of going to the best schools possible has been a heavy burden for them to bear. I will always regard any benefit that my work may bring to others more a result of their contributions then mine.

I am grateful, above all, to Lubna, who has shared with me the trials and tribulations of my work and the pleasure of living in the Himalayas. I could not have done this without her.

Aamir Khan

July 4, 2005

To Lubna,

for your companionship,

and to Jibran and Ammar,

for the joy you have brought us

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Introduction

Acute Lower Respiratory Tract Infections

Acute lower respiratory infections (ALRI) are a group of illnesses transmitted through aerosolized droplets. ALRI occur distal to the epiglottis and include laryngitis, tracheitis, bronchitis, bronchiolitis and pneumonia. The common etiologic agents of viral pneumonia include the respiratory syncytial virus (RSV), influenza A and B viruses, parainfluenza virus and adenoviruses.[1] While most ALRI are non-life threatening viral infections, some such as RSV and influenza A and B viruses can result in severe disease and death.[2] The frequency of viral respiratory infections is highest during infancy and between ages 1-4 years.[3] Viral infections also hinder ciliary action in the bronchioles, which may predispose to super-infection with bacterial pathogens. Pneumonia is the most serious manifestation of ALRI, with *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) reported as the most common causes of bacterial pneumonia in children 2 months to 5 years of age.[4]

Mortality from Pneumonia

There were approximately 10.8 million global deaths among children less than 5 years of age in the year 2000.[5] Bryce and colleagues estimate that 19% of global deaths in children less than 5 years during 2000-2003 were attributable to pneumonia.[6]

Pakistan was fourth in a ranking of countries by the total number of under-5 deaths, with an estimated 565,000 deaths in the year 2000.[7] Good data on the proportion of childhood deaths that are attributable to pneumonia in Pakistan are limited. The cause-specific mortality rate from pneumonia in children less than 5

years of age was reported to be 14 deaths per 1,000 children per year in Abbotabad (altitude 1,200 feet) by Khan and colleagues in 1987 prior to interventions. [8] Marsh and colleagues used verbal autopsy methods to classify 66 deaths in children less than 5 years from 1988-1991 in a village situated near 5,000 feet in the Northern Areas of Pakistan.[9] They estimated that 44% of all deaths in children under 5 years were due to pneumonia. Verbal autopsy of all under-5 deaths was later incorporated into the Aga Khan Health Service Pakistan (AKHSP) program in the Northern Areas, where pneumonia remains the leading cause of death in young children, causing 33% of all deaths in infants and 37% of all deaths in children 1 to 4 years in these areas in 1999.[10]

Incidence of Pneumonia in Pakistan

In a 1984 study designed to characterize the determinants of child health in rural and urban settings in Lahore, a cohort of 1,476 newborns was followed every 4 weeks at home until 24 months of age.[11] The study design had some limitations with regard to respiratory tract infections; the diagnosis of disease was based on a month's recall of the main signs and symptoms of the illness reported and if these were recurring between two home visits they were reported as a single episode. The pneumonia incidence rates reported were 22 per 100 CYO, indicating that pneumonia was a major contributor to morbidity and, potentially, mortality during the first two years of life in this population.[12,13] These data remain the only community based incidence rates for pneumonia from Pakistan reported in peer-reviewed journals.

Rasmussen and colleagues established community based surveillance for pneumonia in Oshikhandass village (located at approximately 5,000 feet in the Northern Areas) between December 1992 and June 1996. They reported 990 episodes

of pneumonia (based on WHO ARI criteria) in 1,800 children followed from 2-59 months of age and estimated the pneumonia incidence to be 44 per 100 child years of observation.[14] The very high incidence rate reported and the fact that the data are from a single village do raise questions about their generalizability.

Risk Factors Associated with Community-Acquired Pneumonia in Children

Pneumonia incidence is most strongly and consistently associated with young age, with the highest reported rates in children between 2-6 months old.[2,3] Other factors associated with pneumonia include male gender,[3] malnutrition,[15,16] micronutrient deficiency,[17,18] low immunization coverage,[19,20] low household income,[21,17] overcrowding,[22] poor breastfeeding practices,[23,24] and exposure to indoor air pollution.[25,26]

The higher incidence rate of pneumonia in children living at high altitudes is well established from studies in the Peruvian Andes and Papua New Guinea.[27,28,29]Much of the research conducted on the physiological responses of children at high altitude has come from populations living above 10,000 feet in the Peruvian Andes. Steinhoff and colleagues showed that it takes newborns between 3-4 years to adapt physiologically to high altitudes, which include compensating by increased ventilation, cardiac output, vital capacity and a shift in the oxy-hemoglobin affinity curve.[30] The degree to which these findings from the Andes in populations living over 10,000 feet may apply to most children in Punial and Ishkoman who live between 5,500 and 8,500 feet is uncertain.

Integrated Management of Childhood Illness (IMCI)

The World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI) strategy has been endorsed by the Government of Pakistan as an effective tool to reduce early childhood morbidity and mortality from pneumonia, diarrhea, malnutrition, measles and malaria.[31] The strategy aims to improve the management of common childhood illnesses by focusing upon 1) health systems development, 2) case management at first-level health care facility, and 3) community and family knowledge and practices.

Health system development takes place by identifying and addressing weaknesses in drug availability, planning and implementation, and health information systems.[32,33]

The guidelines for case management by health center staff are generic and have to be adapted by a national expert committee for use in individual countries.[34] The methods proposed to train health center staff include a standard 11-day training course that comprises supervised clinical assessments on patients and classroom teaching. A follow-up visit to each health center staff is conducted within 4 to 6 weeks of training.

The strategy and plan for the implementation of the third element of IMCI involving community health workers are being considered in Pakistan.

Pneumonia and Severe Pneumonia Classification under IMCI

Pneumonia and severe pneumonia are *mutually exclusive* classifications under IMCI. (See Table 1) A pneumonia classification is made in a child 2-59 months of age with a history of cough or difficulty breathing in the presence of a respiratory rate that is higher than the cut-off established by WHO for infants and young children. A

severe pneumonia classification is made in a child 2-59 months of age with a history of cough or difficulty breathing and any one of the following: chest indrawing, stridor, or any general danger sign. General danger signs include lethargy and unconsciousness, persistent vomiting, convulsions and inability to feed or drink. An increased respiratory rate above the WHO cut-off values is not required to make a classification of severe pneumonia.

National Health Worker Program

The government-run National Health Worker Program enlists village-based, community health workers (CHWs) to make monthly household visits and provide primary care services at home. CHWs are trained to screen children for signs and symptoms that require referral and to treat simple illnesses according to WHO guidelines. Sick children are preferentially referred to government health centers. The guidelines of the national program assign approximately 1,000 persons to a CHW, but due to the greater distances between houses and the difficult terrain involved in the Northern Areas, CHWs are assigned fewer families (between 400-600 persons).

The Northern Areas of Pakistan

The Northern Areas of Pakistan consist of five districts (Ghizer, Gilgit, Diamer, Skardu and Ganche) and form the western limit of the Himalayas that separate South Asia from China (Map). The confluence of four mountain ranges (Karakorum, Hindukush, Pamirs, and the Tian Shan) makes this one of the most geologically active regions of the earth. The Northern Areas is ethnically and linguistically diverse, with an estimated 2001 population of 1.2 million.[35] Aside from Gilgit and Skardu that serve as administrative and urban centers for the region, the

Northern Areas consists of widely dispersed, small, rural agricultural communities located mostly between 5,500 to 8,500 feet.

Some summer pastures and residences are located above 10,000 feet, but are only occupied for 2-3 months of the year. The region has extreme temperature variations, ranging from 42° Celsius in June to -15° Celsius in January.

Health Care in the Northern Areas

The Government and the Aga Khan Health Service, Pakistan (AKHSP) jointly provide health care in the Northern Areas. The government structure is functional in all the districts while the AKHSP provides medical services in the western districts of Ghizer and Gilgit.

The AKHSP primary health care (PHC) program was initiated in the late 1980s and is divided into modular units along the major valley systems of districts

Ghizer and Gilgit. There were 7 PHC modules in 2001, each with a director headquartered within the valley. Each module director worked closely with the General Manager in Gilgit and local health boards. The infant mortality rate (IMR) in AKHSP program areas were 37 per 1000 live births and the under 5 mortality rate (U5MR) were 50 per 1000 live births in 2000.[9]

The Government of Pakistan health system is a relatively recent but more extensive health service. To increase access to health care, the government undertook a national initiative called the National Health Worker (NHW) Program in 1995. Under this initiative, community health workers (CHWs) make household visits every month and provide free basic medical services at home. They are trained to treat febrile, acute respiratory and diarrheal illnesses and some skin diseases according to WHO guidelines. They are also trained to prescribe antibiotic therapy (cotrimoxazole, oral ampicillin and oral amoxicillin) for these illnesses when necessary. The role of CHWs is limited to conducting household visits and to using their personal homes as a 'health house' for the community at large to seek very basic medical attention. CHWs do not see patients at health facilities, although they are supervised in their household visits by health center staff.

CHWs refer patients to their corresponding government health centers or Basic Health Unit (BHU), usually staffed by a physician in this region. Some BHUs have a small laboratory with the ability to do a blood count. Patients seen at BHUs can be referred to a higher level health facility also know as a Civil Hospital with in-patient, X-ray and laboratory facilities that is usually staffed by 1-2 physicians and 2-3 nurses. Tertiary care health facilities in the government system are referred to as District Head Quarter (DHQ) Hospital. In practical terms, facilities are likely to vary and many designated Civil Hospitals will be functioning with the facilities of a BHU.

In Pakistan, a common type of female health center staff is traditionally called Lady Health Visitors (LHVs). LHVs are trained for one year each in nursing and midwifery. AKHSP health centers are staffed by 2 LHVs trained to diagnose common medical conditions and prescribe medications (including antibiotics) using established WHO Integrated Management of Childhood Illness (IMCI) guidelines. They work with the government Expanded Programme on Immunizations (EPI) office to provide community and facility-based immunization services throughout the AKHSP coverage area. AKHSP adheres to the national schedule for EPI (6, 10 and 14 weeks). Newborns receive OPV and BCG at birth. OPV and DPT are administered at 6, 10, and 14 weeks and measles at 9 months of age. In 2000, 71% of children resident in the AKHSP program areas had received all EPI recommended vaccines by one year of age. This decline from 93% in 1997 resulted from the inclusion of the new Gilgit module that had a poorly immunized population, and not due to decline in coverage in other areas. In addition to immunization services, the staff also conduct health center and community based antenatal care clinics and supervise the work of CHWs.

Medical emergencies are referred to secondary or tertiary care facilities. Because of the relative remoteness of the region in general and some villages in particular, village based volunteer local health boards have organized a system in which 4-wheel drive vehicles are available on demand for medical emergencies at a number of points along the valleys. The cost of using the system can vary from 200-500 rupees ($3-8) for a one-way trip. Notwithstanding the expense incurred by the family of the sick individual, this facility is effectively utilized for all forms of medical emergencies.

Structure of Dissertation

This dissertation is structured in the form of three independent but inter-related papers.

Paper 1 is entitled "Incidence of Pneumonia among Children 2-35 Months of Age Living at High Altitudes in Pakistan". This study involved enrolling children at home and tracking their visits to health facilities to identify children with pneumonia based on IMCI criteria.

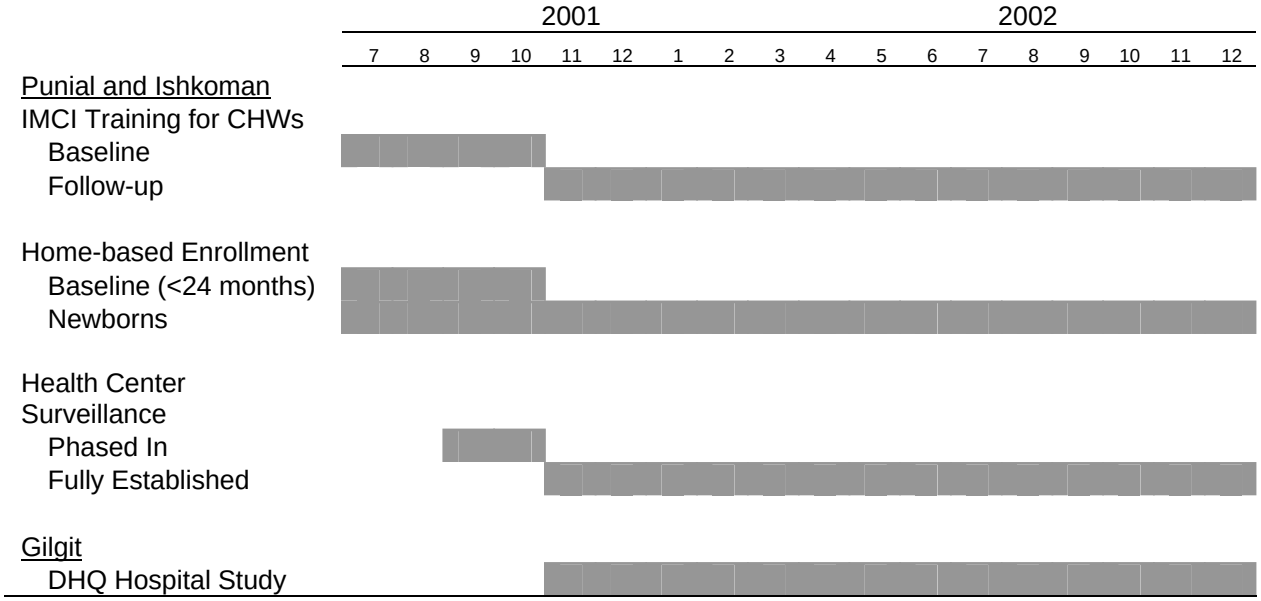
Paper 2 is entitled "Intensive follow-up training of Community Health Workers on Pneumonia Recognition and Referral in Children less than 3 years in Pakistan". Community Health Workers (CHWs) were trained at 6-weekly intervals over 14 months and assessed based on pre- and post-test scores on each training day, the appropriate referral

Paper 3 is entitled "Comparison of health center staff classification of pneumonia based on WHO IMCI criteria with evaluation by pediatricians in an outpatient setting in Gilgit, Pakistan" Health center staff at the tertiary care referral facility in Gilgit (DHQ Hospital) screened children presenting to an out-patient pediatric department for signs and symptoms of pneumonia. The pediatricians' evaluations were used as a gold standard for comparison with the health center staff classification of disease.

The papers are followed by a conclusion that states the key findings of these studies and constructs a case for a probe vaccine trial in the Northern Areas. The Appendix includes the consent and survey forms, and methods for the proposed vaccine trial.

A timeline for some of the major field activities is shown in Figure 1.

Figure 1. Timeline for major field activities in the Northern Areas of Pakistan, April 2001- December 2002.



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Paper 1: Incidence of Pneumonia among Children 2-35 Months of Age Living at High Altitudes in Pakistan

Aamir J. Khan[1,2], Hamidah F. Hussain[1], Saad B. Omer[1], Sajida Chaudry[3], Sajid Ali[4], Adil Khan[2], Zayed Yasin[2], Imran J. Khan[2], Rozina Mistry[5], Imam Yar Baig[5], Franklin White[4], Larry Moulton[1], Neal A. Halsey[1]

[1] Department of International Health, Johns Hopkins Bloomberg School of Public Health
[2] Center for Health Interventions Research, Gilgit
[3] Preventive Medicine Residency Program, Johns Hopkins Bloomberg School of Public Health
[4] Community Health Sciences Department, Aga Khan University
[5] Aga Khan Health Service, Pakistan

Abstract

Pneumonia is the leading cause of death among Pakistani children less than 5 years of age living in the Himalayan regions. The purpose of this study was to determine the incidence of IMCI classified pneumonia and severe pneumonia among these children.

Community Health Workers (CHWs) in Punial and Ishkoman enrolled children at home and conducted follow-up visits every two weeks. Health center staff based at 15 health facilities in Punial and Ishkoman used Integrated Management of Childhood Illness (IMCI) criteria to screen all sick children and identify those 2-35 months of age with cough or difficulty breathing and any one or more of fast breathing, chest indrawing, stridor or general danger signs.

CHWs enrolled 5,204 eligible children at home over a 14 month period. Health center staff identified 1,397 cases of pneumonia and 377 of severe pneumonia in children 2-35 months of age among enrolled children. The reported incidence rates for pneumonia and severe pneumonia were 29.9 and 8.1 per 100 child years of observation (CYO), respectively. Younger age and living at higher altitude were associated with higher incidence rates for pneumonia and severe pneumonia.

Pneumonia incidence rates in the Northern Areas of Pakistan are much higher than rates reported at lower altitudes and in other developing countries. Efforts are needed to determine the etiology of pneumonia in these communities, including the use of 'probe' vaccine trials to evaluate the proportion of disease that could be prevented by pneumococcal and *Haemophilus influenzae* type b (Hib) conjugate vaccines.

Introduction

Pneumonia is a leading cause of childhood death in countries with high under-5 mortality rates and continues to be the second leading cause of death among Pakistani children less than 5 years of age.[36,37] The cause-specific mortality rate from pneumonia in children less than 5 years of age was reported to be 14 deaths per 1000 children per year in Abbotabad (altitude 1,200 feet) by Khan and colleagues[38] in 1987 prior to interventions. Marsh and colleagues,[39] using verbal autopsy methods in a village situated at just over 5,000 feet in the Northern Areas of Pakistan reported that 44% of all deaths in children under 5 were due to pneumonia. Verbal autopsy methods have been used by the Aga Khan Health Service Pakistan (AKHSP) in the Northern Areas where pneumonia is the leading cause of death in young children, causing 33% of all deaths in infants and 37% of all deaths in children 1 to 4 years in these areas in recent years.[40]

In a 1984 study in Lahore (altitude 400 feet above sea level), a cohort of 1,476 newborns followed every 4 weeks at home revealed a pneumonia incidence rate of 22 per 100 child years among infants.[41] The study had some limitations. The diagnosis was based on a maternal recall of signs and symptoms, symptoms recurring between two home visits were reported as a single episode, and concurrent facility-based surveillance was not in place.[42,43] These data remain the only published community based incidence rates for pneumonia from Pakistan. Unpublished studies conducted in Oshkindass during the 1990s indicate an incidence of 30 cases of pneumonia per 100 child years of observation in children less than 5 years of age.[44]

Pneumonia is the most serious manifestation of acute lower respiratory tract infections, with *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib)

reported as the most common causes of bacterial pneumonia in children 2 months to 5 years of age.[45] Studies describing risk factors for community-acquired childhood pneumonia in Pakistan are limited, but appear to be similar to factors identified in other developing countries.[46] Between February and April 2000, Fatmi and White conducted a case control study at the major referral hospital in the Northern Areas (District Head Quarters Hospital, Gilgit), comparing 259 children with pneumonia to 187 children with 'cough and cold' as controls. Risk factors for pneumonia included lack of immunization, history of pneumonia, malnutrition, and younger age.[47]

The World Health Organization's (WHO) strategy for the Integrated Management of Childhood Illness (IMCI) has been endorsed by the Government of Pakistan as an effective tool to reduce early childhood morbidity and mortality from pneumonia, diarrhea, malnutrition, measles and malaria.[48] The purpose of this study was to determine the incidence of IMCI classified pneumonia, severe pneumonia and very severe febrile disease in a cohort of children followed from 2 to 35 months of age that live at high altitudes in the Himalayan regions of Pakistan.

Methods

Setting

The Punial and Ishkoman valleys of the Northern Areas had an estimated population of 59,000 in 2001.[49] Villages in Punial are situated within an altitude range of 5,500-6,499 feet and in Ishkoman between 6,500-8,499 feet, although two villages in Ishkoman are above 8,500 feet. The temperature ranges from 40° C in July to -15° C in January. A household commonly includes more than one generation of married couples and their children sharing a dwelling and kitchen. Wood fires are most

commonly employed for cooking and heating homes. Farming is the primary means of livelihood, although younger men are more likely to seek a career in the military or government.

Village-based organizations and volunteers working with the Aga Khan Development Network (AKDN) have brought about significant improvements in agricultural practices, literacy and health.[50] The Aga Khan Health Service Pakistan (AKHSP) primary health care (PHC) program has reduced infant mortality rates (IMR) to below 40 per 1000 live births in its program areas. Eighty four percent of children are fully immunized by 1 year of age and over 60% of infants are exclusively breast fed till 4 months of age.[51] However, 22% of infants and 24% of children 1-4 years have grade 1 malnutrition. AKHSP had 5 PHC centers (staffed by two LHVs each) and one secondary health care (SHC) center in Punial-Ishkoman during 2001-2002. The government health system in Punial-Ishkoman was more extensive, with 9 PHC and 2 SHC centers. Four PHC and all SHC centers were staffed by physicians and paramedics. Government centers charge a nominal fee relative to AKHSP centers, where cost-recovery is considered essential for sustainability. The government run National Health Worker Program enlists village-based, community health workers (CHWs) to make monthly household visits and provide primary care services at home. CHWs are trained to screen children for danger signs that require referral and to treat simple illnesses according to WHO guidelines. Sick children are preferentially referred to government centers. Due to the remoteness of the region village organizations ensure that 4-wheel drive vehicles are available for medical emergencies along the valleys.

Study Design

This was a longitudinal cohort study in which (1) all children 0-24 months of age were enrolled at baseline and (2) all newborns were enrolled from the baseline until the end of the study. Children were followed by CHWs at home every two weeks, who referred sick children to health center staff. Health center staff screened sick children and identified those with pneumonia or severe pneumonia.

Outcomes

The primary outcomes were pneumonia and severe pneumonia as defined under the Integrated Management of Childhood Illness guidelines for children 2 months to 5 years of age (Table 1). All primary outcomes were determined at health centers. Children under 2 months were not included in this analysis as IMCI guidelines do not have a separate classification for pneumonia or severe pneumonia for this age group

Eligibility for Enrollment

All children less than 24 months of age at the start of the study and all subsequent newborns in Punial and Ishkoman were eligible for home-based enrollment.

Enrollment

CHWs enrolled children less than 24 months of age at their homes between July 24, 2001 and October 31, 2001. All newborns were enrolled from July 24, 2001 onwards until December 31, 2002. Enrolled children were given a unique identification number by incorporating a code based on the area, CHW, household

and mother. An ID card was provided to each mother with the names, gender, age and identification number of all of her enrolled children. Mothers were told to present this card to any health center they visited for a sick visit.

Home Visits

Enrolled children were visited at home every two weeks by the CHWs serving their area. During each home visit, information was recorded on whether the child was alive and present at home; the signs and symptoms of current illness, if any; the symptoms of past illness based on the care-provider's two-week recall; and immunizations received. At the time of each visit, mothers were encouraged to seek care for their sick children based on IMCI counseling guidelines. Families were encouraged to have acutely ill children screened by local CHWs who decided on the need for treatment and referral using IMCI guidelines.

Identification of Sick Children at Health Centers

Surveillance for IMCI-classified pneumonia and severe pneumonia among children 2 to 35 months of age was phased in across health centers in Punial and Ishkoman over a two month period beginning September 1, 2001. Nineteen health centers participated in the study, including 12 government primary health care centers, 5 AKHSP primary health care centers, a commercially run private clinic and a charity-sponsored clinic in Ishkoman. Surveillance was stopped at 4 centers (three government first aid posts and the private clinic) in December of 2001 due to staff leave of absence or extremely low patient turn out. Surveillance at 15 health centers continued until December 31, 2002.

Health center staff screened all children between 2-35 months of age who presented to their center. Children with cough or difficulty breathing and one or more of fast breathing, chest indrawing, stridor, or general danger signs were further evaluated and classified according to IMCI guidelines. As the government IMCI strategy had not been implemented at the time of this study, physicians and health center staff used similar but older government guidelines based on the WHO Acute Respiratory Infections (ARI) Control Programme to treat or refer children with pneumonia or severe pneumonia.

The unique identification number of each child was noted on the health facility visit form. If the attendant did not present the ID card given to mothers of all children enrolled at home, information on the mother and child was collected on a separate form (Red Card) to be sent for follow-up to the CHW assigned to the child's village.

IMCI Training

Health care personnel in Punial and Ishkoman working at government, AKHSP or private centers and all government CHWs from the National Health Workers Program were trained to use WHO IMCI guidelines (see Paper 2). Particular emphasis was placed on the recognition and management of pneumonia and the recognition and referral of severe pneumonia among children 2-59 months of age. Three medical officers and 8 LHVs at AKHSP facilities had been trained in the use of IMCI guidelines and received refresher training. Ninety-nine CHWs, 11 program supervisors, 8 medical officers and 17 paramedical staff in the government health system received IMCI training along with two paramedics in the private sector. All community and facility based staff were visited by a project LHV, nurse and medical officer at least every two weeks to review home visit schedules, data forms, IMCI

classification of disease and referral practices. Cases of pneumonia and severe pneumonia for this study were counted at health facilities.

Statistical Methods

The age-specific incidence of pneumonia and severe pneumonia was calculated by dividing the total number of cases identified at all participating health facilities by the months of observation contributed by children in 2 month age intervals. Incidence rate calculations were based upon the outcomes detected from November 1, 2001 when home based enrollment had been completed until December 31, 2002. Associations between the incidence of disease and age, altitude, and number of other children in the household were explored using Poisson regression.

The records of sick children enrolled at health centers were verified and cases meeting IMCI criteria were included in the analysis. The months of observation contributed by individual children were calculated from the date of enrollment until the date the child 1) became 36 months of age, 2) was reported to have died or 3) migrated out of the surveillance area along with the mother. Provision was made for those children who may have moved out of the surveillance area for shorter periods of time (including moving with the mother to summer-time pastures) by subtracting the weeks of observation the child was reported not to have been at home on 3 or more consecutive visits.

Information collected at the time of home-based enrollment and on subsequent home visits was linked with the information collected at participating health facilities. If the child's surveillance number was unavailable, additional information collected at the time of the facility visit permitted us to procure the surveillance identification number at a later date.

Forms used at the site were optimized for scanning and optical character recognition using TELEform® 6 (Sunnyvale, CA) and Microsoft Access® 2000 was used for checking data integrity. Data were analyzed using SPSS® version 11.5 for frequency analysis and cross-tabulation and STATA® version 8.0 (College Station, TX) for Poisson regression.

IRB Approvals

This study was approved by the institutional review boards (IRB) at the Johns Hopkins Bloomberg School of Public Health and the Aga Khan University. Written informed consent from parents or legal guardians was obtained at home and at health facilities.

Results

There were 5,204 children enrolled at home; 3,436 were children less than 24 months of age at the start of surveillance, 1,685 were born during the surveillance period and 83 eligible children migrated into the area. There were 54,047 months (4,504 years) of observation contributed by enrolled children 2 to 35 months of age between November 1, 2001 and December 31, 2002.

Health center staff at participating facilities reported 2,147 eligible cases of pneumonia, severe pneumonia and very severe febrile disease among the 5,204 children enrolled. There were 1,790 (83%) cases correctly classified by health center staff (based on an internal consistency check of signs and symptoms recorded) and included 1,397 cases of pneumonia, 377 of severe pneumonia, and 16 of very severe febrile disease. The distribution of children with pneumonia presenting to health

facilities by altitude is shown in Table 2. The signs, symptoms and other observations reported with these IMCI classified illnesses are shown in Table 3. The seasonal distributions of pneumonia and severe pneumonia are shown in Figure 2.

A total of 1,348 episodes of pneumonia were reported among 949 children and 347 episodes of severe pneumonia among 311 children by health center staff between November 1, 2001 and December 31, 2002, when home-based enrollment had been completed and surveillance was fully established at 15 health facilities. Two hundred and sixty two children (28%) with pneumonia and 24 children (8%) with severe pneumonia had multiple episodes of the disease. Thirty-eight episodes of pneumonia and four of severe pneumonia were reported among children who presented to health facilities twice within one month and in whom the duration of symptoms overlapped for the two visits.

The annual community based incidence of pneumonia was 29.9 per 100 child years of observation (CYO) and 8.1 per 100 CYO for severe pneumonia among children 2 to 35 months of age in Punial-Ishkoman. The average incidence of pneumonia and severe pneumonia by altitude are shown in Table 2 and the incidence rates by age are shown in Figure 3. The incidence of pneumonia and severe pneumonia by age are shown in Table 4.

Pneumonia incidence rate ratios were calculated in a Poisson regression using age, altitude, number of infants in a household, and gender as covariates (Table 5). Incidence rate ratios were highest at 6.63 in children 4- <5 months of age (p-value<.001; 95% confidence limits 5.17, 8.49) in comparison to children in the reference age group (24-35 months). This ratio decreased for older children but remained significantly higher (p-value<.05) for all subsequent age groups in comparison to children 24-35 months of age.

The pneumonia incidence rate was 1.66 times higher ($p<0.01$; 1.45,1.89) in children living at 6,500-7,499 feet than children living at 5,500-6,499 feet, the reference group. The incidence rate ratio for children living at 7,500-8,499 was close to 1 and not significantly different than the reference group (Table 5). However, the incidence rate ratio was 0.15 for children living above 8,500 feet ($p<0.01$; 0.07,0.32) in comparison to the reference group.

The incidence rate ratios (IRR) among children living in households with 1-2 children less than less than 36 months of age (IRR 1.03; 95% confidence limits 0.91, 1.17) and those with 3 or more children less than 36 months of age (IRD 0.90; 0.4, 2.0) were not significantly different ($p>0.05$) than the ratio among those children living in households that did not have another child less than 36 months of age.

Discussion

The incidence rate of pneumonia and severe pneumonia combined (38 per 100 child years of observation) among children 2 to 35 months of age living in this area is much higher than rates reported at lower altitudes in Pakistan and other settings (Table 6).

Possible explanations for these high rates may include over-diagnosis by health workers, harsh winter seasons that entail spending long durations of time in overcrowded homes, heating and cooking by wood-fires, and increased baseline respiratory rates among infants and children living at high altitudes.

The classification of sick children made by facility based health workers were checked for internal consistency based upon the signs and symptoms recorded on the Health Facility Visit Form. (See Appendix) A household socioeconomic survey

conducted in 2002 in this area revealed an average of 9.5 persons (median 8, range 1-37) per household and 2.7 rooms per household (median 2, range 1-13).[52] The mean number of persons per room was 3.5 (median 3.7, range <1-24). Almost all households (98%) used wood-stove (*bukhari*) fires for cooking and keeping the sleeping area warm throughout the year. Children living in households that had 3 or more other children less than 3 years of age residing in them had substantially higher rates of pneumonia than those living in households with no infants. This relationship was not seen for the number of children 2 years or older living in a household. While it is possible that exposure to nasopharyngeal pathogens (including *Haemophilus influenzae* type b and *Streptococcus pneumoniae*) may be higher per person on average in households with 3 or more children under 3 years living in the same household, this association was not observed in the Poisson regression.

One limitation of this study was that regular, home-based enrollment was not possible in two small villages of approximately 20 households each. The path to one of these (Shamsabad) was blocked off in winter as it crosses an altitude of over 10,000 feet. Another group of households in Punial valley consistently refused government CHWs entry into their village prior to our project.

High baseline respiratory rates among infants and young children residing at high elevations could possibly contribute to high pneumonia incidence rates. Disease that might not be classified as pneumonia at lower altitudes could result in respiratory rates sufficient to be classified as pneumonia at higher altitudes. This may also explain the small but significant population of children who have had recurrent pneumonia. It is also likely that many children in developing countries who have recurrent pneumonia have underlying asthma that predisposes to fast breathing even with mild illness.[53] However, the IMCI classification of severe pneumonia is not

dependent upon the respiratory rate at the time of illness. Yet 8 out of 100 children 2 to 35 years of age followed over the course of a year will develop severe pneumonia in this population. If we postulate that up to a third of the pneumonia cases reported were attributable to higher respiratory rates in children with mild respiratory infections, the incidence of pneumonia would still be high (20 cases per 100 CYO).

The lack of bacteriology services and small number of blood culture results available during the course of surveillance in Punial and Ishkoman limits our ability to determine the proportion of pneumonia that is attributable to specific pathogens. Viral infections, especially respiratory syncytial virus and influenza, are likely to be responsible for a large proportion of pneumonia in young children living in these communities. Efforts were underway to enhance diagnostic bacteriology capabilities in health centers, but conflicts in neighboring Afghanistan and terrorist attacks in Pakistan during 2002 resulted in decisions by donors to withdraw support for the second phase of this project. Further studies are needed to determine the etiology of the high burden of disease from pneumonia in these communities and consideration should be given to 'probe' trials using pneumococcal and *Haemophilus influenzae* type b conjugate vaccines.

Acknowledgements

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Table 1. Diagnostic classification for pneumonia, severe pneumonia and very severe febrile disease based upon the World Health Organization Integrated Management of Childhood Illness (IMCI) strategy for children aged 2-59 months.

IMCI Classification	Clinical Signs
Pneumonia [a]	Cough *or* difficulty breathing (by history) *and* fast breathing [b]
Severe Pneumonia [a]	Cough *or* difficulty breathing (by history) *and* chest in-drawing *or* stridor *or* any general danger sign [c]
Very Severe Febrile Disease	Fever *and* any general danger sign *or* neck stiffness

[a] Pneumonia and Severe Pneumonia are mutually exclusive classifications under IMCI

[b] ≥50 breaths per minute in a child 2-11 months old or ≥40 breaths per minute in a child 12-59 months old

[c] Defined as the presence of any one or more of the following signs: 1) inability to breastfeed or swallow fluids; 2) persistent vomiting; 3) convulsions; and 4) unconscious or lethargic

Table 2. Distribution and incidence of IMCI-classified pneumonia and severe pneumonia among children 2 to 35 months of age by altitude and health facility, Sep 2001 – December 2002, Punial and Ishkoman, Northern Areas of Pakistan.

				All Health Facilities Under Surveillance			
Altitude range (in feet)	Children Enrolled N (%)[a]	Pneumonia Incidence per 100 CYO[b]	Severe Pneumonia Incidence per 100 CYO[b]	Primary Health Centers N[c]	Pneumonia cases N (%)[f]	Severe pneumonia cases N (%)[d]	All pneumonia cases N (%)
5,500-6,499	2,656 (51)	20	8.7	8	702 (75)	229 (25)	931 (53)
6,500-7,499	1,511 (29)	40.2	8.5	4	530 (84)	102 (16)	632 (36)
7,500-8,499	817 (16)	30.5	11	5	165 (81)	37 (19)	202 (11)
≥ 8,500	220 (4)	NA[e]	18.4	2	0	9 (100)	9 (<1)
All altitudes	5,204 (100)	29.9	8.1	19	1,397 (79)	377 (21)	1,774 (100)

[a] Percent of all children enrolled at home [b] Child years of observation (incidence rate based on cases reported at 15 health facilities between November 1, 2001 and December 31, 2002) [c] Facilities under surveillance; includes 2 government civil hospitals functioning at the level of primary health care centers during 2001 and 2002 [d] Percent of all pneumonia cases seen at all facilities under surveillance [e] Not applicable

Table 3. Characteristics of children aged 2-35 months with pneumonia and severe pneumonia seen at first-level health facilities in Punial and Ishkoman, Northern Areas, Pakistan. September 2001-December 2002

	Pneumonia (n=1,397)	Severe Pneumonia (n=377)
Parental History	*n(%* or *SD)*	*n(%* or *SD)*
Mother is information provider	1,256 (90%)	337 (88%)
Mean age of children in months	12.1 (7.8)	11.7 (7.5)
Male sex of the child	757 (52%)	201 (53%)
Antibiotic received prior to current visit	110 (8%)	80 (20%)
Co-trimoxazole	55 (4%)	34 (9%)
Amoxicillin	46 (3%)	34 (9%)
Others	4 (<1%)	4 (<1%)
Child is able to breast feed or drink	1,396	331 (88%)
Child vomits everything	0	79 (21%)
Mean number of days	-	2.1 (1.8)
Child had convulsions	0	33 (9%)
Mean number of days	-	2.9 (1.7)
Child has a cough	1,380 (99%)	366 (97%)
Mean number of days	2.9 (2.5)	3.3 (2.8)
Child has difficulty breathing	466 (33%)	263 (70%)
Mean number of days	2.4 (3.0)	2.3 (1.7)
Child has a fever	1,358 (97%)	350 (93%)
Mean number of days	2.6 (1.4)	3.4 (6.1)
If fever >7 days, present every day	9 (<1%)	11 (3%)
Child has diarrhea	66 (5%)	35 (9%)
Mean number of days	3.9 (7.2)	5 (3.8)
Observation	*n(%)*	*n(%)*
Lethargic/Unconscious	0	30 (8%)
Febrile > 37.5 C	572 (41%)	193 (52%)
Fast breathing	1,397	368 (98%)
Chest indrawing	0	262 (70%)
Stridor	0	144 (38%)
Stiff neck	0	1 (<1%)
Classification	*n(%)*	*n(%)*
Correctly classified by health worker	1,376 (99%)	273 (72%)

Figure 2. Seasonal distribution of pneumonia and severe pneumonia (based upon World Health Organization Integrated Management of Childhood Illness classification) presenting to 19 health facilities in Punial and Ishkoman, Northern Areas of Pakistan. September 1, 2001 to December 31, 2002.

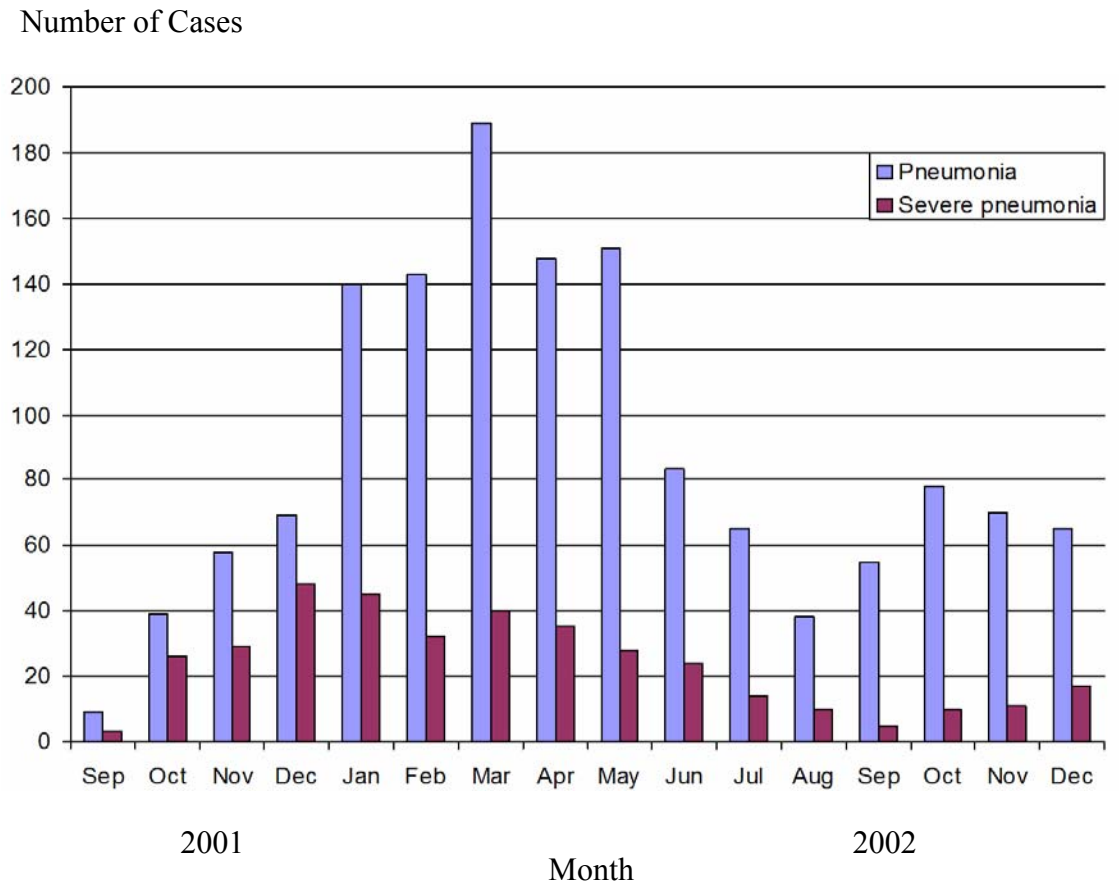

Figure 3. Incidence of pneumonia, severe pneumonia and the two combined (based upon World Health Organization Integrated Management of Childhood Illness classification) among children 2 to 35 months of age, Punial-Ishkoman, Northern Areas of Pakistan. November 1, 2001 to December 31, 2002.

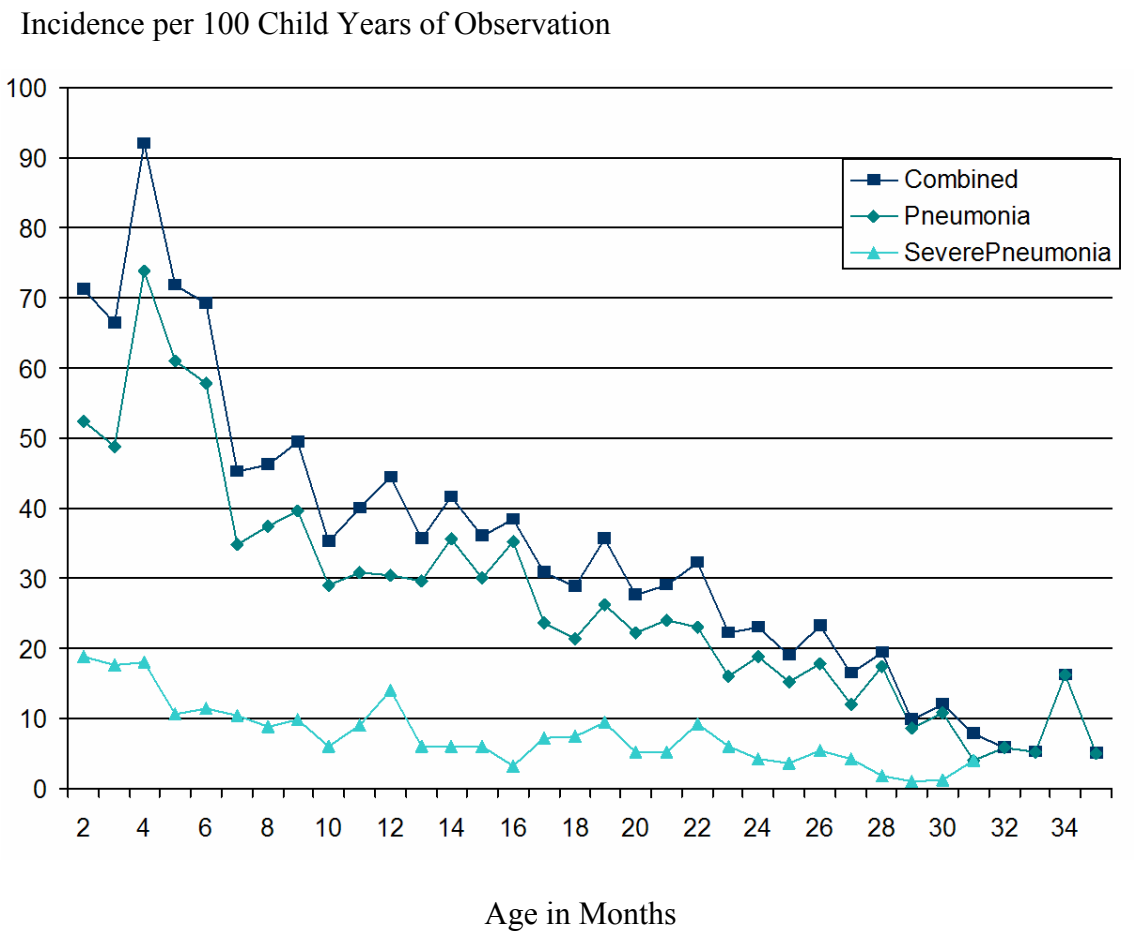

Table 4. Incidence of IMIC-classified pneumonia among children 2-35 months of age identified in Punial and Ishkoman, Northern Areas of Pakistan. November 2001-December 2002.

Age Group	Incidence Rate per 100 Child Years of Observations
Age 2 - <3 months	71.2
Age 3 - <4 months	66.5
Age 4 - <5 months	92.1
Age 5 - <6 months	71.8
Age 6 - <7 months	69.2
Age 7 - <8 months	45.3
Age 8 - <9 months	46.2
Age 9 - <10 months	49.5
Age 10 - <11 months	35.2
Age 11 - <12 months	40.0
Age 12 - <13 months	44.4
Age 13 - <14 months	35.7
Age 14 - <15 months	41.7
Age 15 - <16 months	36.1
Age 16 - <17 months	38.5
Age 17 - <18 months	30.9
Age 18 - <19 months	28.8
Age 19 - <20 months	35.6
Age 20 - <21 months	27.6
Age 21 - <22 months	29.1
Age 22 - <23 months	32.2
Age 23 - <24 months	22.2
Age 24 - <25 months	23.0
Age 25 - <26 months	19.7
Age 26 - <27 months	23.3
Age 27 - <28 months	16.4
Age 28 - <29 months	19.4
Age 29 - <30 months	9.8
Age 30 - <31 months	12.0
Age 31 - <32 months	7.9
Age 32 - <33 months	5.9
Age 33 - <34 months	7.0
Age 34 - <35 months	16.2
Age 35 - <36 months	5.0

Table 5. Pneumonia incidence rate ratios for age, altitude, number of infants in a household, and gender as covariates in a Poisson regression. Punial and Ishkoman, Northern Areas, Pakistan. November 2001 – December 2002.

Covariate	Incidence Rate Ratio [a]	95% Confidence Limits	
		Lower Limit	Upper Limit
Age Group (reference = 24-35 months)	-		
Age 2 - <3 months	**5.20**	3.96	6.84
Age 3 - <4 months	**4.76**	3.63	6.24
Age 4 - <5 months	**6.63**	5.17	8.49
Age 5 - <6 months	**5.18**	3.98	6.73
Age 6 - <7 months	**4.85**	3.70	6.35
Age 7 - <8 months	**3.24**	2.10	3.79
Age 8 - <9 months	**3.27**	2.12	3.77
Age 9 - <10 months	**3.47**	2.24	4.06
Age 10 - <11 months	**2.51**	1.60	2.98
Age 11 - <12 months	**2.85**	1.85	3.37
Age 12 - <13 months	**3.16**	2.04	3.68
Age 13 - <14 months	**2.59**	1.68	3.11
Age 14 - <15 months	**3.03**	1.89	3.44
Age 15 - <16 months	**2.62**	1.65	3.10
Age 16 - <17 months	**2.76**	1.82	3.51
Age 17 - <18 months	**2.19**	1.48	2.92
Age 18 - <19 months	**2.02**	1.33	2.71
Age 19 - <20 months	**2.45**	1.67	3.25
Age 20 - <21 months	**1.97**	1.36	2.70
Age 21 - <22 months	**2.11**	1.47	2.87
Age 22 - <23 months	**2.32**	1.52	3.07
Age 23 - <24 months	**1.62**	1.08	2.32
Altitude range (reference = 5,500-6,499 feet)	-		
Altitude range 6,500-7,499 feet	**1.66**	1.45	1.89
Altitude range 7,500-8,499 feet	1.01	.92	1.30
Altitude above 8,500 feet	**.15**	.07	.32
Children <36 months in household (reference = 0)	-		
1-2 children <36 months in household	1.03	.91	1.17
3 or more children <36 months in household	.90	.40	2.00
Gender (reference = Female)	-		
Male	**1.14**	1.01	1.29

[a] In comparison to reference group; bold font have p-value <0.05

Table 6. A comparison of community acquired pneumonia incidence rates at selected sites. Adapted from Pechere JC. Ed. Community Acquired Pneumonia in Children, 1995.

City/Country	Age Group	Annual Incidence per 100 Child Years of Observations
Seattle[1]	< 5 years	3.0
Bangkok[1]	< 5 years	7.0
Maragna, Kenya[1]	< 5 years	18
Gilgit 1991[1]	< 5 years	30
Punial and Ishkoman 2001-2002[2]	2-35 months	38
Lahore 1987[3]	< 1 year	22
PNG[1]	< 1 year	25
Haryana, India[1]	< 1 year	30-40

[1] Pechere JC. Ed. Community Acquired Pneumonia in Children, 1995
[2] Combined pneumonia and severe pneumonia rates reported in this study
[3] Zaman S, Jalil F, Karlber J, Hanson LA. Early child health in Lahore, Pakistan: VI. Morbidity. Acta Paediatri 1993; Suppl 390:63-78

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Paper 2: Intensive Follow-up Training of Community Health Workers on Pneumonia Recognition and Referral in Children less than 3 years in Pakistan

Aamir J. Khan[1,2], Hamidah F. Hussain[1], Saad Omer[1], Sajida Chaudry[3], Agha Ajmal[4], Nahida Shah[2], Rozina Mistry[5], Imam Yar Baig[5], Larry Moulton[1], Neal A. Halsey[1]

[1] Department of International Health, Johns Hopkins Bloomberg School of Public Health
[2] Center for Health Interventions Research, Gilgit
[3] Preventive Medicine Residency Program, Johns Hopkins Bloomberg School of Public Health
[4] Community Health Sciences Department, Aga Khan University
[5] Aga Khan Health Service, Pakistan

Abstract

Background: Pakistan's National Health Worker Program enlists community health workers (CHWs) to provide primary care services at home. This study was conducted to measure the impact of intensive follow-up training of CHWs on pneumonia recognition and referral.

Methods: Ninety-nine CHWs were offered intensive follow-up training in the use of the World Health Organization Integrated Management of Childhood Illness (IMCI) guidelines every 6 weeks during the course of a 14-month cohort study. CHWs were evaluated by three methods: (1) their results on pre- and post-tests in multiple trainings targeted to address areas of weakness; (2) their assessment and referral of sick children with severe disease in the cohort during two-weekly home visits; (3) the calculated pneumonia incidence rates for children in their coverage area based upon paramedical staff and physician evaluations of children seen at health facilities.

Results: Ninety-seven CHWs attended one or more training sessions (median 5, range 1-7). Significant improvements were reported between the pre- and post-test results of CHW in all 10 tests conducted (paired sample t-test p-value <0.001) over 14 months. Mean post-test scores improved from 76.9% for those who attended 1-3 trainings, to 79.2% for 4-5 sessions, and 89.3% for 6-8 sessions. The correct classification of IMCI general danger signs and appropriate referrals for severe pneumonia among children evaluated during home visits increased from zero to over 80% over 14 months. The pneumonia incidence rates reported in children 2-35 months of age in a CHW's coverage area was 24 per 100 child years of observation

(CYO) for children served by CHWs who had attended 1-3 sessions, 29 per 100 CYO for CHWs who had attended 4-6 sessions, and 38 per 100 CYO for CHWs who had attended 7-8 sessions.

Conclusion: Sequential follow-up training of CHWs in the use of IMCI guidelines resulted in sustained improvements in test performance and disease referral over the course of 14 months. Incorporating these training and evaluation methods should be considered for training of community health workers in all areas. Surveillance using less intensively trained CHWs is likely to lead to an underestimation of the true incidence of pneumonia.

Introduction

The World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI) strategy has been endorsed by the Government of Pakistan as an effective tool to reduce early childhood morbidity and mortality from pneumonia, diarrhea, malnutrition, measles and malaria.[54] The strategy focuses upon 1) health systems development, 2) case management at first-level health care facility, and 3) community and family knowledge and practices. The strategy and plan for the implementation of the third element of IMCI have not been finalized in Pakistan. The government-run National Health Worker Program enlists village-based, community health workers (CHWs) to make monthly household visits and provide primary care services at home. CHWs are trained to screen children for signs and symptoms that require referral and to treat simple illnesses according to WHO guidelines. Sick children are preferentially referred to government health centers.

The purpose of this study was to determine whether intensive follow-up training of government CHWs in the use of IMCI guidelines (Table 7) would result in improved (1) average pre- and post-test scores, (2) detection and appropriate referral of children who have general danger signs or severe pneumonia, and (3) estimates of pneumonia incidence rates.

Methods

Setting

The Punial and Ishkoman valleys of the Northern Areas had an estimated population of 59,000 in 2001.[55] Villages in Punial are situated at altitudes of 5,500-6,499 feet and in Ishkoman between 6,500-9,499 feet. The temperature ranges from

40° C in July to -20° C in January. A household commonly includes more than one generation of married couples sharing a dwelling and kitchen. Farming is the primary means of livelihood.

Village-based organizations and volunteers working with the Aga Khan Development Network (AKDN) have brought about significant improvements in agricultural practices, literacy and health.[56] Areas served by the Aga Khan Health Service Pakistan (AKHSP) primary health care (PHC) program have had reductions in infant mortality rates (IMR) from above 100 per 1,000 live births in the 1988 to below 40 per 1,000 live births in 2000. In comparison, IMR decreased less substantially in other areas in Pakistan (from above 100 per 1,000 to 94 per 1,000 in 2000). Eighty four percent of children served by AKHSP had received all EPI-recommended vaccines by 1 year of age in 2001 in comparison to less than 40% of children by 1 year of age in adjacent, non-AKHSP program areas. Over 60% of infants in AKHSP areas were exclusively breast-fed till 4 months of age compared to less than 30% of children in adjacent areas.[57] However, 22% of infants and 24% of children in the study area 1-4 years of age have grade 1 malnutrition. The Aga Khan Health Service and Government of Pakistan health system in Punial and Ishkoman are described in detail in Paper 1.[58]

Training and Materials

The IMCI training program for first-level health facility-based paramedical staff and physicians involves an 11-day program. However, a standardized IMCI training program has not been developed for CHWs by WHO.[59] IMCI training materials for first-level health facility staff were adapted for CHWs and translated into Urdu by a preventive medicine resident from Johns Hopkins certified as an IMCI

Master Trainer.[60] The four-page booklet developed in collaboration with the Aga Khan Health Service Pakistan (AKHSP) Health Promotion Resource Centre included the modules for "general danger signs" and "cough and difficulty breathing" on page 1, "fever" on page 2, and the "child less than 2 months" on page 3, exactly as outlined in the IMCI training materials for personnel at first-level health facilities. The fourth page included patient management and counseling guidelines, but these were modified to keep them appropriate to the educational level of the CHWs and in accordance with the guidelines of the National Health Worker Program. All of the recommendations made by the national IMCI expert committee during 2000 were incorporated into these training materials. Additional wall charts and manuals in English and Urdu were later procured from the National IMCI Coordinator as they became available and used in the training. IMCI training was simultaneously conducted for paramedical staff and their supervising physician (where present) at 15 first-level health facilities in Punial and Ishkoman. Children referred by CHWs to these facilities were generally managed in accordance with IMCI guidelines, although physicians and paramedical staff were not compelled to do so.

Baseline Training and Enrollment

Beginning in July 2001 onwards, all 99 government CHWs across Punial and Ishkoman were given three-day introductory training at their assigned health center using the IMCI materials developed for them. This was followed by two-weeks of closely supervised home visits to enroll children after consent using surveillance forms. Initial enrollment of children less than 24 months old was completed at all sites by November 2001; ongoing enrollment of newborns continued until December 31, 2002. For details on surveillance methods, see Paper 1.[4]

Follow-up IMCI Training for CHWs

Follow-up training was conducted by an AKHSP community health nurse with extensive experience of training health workers in the Northern Areas, who was also certified as an IMCI Master Trainer. While training was conducted primarily in Urdu, she used two of the local languages (Sheena and Khwar) to translate words or concepts as necessary. Each training session began with a revision of the IMCI booklet developed for CHWs. IMCI modules on diarrhea, sore throat, ear problem and malnutrition and anemia were subsequently added over the course of the year. The program combined classroom work using a mother's card, a photo exercise booklet, wall charts and videos followed by evaluations of sick patients visiting health facilities. Knowledge and evaluation skills covered during training included: assess and classify the sick child age 2 months up to 5 years; determine the need for referral; treat the child if required; counsel the mother; and follow-up at home. Training sessions generally lasted from between 4-6 hours, and CHWs were asked to attend follow-up training every 6 weeks during which they would also be evaluated using pre- and post-tests.

Pre- and Post-tests

At the beginning of each training session, attendees were administered a pre-test to complete independently within 15 minutes and the same test was administered at the end of the training day. Tests were adapted from exercises in the IMCI training materials produced by the Ministry of Health in collaboration with the WHO and UNICEF for facility-based paramedical staff.[61] All tests were conducted in Urdu. Each test evaluated a CHWs comprehension of the general danger signs; the signs, symptoms and classification of pneumonia and severe pneumonia; and appropriate

referral decisions for seriously ill children. Other IMCI classifications that were also routinely covered included Very Severe Febrile Disease, Serious Bacterial Infections and the three categories of measles and its complications. Tests were graded by the AKHSP IMCI Master Trainer. There were between 10-15 questions per test and a maximum of 20 points could be obtained. For smaller groups and those located in difficult to access areas, pre- and post-tests were graded at the end of the training day and reviewed with individual CHWs. For larger groups, CHWs were visited at their homes or their assigned centers within a week of the training. Discussions focused on areas identified as weaknesses in the post-tests. If the same area of weakness was identified for 2 or more members of a training group, it was reviewed again with the whole class during the next follow-up training. The questions varied for pre- and post-test exams by providing different scenarios and decision outcomes to allow the IMCI Master Trainer to target areas of weakness. Pre- and post-test evaluations for follow-up training began in November 2001 after CHWs in all regions of Punial and Ishkoman had completed baseline training and enrollment. Follow-up training and evaluations were conducted every six weeks until December 2002,

Enrollment and Recognition of General Danger Signs and Referral of Sick Children

CHWs enrolled all children in their coverage area under 24 months of age at the beginning of the surveillance project and continued enrollment of newborns until December 2002. Children were followed at home every two weeks and screened using the Home Visit Form. (See Appendix) Sick children were assessed using the Disease Information Form, which required the CHW to identify general danger signs and determine the need for referral. Information was collected using Home Visit Forms and Disease Information Forms between July 25 2001 and August 31 2002, at

which time two-weekly household visits were discontinued because of lack of funding. Home based enrollment of all newborns continued until December 2002.

Pneumonia Incidence Data

Health center staff used IMCI criteria to screen children 2-35 months of age presenting to first-level health facilities for pneumonia or severe pneumonia. Health center staff identified all children with cough or difficulty breathing and one or more of fast breathing, chest indrawing, stridor, or any general danger signs were evaluated. Facility based surveillance for pneumonia was fully established in Punial and Ishkoman by November 3, 2001 and continued until December 2002.

Monitoring

CHWs were visited by the AKHSP IMCI Master Trainer and a data editor every three weeks to review home visit schedules, data forms, IMCI classification of disease and referral practices. A quality management form was used to evaluate each CHWs adherence to home visit schedules. CHWs were also assessed for their comprehension of IMCI guidelines for the recognition of general danger signs and referral of disease.

Data Management

Surveillance forms were optimized for scanning and optical character recognition. TELEform® 6 was used for data capture, Microsoft Access® 2000 for checking data integrity, and SPSS® version 11.5 for data analysis. Information collected at the time of home-based enrollment and on subsequent home visits was linked with the information collected at participating health facilities. If the child's

surveillance number was unavailable, additional information collected at the time of the facility visit permitted us to procure the surveillance identification number at a later date. Pre- and post-test forms were graded by hand and the final score entered into a Microsoft © Excel sheet..

Statistical Methods

The mean difference between pre- and post-test scores at each training was compared using a paired sample t-test. The difference in the means of scores for two groups was compared using a student's t-test. The presence of differences between groups when comparing three or more groups was measured using one-way analysis of variance (ANOVA). To measure the differences in pneumonia incidence rates among children based on a CHW's performance on post-tests, CHWs were categorized into three groups by their mean post-test scores (90% or higher, 80%-89.9% and <80% on their post-tests). The numbers of trainings attended were categorized into three groups (1-3, 4-5 and 6-8). Incidence rates for pneumonia and severe pneumonia were calculated for children in a CHWs coverage area by counting the cases from the area that presented to health facilities as the numerator and summing the total years of observation for all children in the area as the denominator. Altitude was categorized into four groups (5,500-6,499, 6,500-7,499, 7,500-8499, and 8,500 and above) for ease of comparison. CHW ages were categorized into three age groups (15-24, 25-29, 30 and above). Experience in the NHW Program was categorized by the year of recruitment (1994-1996, 1997-1999, 2000-2002).

IRB Approval

This study was approved by the institutional review boards (IRB) at the Johns Hopkins Bloomberg School of Public Health and the Aga Khan University. Written informed consent was obtained from the parents or legal guardians of children enrolled at home or at the time of health facility visits.

Results

CHW Characteristics and Training

The mean age of CHWs was 28 years (range 17-36) and 73 (75%) worked for the National Health Worker Program for 5 or more years. Nine CHWs were single, 86 were married and 2 were widowed. Seventeen CHWs (18%) had no children, 24 (25%) had 1-2, and 56 (57%) had 3 or more children. Forty-nine (51%) lived at between 5,500-6,499 feet, 32 (33%) between 6,500-7,499 feet, 13 (13%) between 7,500-8,499 feet and 3 (3%) at 8,500 feet or above.

Training sessions were conducted at government or AKHSP health centers based upon their accessibility to CHWs. Ninety-seven CHWs attended a median of 5 training sessions (mean 4.7, mode 5, range 1-7) out of the 10 offered during 14 months. Two CHWs out of 99 did not attend any IMCI follow-up sessions following their baseline training. One had completed enrollment of eligible children in her village but was subsequently refused permission by male members of her family to attend training sessions. The second CHW was recruited into the government program in early 2002 but then went on an extended maternity leave.

No significant differences (one-way ANOVA p-value > 0.1) were noted in the mean number of training sessions attended based on the CHW's age marital status, number of children, number of people living in her household, and the household

income per number in household. CHWs living at altitudes above 8,500 feet attended significantly fewer training sessions (mean of 2.3, p-value =0.025) than CHWs living at 5,500-6,499 feet (4.7), 6,500-7,499 feet (4.8) or 7,500-8,499 feet (4.15). CHWs who had been working in the government program for less than 2 years also attended fewer follow-up training sessions (mean of 3.3, p-value< 0.001) than those who were recruited between 1994-1995 (4.8) and 1996-1998 (5.0) . A total of ninety-one training sessions were held over the course of 14 months. The median size of a training group was 7 (range 2-36).

Pre- and Post-test Scores.

Pre-tests scores averaged 72.7% at the first follow-up training, 52.5% at the third training, and 79.0% at the ninth training. The mean post-test scores were 80.9% at the first follow-up training, 70.8% at the third, and 90.9% at the ninth. The pre- and post-test scores for all 10 tests conducted are shown in Figure 4. Significant improvements were reported between the pre- and post-test results of CHW in all 10 tests conducted (paired sample t-test p-value <0.001) over 14 months. Mean post-test scores also improved by the total number of training sessions attended, from 62.7% to 76.9% for those who attended 1-3 sessions, 67.2% to 79.2% for 4-5 sessions, and 78.0% to 89.3% for 6-8 sessions. Mean pre- and post-test scores were significantly lower for those aged 15-24 years (64.2% to 77.5%) in comparison to those aged 25-34 years (69.4% to 81.2%, p-value < 0.05) and 35-44 years (71.4% to 83.5%, p<0.05). The distribution of CHWs and the reported incidence rates for pneumonia and severe pneumonia among enrolled children are shown in Table 8. CHWs living at higher altitudes attained lower pre- and post-test averages than CHWs living at lower altitudes (p-value<0.02) (Table 9). CHWs that had been working in the

government program for less than 2 years prior to the start of surveillance also attained lower mean pre-test (61.1%) and post-test (73.2%) scores than CHWs recruited between 1994-1995 (70.8% and 83.9%) and 1996-1999 (70.9% and 82.7%) into the government program (p-value< 0.02).

Identification and Referral of General Danger Signs and Severe Pneumonia during Home Visits

The correct classification of IMCI general danger signs and severe pneumonia and their appropriate referral increased from below 40% in October of 2001 to over 80% in August 2002. (Figure 5)

Pneumonia Incidence Rates by CHW Coverage Area

The incidence of pneumonia among children living in areas served by CHWs that achieved high mean post-test scores (90% or above) was higher than for children served by CHWs who achieved lower scores (Figure 6). Details of pneumonia incidence rates by altitude are shown in Table 8.

Discussion

Many of the guidelines from the original WHO Acute Respiratory Infections (ARI) Control and Control of Diarrheal Disease Programs were incorporated into the IMCI strategy. The inclusion of these earlier guidelines in the training of government CHWs at the time of entry into the program and during the course of their work provided them the knowledge and skills that helped them to assimilate and implement IMCI guidelines.

CHWs dropped their mean pre- and post-test scores for training D. This was a result of the change from repeated testing focusing on comprehension of general danger signs, pneumonia and severe pneumonia to more complex case scenarios and inclusion of additional IMCI modules such as for diarrheal disease. From training D onwards, CHWs improved and maintained their performance during the course of the follow-up training. However, the duration of these benefits beyond the last training was not measured.

The National Health Worker Program in the Northern Areas of Pakistan can improve CHW performance by providing follow-up training and evaluation at regular intervals. The cost and feasibility of implementing similarly intensive follow-up trainings and supervision of CHWs over a one-year period should be evaluated by the NHW Program managers. Some of the challenges in implementing such a program will include determining strategies to reach the CHWs need the most support. These may include targeting those with shorter duration of work experience or those living in less accessible areas. This intensive training program can also provide other important benefits, including a more accurate assessment of disease burden in the community. In settings where up to 40% of childhood deaths may be attributable to a single IMCI classified illness, the improved accuracy in measuring disease burden can result in better allocation of program resources and the potential for more accurately measuring the impact of new interventions.

Acknowledgements

We would like to thank the following for their field work on this study: Government Community Health Workers from the National Health Worker Program, NHW Program Supervisors, Dispensers and Medical Officers, AKHSP Lady Health Visitors and medical officers; and Hina Rehman, Irum Khan and Jawad Kayani, elective students from the Aga Khan University. We are grateful to the following for their administrative support and guidance: Nazim Somani from AKHSP Northern Areas; Dr. Wazir Khan, the District Health Officer of District Ghizer; Mr. Mehboob Khan, Logisitical Officer for the government National Health Workers Programme in Ghizer; Dr. Zahid Larik from the Primary Health Care Cell at the Ministry of Health; Dr. Syed Jaffar Hussain from the WHO IMCI team in Islamabad; and Dr. Masood Kadir and Dr. Zeba Rasmussen from the Aga Khan University.

Table 7. Diagnostic classification for pneumonia and severe pneumonia based upon the World Health Organization Integrated Management of Childhood Illness (IMCI) strategy for children aged 2-59 months.

IMCI Classification	Clinical Signs
Pneumonia [a]	Cough *or* difficulty breathing (by history) *and* fast breathing [b]
Severe Pneumonia [a]	Cough *or* difficulty breathing (by history) *and* chest in-drawing *or* stridor *or* any general danger sign [c]

[a] Pneumonia and Severe Pneumonia are mutually exclusive classifications under IMCI

[b] ≥50 breaths per minute in a child 2-11 months old or ≥40 breaths per minute in a child 12-59 months old

[c] Defined as the presence of any one or more of the following signs: 1) inability to breastfeed or swallow fluids; 2) persistent vomiting; 3) convulsions; and 4) unconscious or lethargic

Figure 4. Mean pre- and post-test scores achieved by government community health workers trained in the use of World Health Organization Integrated Management of Childhood Illness guidelines over 14 months in Punial and Ishkoman, Northern Areas of Pakistan. November 1, 2001 to December 31, 2002.

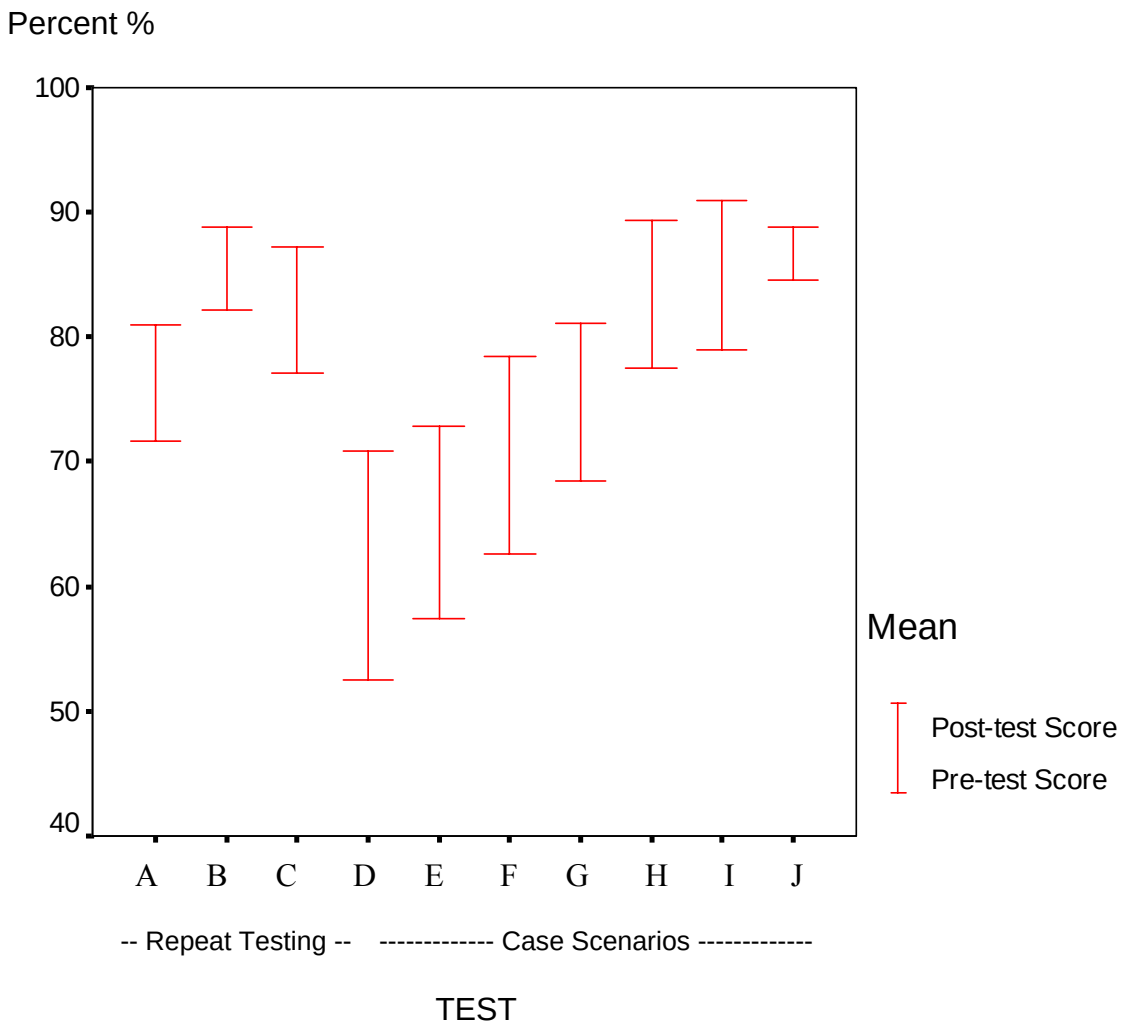


Table 8. Distribution of Government CHWs[1], enrolled children and pneumonia incidence by altitude (in feet), Punial Ishkoman, Northern Areas of Pakistan, November 2001-December 2002.

Punial and Ishkoman	All Altitudes	5,500-6,499 feet	6,500-7,499 feet	7,500-8,499 feet	≥8,500 feet
Government CHWs	99	51	32	13	3
Children 2-35 months of age	5,204	2,656	1,511	817	220
(% of total enrolled)	(100)	(51)	(29)	(16)	(4)
Pneumonia Incidence[2]	29.9	20	40.2	30.5	NA
Severe Pneumonia Incidence[2]	8.1	8.7	8.5	11	18.4

[1] Community Health Workers employed by the government National Health Worker Program. [2] Incidence per 100 child years of observation

Table 9. Distribution of mean pre- and post-test scores achieved in follow-up trainings for Government CHWs by altitude (in feet), Punial Ishkoman, Northern Areas of Pakistan, November 2001-December 2002.

Punial and Ishkoman	All Altitudes	5,500-6,499 feet	6,500-7,499 feet	7,500-8,499 feet	≥8,500 feet
Follow-up Training	Mean Pre-test Score / Mean Post-test Score [Number of CHWs that Attended Training]				
A	72.7 / 80.9 [60]	76.9 / 83.9 [36]	65.7 / 76.9 [22]	72.7 / 75.0 [2]	[0]
B	82.1 / 88.4 [58]	84.5 / 90.9 [39]	78.9 / 86.4 [11]	75.0 / 80.3 [8]	[0]
C	77.2 / 87.2 [37]	82.3 / 90.0 [10]	85.8 / 92.6 [16]	67.1 / 87.5 [8]	40.9 / 48.5 [3]
D	52.5 / 70.8 [54]	48.1 / 71.8 [32]	60.2 / 70.9 [18]	53.3 / 62.5 [4]	[0]
E	58.0 / 72.8 [32]	58.3 / 65.8 [4]	63.2 / 75.5 [17]	50.0 / 71.0 [10]	43.3 / 73.3 [1]
F	63.0 / 78.4 [49]	61.8 / 79.4 [36]	73.3 / 82.2 [9]	43.3 / 53.3 [1]	50.0 / 65.4 [3]
G	68.5 / 81.5 [50]	68.3 / 84.9 [24]	70.0 / 75.4 [18]	65.4 / 84.6 [8]	[0]
H	77.6 / 89.2 [59]	75.7 / 91.0 [28]	80.0 / 87.1 [25]	76.1 / 88.9 [6]	[0]
I	79.0 / 90.9 [43]	81.0 / 91.2 [28]	79.1 / 89.4 [11]	65.0 / 89.2 [4]	[0]
J	84.5 / 88.8 [11]	64.4 / 71.1 [3]	92.8 / 95.0 [6]	90.0 / 96.7 [2]	[0]

[1] Community Health Workers employed by the government National Health Worker Program.

Figure 5. Proportion of children 2-35 months of age with general danger signs and severe pneumonia (based upon World Health Organization Integrated Management of Childhood Illness criteria) correctly classified by government community health workers and appropriately referred to a first-level health facility in Punial and Ishkoman, Northern Areas of Pakistan. August 1, 2001 to August 31, 2002.

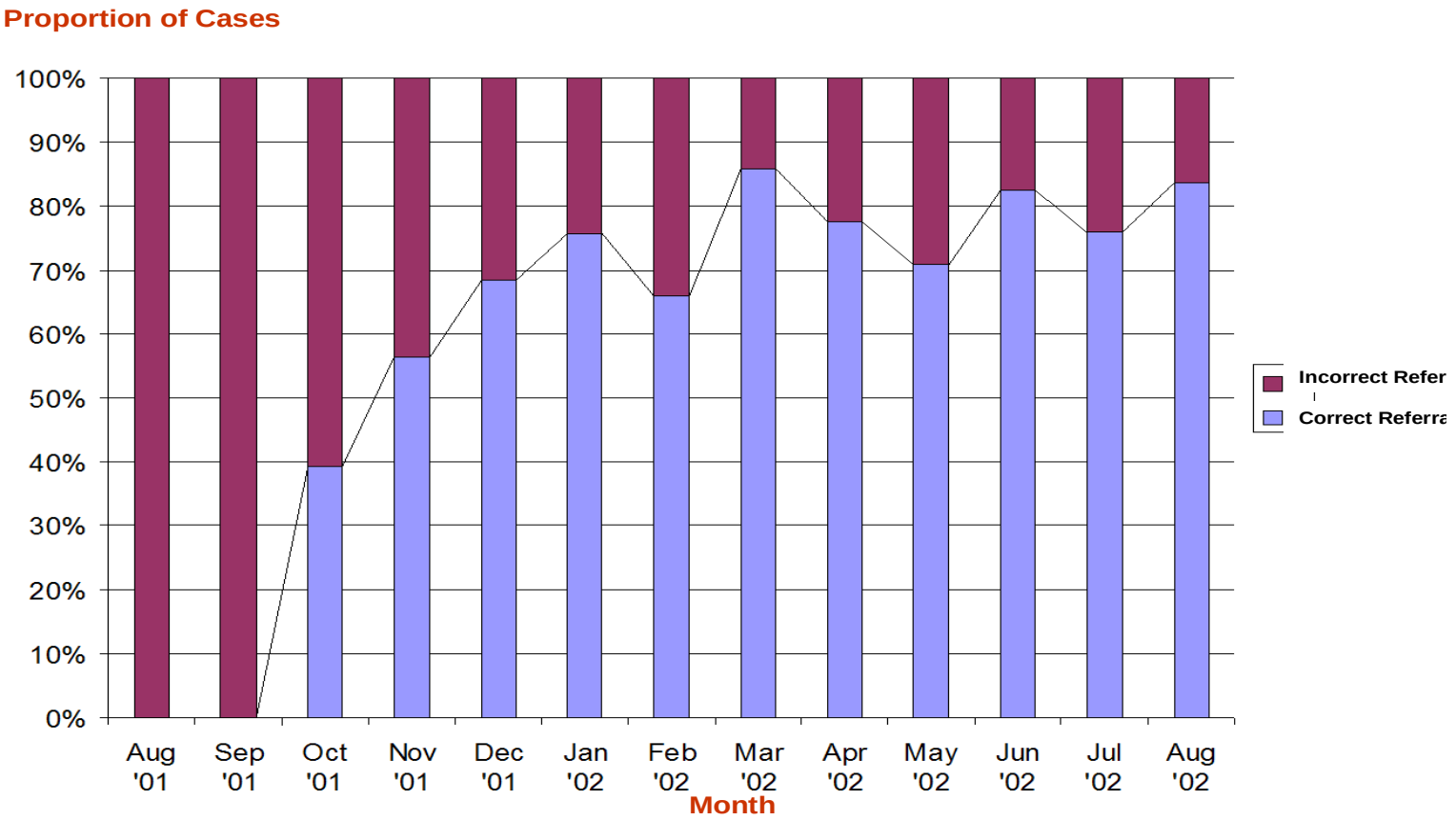
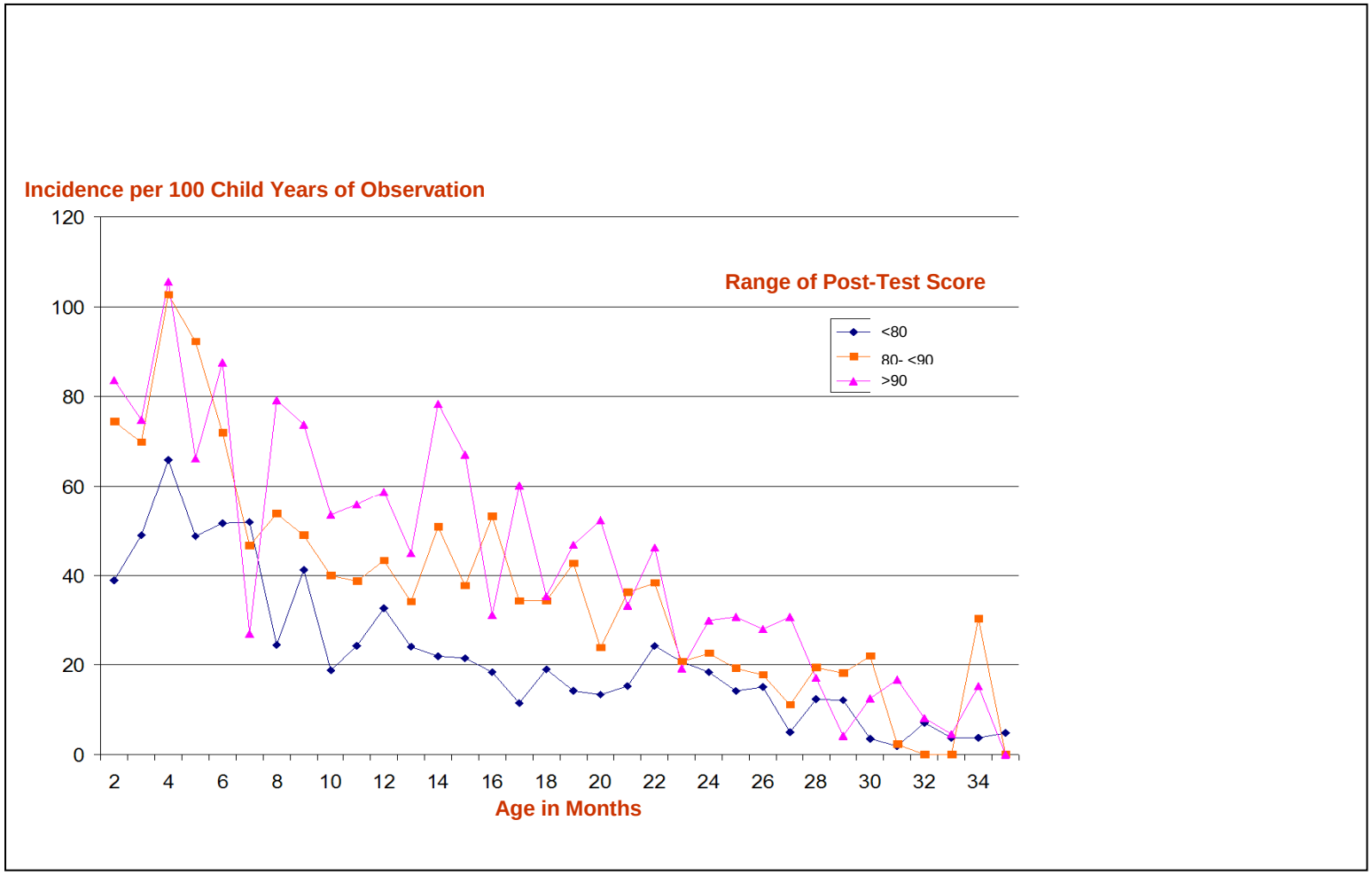


Figure 6. Differences in the incidence of pneumonia (World Health Organization Integrated Management of Childhood Illness classification of pneumonia and severe pneumonia) in children 2-35 months living by the mean score achieved on all post-tests taken by government community health workers in Punial and Ishkoman, Northern Areas of Pakistan. August 1, 2001 to December 31, 2002



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Paper 3: Comparison of health center staff classification of pneumonia based on WHO IMCI criteria with evaluation by pediatricians in an outpatient setting in Gilgit, Pakistan

Aamir Khan[1,2], Saad Omer[1], Hamidah Hussain[1], Azizullah Baig[2], Zafar Fatmi[3], Fauzia Ajmal[3], Sajida Chaudry[4], Imam Yar Baig[5], Rozina Mistry[5], Neal Halsey[1]

[1] Department of International Health, Johns Hopkins Bloomberg School of Public Health
[2] Center for Health Interventions Research, Gilgit
[3] Community Health Sciences Department, Aga Khan University
[4] Preventive Medicine Resident, Johns Hopkins Bloomberg School of Public Health
[5] Aga Khan Health Service, Pakistan

Abstract

Background: World Health Organization Integrated Management of Childhood Illness (IMCI) criteria were used to evaluate ill children living in a Himalayan region of Pakistan. This study assessed health center staff classification of pneumonia using a pediatrician's evaluation as gold standard.

Methods: Two health center staff used IMCI criteria to screen children between 2-35 months of age presenting to a pediatric out-patient department at a government tertiary care facility for pneumonia or severe pneumonia. Children with cough or difficulty breathing and one or more of fast breathing, chest indrawing, stridor, or general danger signs were evaluated by pediatricians whose clinical diagnosis served as the standard reference for comparison.

Results: Health center staff screened 32,213 children presenting to the clinics over a 14-month period. Of the 3,438 children with one or more IMCI criteria, 2,864 (83.3%) were classified as having pneumonia and 453 (13.2%) as having severe pneumonia by the health center staff. Pediatricians diagnosed 3,145 (91.5%) children with pneumonia and 167 (4.9%) with severe pneumonia. The overall agreement between staff and pediatricians was 87.2% for pneumonia (kappa of .427, $p<0.001$) and 89.2% for severe pneumonia (kappa of .358, $p<0.001$). Using the pediatrician's diagnosis as gold standard, staff correctly classified 2,784 (88.5%) of the children with pneumonia and failed to identify 361 (11.5%) of the children with pneumonia. Staff correctly classified 125 (74.9%) of the children with severe pneumonia, and failed to identify 42 (25.1%) of the children with the disease. Of the 453 children

classified as severe pneumonia by staff, 328 (72.4%) were incorrectly assigned the classification.

Conclusion: Health center staff trained in the use of IMCI criteria correctly classified the majority of children with signs or symptoms of pneumonia. However, misclassification of severe disease by staff using IMCI criteria can result in an overestimation of severe disease incidence rates. Consideration should be given to conducting similar evaluations in other populations to determine if adjustments should be made in estimates of disease incidence.

Introduction

The World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI) strategy has been endorsed by the Government of Pakistan as an effective tool to reduce early childhood morbidity and mortality from pneumonia, diarrhea, malnutrition, measles and malaria.[62] The strategy is focused upon 1) health systems development, 2) case management at first-level health care facility, and 3) community and family knowledge and practices. The plans for the implementation of the second element of the IMCI strategy have been finalized by the Ministry of Health but have yet to be implemented.

Training facility-based health workers in the use of IMCI guidelines results in significant improvements in the care provided, including improvements in the correct classification of disease.[63] In the north-western states of Brazil, IMCI trained health workers were twice as likely to check for signs of cough, diarrhea or fever and correctly classify a sick child in comparison to those not trained in IMCI.[64] Similar observations have been made in other countries in the multi-country evaluation (MCE) of the IMCI strategy during the 1990s. In a 1997 evaluation of facility-based government health workers trained in IMCI guidelines in the Western Province of Kenya, the proportion of children who were correctly classified with pneumonia fell from 90% at the end of training to 78% in the 1-3 months post-training period.[65] The study also found that misclassification was more common for more severe diseases, with just 45% of children with severe pneumonia correctly classified at the end of training declining to 32% at 1-3 months post-training.

The classification of pneumonia and other clinical syndromes in IMCI is based upon detection of a few key signs and symptoms.[66] At the Medical Research

Council (MRC) Laboratories in the Gambia, health worker's classification of pneumonia as measured against a pediatrician diagnosis had a sensitivity of 81% and a specificity of 89%, but pneumonia and severe pneumonia were not reported separately in this study.[67] A severe pneumonia classification by health workers who had received one-week training in IMCI guidelines at a rural district hospital in western Uganda had low sensitivity (53%) and high specificity (93%). In a similar evaluation in Tanzania, diseases that were more severe were less likely to be classified correctly (60% for severe pneumonia versus 92% for pneumonia). [68] The Tanzania study conducted the full 11-day IMCI training course for facility-based health workers, at the end of which there were demonstrable improvements in the assessment, classification and treatment of sick children. The sensitivity and specificity of the IMCI criteria have not been reported in a Pakistani setting.

The purpose of this study was to determine the proportion of children with pneumonia or severe pneumonia as diagnosed by a pediatrician that were misclassified by health center staff using IMCI criteria. The study was conducted at the major referral hospital in Gilgit in the Himalayan regions of Pakistan, where pediatricians were available to provide a clinical diagnosis that could serve as a standard for comparison with the diagnosis of health center staff. This study complemented a larger cohort study conducted simultaneously in Punial and Ishkoman valleys, a 2- to 6-hour jeep-ride north-west of Gilgit depending upon the final destination. In that study (see Paper 1), health center staff based at first-level health facilities were trained in the use of IMCI guidelines and conducted pneumonia surveillance between November 2001 and December 2002. Children were enrolled at home by community health workers (see Paper 2) and screened for cough or difficulty breathing and one or more of fast breathing, chest indrawing, stridor, or

general danger signs by health center staff when they presented to participating health center. At the end of surveillance in Punial and Ishkoman, incidence rates for pneumonia were calculated based on the reported number of cases at health centers and months of follow-up. This validation study in Gilgit used pediatricians' clinical diagnosis as a standard against the diagnosis of health center staff to determine whether the reported incidence rates for pneumonia in Punial and Ishkoman required adjustment to correct for possible misclassification.

Methods

Setting

Gilgit is the administrative head quarters of the Northern Areas of Pakistan with an estimated population of 40,000 in 2001.[69] The town is situated within an altitude range of 4,500-5,499 feet and is readily accessible throughout the year by road from Hunza and Nagar valleys in Gilgit district and Punial and Ishkoman valleys in Ghizer district. The temperature ranges from 40° C in July to -5° C in January. While small farms on the periphery of the town provide staple foods for many households, the primary means of livelihood comes from trade and employment in the military, government and private sector.

The Gilgit District Head Quarter (DHQ) Hospital serves as the major referral hospital in the Northern Areas. Established in 1939, the DHQ Hospital is a 214 bed facility with a uniformed military officer as its administrative head. It is relatively well-equipped and funded in comparison to government district hospitals in other provinces. There were three full-time pediatricians serving an out-patient department (OPD) that averaged between 150-200 visits a day and a 20-bed in-patient pediatric

ward. On working days (Monday-Saturday), two pediatricians conducted out-patient clinics between 8 am to 2 pm while the third conducted in-patient rounds.

Patients presenting to the OPD were assigned a number by hospital staff in the waiting room. All patients between 2-35 months of age in the waiting area were screened by health center staff using IMCI criteria for the presence of cough or difficulty breathing and one or more of fast breathing, chest indrawing, stridor, or general danger signs. Written consent was sought from parents or guardians to enroll children who met these criteria. A history and observation based on IMCI assessment guidelines were carried out by the health center staff who assigned an IMCI classification of disease on the study form. (Table 10) The child was referred (with the study form) to one of the pediatricians in the OPD. During our initial discussions at the Gilgit DHQ hospital, the pediatricians had stated their inability to conduct a detailed physical examination and fill a study form given the number of patients they saw during the OPD. Upon their suggestion, a study physician was recruited to sit alongside one of the pediatricians to conduct a physical examination on all children referred by health center staff and to fill the study form and present the findings to the pediatrician. The pediatrician reviewed the findings and made a diagnosis using the IMCI classification of disease for pneumonia or severe pneumonia, which was noted on the study form. All treatment decisions were made by the pediatrician, who wrote out separate prescriptions and advised hospital admission or follow-up visits. The pediatricians in the OPD saw all 32,213 children 2-35 months of age during this 14 month period and referred a small number of patients back to the paramedical staff whom they considered eligible for the study that were missed based on the IMCI criteria. The exact number of such cases were unrecorded, but are believed to be less than 50.

Training and Materials

Training materials in Urdu had been translated by a preventive medicine resident from Johns Hopkins certified as an IMCI Master Trainer working in collaboration with the AKHSP Health Promotion Resource Centre. All of the recommendations made by the national IMCI expert committee during 2000 were incorporated into these training materials. Additional wall charts and manuals in English and Urdu were later procured from the national IMCI coordinator as they became available.

Two health center staff were recruited based on their work experience at first-level health facilities. In Pakistan, a common type of health center staff are women who are traditionally called Lady Health Visitors (LHVs). LHVs have 12 years of schooling and are trained for one year each in nursing and midwifery. AKHSP health centers are staffed by two LHVs trained to diagnose common medical conditions and prescribe medications (including antibiotics) using established WHO IMCI guidelines. Many government health centers also have an LHV posted to them. One of the health center staff on this study was an AKHSP LHV. A second common type of health center staff in Pakistan are men who are traditionally called dispensers. Dispensers may have 12 years of schooling but are not required to do so. They usually receive training with a general physician (GP) as an assistant and their role involves preparing patients for physical exams, dispensing common drugs prescribed by doctors and administering injections. Training occurs on the job and may include running the GP clinic as the principal health care provider while the GP is out. Many dispensers intern with government medical officers in the morning and at private clinics at evenings. The second health center staff on this study was a dispenser at a government health center.

The study physician assigned to support the pediatrician in evaluating patients was the best graduate of his medical school class and had completed an internship at a government hospital. He had also completed a 6 month rotation in a pediatric ward at the Chilas DHQ hospital (two hours from Gilgit) under the supervision of the senior pediatrician who was later reassigned to the Gilgit DHQ hospital and also participated in this study.

Health center staff were trained and evaluated prior to the beginning of surveillance and at regular intervals thereafter using the same training program developed for health center staff in Punial and Ishkoman. This training program was based upon but was not the standard 11-day IMCI training, because the government and AKHSP health center staff could not leave their assigned duties for that long a duration. The training we provided to health center staff in Punial and Ishkoman (and the two health center staff participating in this study) included a two-day classroom review of IMCI criteria in October 2001, with an emphasis on the modules for general dangers signs and cough or difficulty breathing. The Ministry of Health IMCI booklet for assessing, classifying and treating the sick child age 2 month up to 5 years was a key component of this training, with an emphasis on the modules for general danger signs, cough or difficulty breathing and fever. Training also included extensive use of the IMCI photo exercise booklet, wall charts and videos. Training on sick patients visiting health facilities was supervised by the IMCI Master Trainer from AKHSP and study coordinators.

In Punial and Ishkoman, training was followed by visits every three weeks conducted by a study physician to the health centers to review the use of IMCI guidelines with individual health staff. Each visit involved reviewing IMCI charts and evaluation of patients present at the time. The study physician visits continued

until December 2002. A seperate study physician and three pediatricians at the Gilgit DHQ hospital were trained once just prior to the beginning of surveillance, and then 6 months later. The senior pediatrician was the coordinator for the National Acute Respiratory Infections (ARI) Control Program for the Northern Areas and the two other pediatricians had received multiple trainings under this program.

A provision had been made to report findings on chest radiographs but a policy was implemented at the DHQ a few months prior to the start of this study prevented the administration from charging chest radiograph costs to patients, resulting in the inability of the radiology unit to generate funds for the purchase of films and chemicals. The limited supplies that could be procured within the DHQ budget were restricted for use to patients with trauma or other surgical emergencies.

Statistical Methods

The classification of pneumonia and severe pneumonia by health center staff and pediatricians were cross-tabulated to determine: the proportion of children they agreed upon (overall agreement and kappa statisitic); the number of children missed by the health center staff using the pediatricians diagnosis as reference; and the number of children incorrectly identified as having the disease by health center staff. Adjustments in disease incidence rates were made by adding the number of children missed and subtracting the number of children incorrectly identified as having the disease to the numerator. Forms used at the site were optimized for scanning and optical character recognition. TELEform® 6 was used for data capture, Microsoft Access® 2000 for checking data integrity and SPSS® version 11.5 for data analysis.

IRB Approvals

This study was approved by the institutional review boards (IRB) at the Johns Hopkins Bloomberg School of Public Health and the Aga Khan University. Written informed consent was obtained from parents or legal guardians prior to enrollment.

Results

A total of 59,654 children presented to the Gilgit DHQ Hospital OPD between November 1, 2001 and December 31, 2002. Health center staff screened 32,213 children between 2-35 months of age and identified 3,438 children with cough or difficulty breathing along with any one of fast breathing, chest indrawing, stridor, or any general danger sign. Information on these 3,438 children and the signs and symptoms reported by the physician at Gilgit DHQ Hospital are presented in Table 11.

Health center staff screened 32,213 children presenting to the clinics over a 14-month period. Of the 3,438 children with one or more IMCI criteria, 2,864 (83.3%) were classified as having pneumonia and 453 (13.2%) as having severe pneumonia by the health center staff (Table 12). Pediatricians diagnosed 3,145 (91.5%) children with pneumonia and 167 (4.9%) with severe pneumonia. The overall agreement between staff and pediatricians was 87.2% for pneumonia (kappa of .427, $p<0.001$) and 89.2% for severe pneumonia (kappa of .358, $p<0.001$).

Using the pediatrician's diagnosis as reference, health center staff correctly classified 2,784 (88.5%) of the children with pneumonia and failed to identify 361 (11.5%) of the children with pneumonia. Of the 2,864 children classified with pneumonia by health center staff, 80 (2.8%) were incorrectly assigned the

classification. Similar comparisons for key IMCI signs and symptoms for pneumonia and general danger signs are presented in Table 12.

Examined by age, the proportion of children with pneumonia missed by health center staff was 10.3% among children 2-11 months of age, 11.4% in those 12-23 months and 15.7% in those 24-35 months (Table 13). The proportion of children that were incorrectly labeled as having pneumonia by health center staff was 2.2-3.1% in each of these age categories. The proportion of children with severe pneumonia that was missed was 21.4% among children 2-11 months of age, 37.9% for those 12-23 months and 28.6% for those 23-35 months (Table 14). The proportion of children that were incorrectly labeled as severe pneumonia when they did not have severe pneumonia was 62.9% for those 2-11 months, 85.9% for those 12-23 months and 80.5% for those 24-35 months.

The mean age of children with pneumonia was similar (t-test p-value >0.05) between Gilgit DHQ Hospital (13.2 months) and the health centers in Punial and Ishkoman (12.1 months) (Table 11). The mean age of children with severe pneumonia was also similar (t-test p-value >0.05) between the Gilgit DHQ Hospital (10.4 months) and the health centers in Punial and Ishkoman (11.7 months). A larger proportion of children at the Gilgit DHQ Hospital were male (63% versus 53% for the entire population) and fewer were accompanied by their mothers (58% versus 90% respectively). Children with pneumonia in Gilgit had more signs and symptoms for longer average durations and had higher antibiotic usage (36% versus 8%) than children presenting to health centers in Punial and Ishkoman.

Assuming the pediatrician assessment rates are the correct diagnoses and that the rates of over and under-diagnoses for health center staff were similar throughout the area, the incidence rates for pneumonia should be adjusted from the observed

29.9 per 100 CYO to 32.5 per 100 CYO (Table 13). The incidence rates for severe pneumonia should be adjusted from 8.1 per 100 CYO to 4.3 per 100 CYO (Table 14).

Discussion

Training facility-based health workers in the use of IMCI guidelines results in significant improvements in the care provided, including improvements in the correct classification of disease. The over-classification of severe disease found in this study is expected when using IMCI criteria, as these were designed to minimize the risk of not referring children who might have severe disease to a higher level health facility. Health center staff in this study did not receive the standard 11-day IMCI training, but did receive much more critical review and training on site every three weeks over one year. Given the limitations placed by program managers from the government and AKHSP, the 11-day standard IMCI course was not feasible.

Fast breathing was common in the 3,438 children identified through screening, and was very rarely missed or mistakenly assigned to children who did not have it. Because fast breathing can be objectively assessed by counting respiratory rates and using defined cut-off points, the use of this IMCI criterion results in high agreement between health center staff classification and pediatricians for identifying pneumonia. Chest indrawing was uncommon in the 3,438 children identified and was less frequently missed or mistakenly assigned than stridor or the two more subjectively assessed general danger signs of convulsions and 'lethargic or unconscious'. The general danger signs are important for increasing the sensitivity of IMCI criteria to detect severe disease but they also lead to an over-classification of disease. Their inclusion in the IMCI classification of severe disease needs to be

reviewed if these criteria are to be used in disease surveillance as well as for determine the impact of the IMCI strategy on specific illnesses.

As children in Punial and Ishkoman were more likely to present with their mothers, who were probably better historians of illness than other caretakers. As children in Punial and Ishkoman were more likely to have acute illness and less likely to have co-morbidity, health center staff with the same level of experience and training may have found it less difficult to accurately classify sick children there than at the Gilgit DHQ Hospital.

An important limitation regarding the adjustment of incidence rates is that the disease classifications made by health center staff in Punial and Ishkoman were not compared against a reference standard, and were verifiable only by an internal consistency check based on IMCI criteria. Even if certain signs and symptoms were incorrectly identified by paramedical staff, an internally consistent and correct IMCI classification could still be made.

While an attempt was made to select health center staff representative of those conducting surveillance in Punial and Ishkoman, there will be differences in training and experience between them that we can not account for completely. There were also differences in the level of supervision, with health center staff working on this study in Gilgit monitored on a daily basis whereas those in Punial and Ishkoman were visited once every two weeks. The presence of a pediatrician is likely to have resulted in quicker and perhaps more sustained skills development among health center staff at Gilgit than for staff that were relatively less frequently supervised in Punial and Ishkoman.

Another potential limitation is that the cohort surveillance site in Punial and Ishkoman spans an altitude range between 5,500-9,499 feet whereas Gilgit town is

located between 4,500-5,499 feet. Although 51% of children enrolled in the Punial and Ishkoman cohort lived within an altitude of 5,500-6-499 feet, those residing at higher altitudes may have had higher baseline respiratory rates relative to children at lower altitudes, with the potential for over-classification of pneumonia based on fast breathing.

If we assume that the rates of over and under-diagnosis are similar for health center staff throughout the study area, the results from this study can be used to adjust the estimated incidence rates of disease collected by similarly trained health center staff at first-level health facilities in Punial and Ishkoman. The adjustment in the incidence rate of pneumonia is minor because of the high degree of agreement between health center staff and pediatrician in using respiratory rate cut-offs for fast breathing. The adjustment in the incidence rate for severe pneumonia following adjustment is large, decreasing by almost half for children 2-35 months of age.

Misclassification of disease by health workers using IMCI criteria can result in considerable overestimation of severe pneumonia and this should be taken into consideration when reporting incidence data. While this is an important safeguard within the IMCI strategy to identify and refer all children with severe disease, it is important to adjust for this misclassification when reporting incidence data in the Northern Areas. Similar studies in other programs will provide a useful assessment of the degree of misclassification in outcomes and may indicate a similar need for adjustments in disease incidence rates.

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Table 10. Diagnostic classification for pneumonia and severe pneumonia based upon the World Health Organization Integrated Management of Childhood Illness (IMCI) strategy for children aged 2-59 months.

IMCI Classification	Clinical Signs
Pneumonia [a]	Cough *or* difficulty breathing (by history) *and* fast breathing [b]
Severe Pneumonia [a]	Cough *or* difficulty breathing (by history) *and* chest indrawing *or* stridor *or* any general danger sign [c]

[a] Pneumonia and Severe Pneumonia are mutually exclusive classifications under IMCI

[b] ≥50 breaths per minute in a child 2-11 months old or ≥40 breaths per minute in a child 12-59 months old

[c] Defined as the presence of any one or more of the following signs: 1) inability to breastfeed or swallow fluids; 2) persistent vomiting; 3) convulsions; and 4) unconscious or lethargic

Table 11. Characteristics of children (aged 2-35 months) with pneumonia or severe pneumonia, Gilgit District Head Quarter Hospital, Northern Areas, Pakistan. November 2001-December 2002

	Pneumonia (n=3,145)	Severe Pneumonia (n=167)
Parental History	*n(%) or M (SD)*	*n(%) or M (SD)*
Mother is information provider	1,818 (58%)	97 (58%)
Mean age of children in months	13.2 (8.6)	10.4 (8.4)
Male sex of the child	1,986 (63%)	110 (66%)
Antibiotic received within 7 days prior to visit	1,132 (36%)	103 (62%)
Co-trimoxazole	294 (9%)	12 (7%)
Amoxicillin	674 (21%)	57 (34%)
Others	206 (7%)	48 (29%)
Child is able to breast feed or drink	3,145	118 (71%)
Child vomits everything	0	47 (28%)
Mean number of days	-	5.2 (13.5)
Child had convulsions	0	12 (7%)
Mean number of days	-	2.2 (1.9)
Child has a cough	3,112 (99%)	165 (99%)
Mean number of days	2.9 (2.5)	3.3 (2.8)
Child has difficulty breathing	1,879 (60%)	108 (65%)
Mean number of days	6.1 (7.9)	10.6 (16.4)
Child has fever	3,105 (99%)	164 (98%)
Mean number of days	5.1 (7.4)	6.6 (10.8)
If fever >7 days, present every day	311 (10%)	35 (21%)
Child has diarrhea	686 (22%)	35 (21%)
Mean number of days	4.2 (9.6)	3.1 (6.0)
Observation	*n(%)*	*n(%)*
Lethargic/Unconscious	0	40 (24%)
Febrile > 37.5 C	515 (16%)	75 (45%)
Fast breathing	3,145	162 (97%)
Chest indrawing	0	143 (86%)
Stridor	0	12 (7%)
Stiff neck	0	2 (1%)

Table 12. Evaluation of 3,438 children aged 2-35 months who had cough or difficulty breathing and any one or more of fast breathing, chest indrawing, stridor or any general danger signs by health center staff and physician, Gilgit District Head Quarter Hospital, Northern Areas, Pakistan, November 2001-December 2002

		Pediatrician's Clinical Evaluation			
Signs and Symptoms or Classification	Health Center Staff IMCI Evaluation	Pediatrician's Clinical Diagnosis	Health Center Staff Correctly Identified (True Positives)[a]	Health Center Staff Missed (False Negatives)[a]	Health Center Staff Incorrectly Labeled Those That Do Not Have Disease (False Positives)[a]
Fast breathing	3,278 (95%)[b]	3,292 (96%)[b]	3,262 (99.5%)[c]	30 (0.9%)[c]	16 (0.5%)[d]
Chest indrawing	173 (5.0%)	166 (4.8%)	157 (90.8%)	9 (5.4%)	16 (9.2%)
Stridor	29 (0.8%)	26 (0.8%)	18 (69.1%)	8 (30.8%)	11 (37.9%)
Convulsions	74 (2.2%)	12 (0.3%)	10 (83.3%)	2 (16.7%)	64 (86.5%)
Lethargic or unconscious	219 (6.4%)	99 (2.9%)	78 (78.8%)	21 (21.2%)	141 (64.4%)
Pneumonia	2,864 (83.3%)	3,145 (91.5%)	2,784 (88.5)	361 (11.5%)[c]	80 (2.8%)[d]
Severe pneumonia	453 (13.2%)	167 (4.9%)	125 (74.9%)	42 (25.1%)	328 (72.4%)

[a] Measured using pediatricians' clinical evaluations as standard [b] Percent of 3,438 children evaluated [c] Percent of pediatrician evaluation or diagnosis [d] Percent of health center staff evaluation or classification

Table 13. Proposed adjustment of incidence rates for pneumonia in Punial and Ishkoman based upon health center staff misclassification of pneumonia at the Gilgit DHQ Hospital, Northern Areas of Pakistan. November 2001-December 2002.

	Gilgit DHQ Hospital					Punial and Ishkoman	
Age in months	Number of Children Enrolled[a]	Pediatrician Diagnosis of Pneumonia	Health Center Staff Classification of Pneumonia	Health Center Staff False Negatives[b]	Health Center Staff False Positives[b]	Reported Incidence Rate per 100 CYO[c]	Adjusted Incidence Rate per 100 CYO[c]
2-3	439	364 (83%)[d]	339 (77%)[d]	39 (11%)[e]	14 (4%)[f]	50.6	53.9
4-5	455	418 (92%)	391 (86%)	31 (7%)	4 (1%)	67.5	71.8
6-7	415	375 (90%)	350 (84%)	39 (10%)	14 (4%)	46.3	49.3
8-9	292	264 (90%)	238 (82%)	34 (13%)	8 (3%)	38.5	42.2
10-11	258	244 (95%)	223 (86%)	29 (12%)	8 (4%)	30	32.5
12-13	280	266 (95%)	240 (86%)	31 (12%)	5 (2%)	30	32.9
14-15	194	182 (94%)	162 (84%)	24 (13%)	4 (2%)	32.85	36.4
16-17	176	165 (94%)	148 (84%)	20(12%)	3 (2%)	29.5	32.5
18-19	170	158 (93%)	149 (88%)	14 (9%)	5 (3%)	23.85	25.2
20-21	104	97 (93%)	93 (89%)	10 (10%)	6 (6%)	23.15	24.0
22-23	154	146 (95%)	129 (84%)	17 (12%)	0	19.55	21.8
24-25	183	173 (95%)	150 (82%)	27 (16%)	4 (3%)	17.05	19.3
26-27	71	64 (90%)	53 (75%)	14 (22%)	3 (6%)	15	17.4
28-29	64	60 (94%)	51 (80%)	9 (15%)	0	13.1	15.1
30-31	73	66 (90%)	58 (79%)	9 (14%)	1 (2%)	7.4	8.3
32-33	63	58 (92%)	48 (76%)	10 (17%)	0	5.55	6.5
34-35	47	45 (96%)	42 (89%)	4 (9%)	1 (2%)	10.6	11.3
All ages	3,438	3,145 (91%)	2,864 (83%)	361 (11%)	80 (3%)	29.9	32.5

[a] 3,438 children from 32,213 screened who had cough or difficulty breathing with any of the following: fast breathing, stridor, chest indrawing or any general danger sign [b] Measured using pediatricians' diagnosis as reference standard [c] Child Years of Observation [d] Percent of total children enrolled [e] Percent of pneumonia diagnosed by pediatricians [f] Percent of pneumonia classified by health center staff

Table 14. Proposed adjustment of incidence rates for severe pneumonia in Punial and Ishkoman based upon paramedical misclassification of severe pneumonia at the Gilgit DHQ Hospital, Northern Areas of Pakistan. November 2001-December 2002.

	Gilgit DHQ Hospital					Punial and Ishkoman	
Age in months	Number of Children Enrolled[a]	Pediatricians' Diagnosis of Severe Pneumonia	Health Center Staff Classification of Severe Pneumonia	Health Center Staff False Negatives[b]	Health Center Staff False Positives[b]	Reported Incidence Rate per 100 CYO[c]	Adjusted Incidence Rate per 100 CYO[c]
2-3	439	42 (10%)[d]	66 (15%)[d]	10 (24%)[d]	34 (52%)[d]	18.25	13.2
4-5	455	23 (5%)	53 (12%)	0	30 (57%)	14.4	6.2
6-7	415	29 (7%)	53 (13%)	8 (28%)	32 (60%)	10.95	7.4
8-9	292	18 (6%)	46 (16%)	4 (22%)	32 (70%)	9.4	4.9
10-11	258	5 (2%)	30 (12%)	3 (60%)	28 (93%)	7.6	5.1
12-13	280	5 (2%)	31 (11%)	2 (40%)	28 (90%)	10	5.0
14-15	194	7 (4%)	30 (15%)	1 (14%)	24 (80%)	6.05	2.1
16-17	176	7 (4%)	24 (14%)	3 (43%)	20 (83%)	5.2	3.1
18-19	170	5 (3%)	12 (7%)	3 (60%)	10 (83%)	8.4	6.4
20-21	104	2 (2%)	10 (10%)	2 (100%)	10 (100%)	5.25	5.3
22-23	154	3 (2%)	21 (14%)	0	18 (86%)	7.65	1.1
24-25	183	6 (3%)	27 (15%)	3 (50%)	24 (89%)	3.9	2.4
26-27	71	6 (3%)	14 (20%)	2 (33%)	10 (71%)	4.85	3.0
28-29	64	2 (3%)	11 (17%)	0	9 (82%)	1.5	0.3
30-31	73	4 (5%)	10 (14%)	1 (25%)	7 (70%)	2.6	1.4
32-33	63	3 (5%)	13 (21%)	0	3 (23%)	0	NA
34-35	47	0	2 (4%)	0	2 (100%)	0	NA
All ages	3,438	167 (5%)	453 (13%)	42 (25%)	328 (72%)	8.1	4.3

[a] 3,438 children from 32,213 screened who had cough or difficulty breathing with any of the following: fast breathing, stridor, chest indrawing or any general danger sign [b] Measured using pediatricians' diagnosis as reference standard [c] Child Years of Observation [d] Percent of total children enrolled [e] Percent of pneumonia diagnosed by pediatricians [f] Percent of pneumonia classified by health center staff

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Conclusion

Key Findings

The incidence rates for pneumonia and severe pneumonia were 29.9 and 8.1 per 100 child years of observation (CYO), respectively. Younger age and altitude were associated with higher incidence rates of pneumonia and severe pneumonia. Further studies are needed to determine the etiology of the high burden of disease from pneumonia in these communities and consideration should be given to 'probe' trials using pneumococcal and *Haemophilus influenzae* type b conjugate vaccines.

Sequential follow-up training of CHWs in the use of IMCI guidelines resulted in sustained improvements in test performance and disease referral over the course of 14 months. Incorporating these training and evaluation methods should be considered for training of community health workers in all areas. Surveillance using less intensively trained CHWs is likely to lead to an underestimation of the true incidence of pneumonia.

Health center staff trained in the use of IMCI criteria correctly classified the majority of children with signs or symptoms of pneumonia. However, misclassification of disease by health workers using IMCI criteria can result in considerable overestimation of severe pneumonia and this should be taken into consideration when reporting incidence data.

Future Research: the Case for Probe Trials in the Northern Areas of Pakistan

The epidemiology of invasive *Streptococcus pneumoniae* (SPn) and *Haemophilus influenzae* type b (Hib) disease reported in young Pakistani children with acute lower respiratory tract infections (ALRI) is unlike that seen in other countries, including neighboring India. Two studies conducted in the late 1980's in Islamabad and Rawalpindi demonstrated an extremely high burden of invasive bacterial pneumonia. Ghafoor and colleagues isolated SPn from 132 (10%) and *Haemophilus* species from 144 (11%) of 1,331 blood specimens collected from children under 5 of years of age in a mixed population of hospital inpatients and out-patients with ALRI.[70] A higher than expected proportion of the *Haemophilus* isolates characterized were non-typeable *Haemophilus influenzae* (36%); the remaining (64%) were due to Hib.[71] Mastro and colleagues enrolled 601 children 2-59 months old who presented with ALRI to two hospitals in Rawalpindi during a six month period between October 1989 and April 1990. [72] SPn was isolated from 108 (18%) and *Haemophilus* species from 100 (17%) blood culture specimens. Only 3 (3%) of the 89 *Haemophilus* isolates subsequently characterized were Hib, the remainder being non-typeable (92%) or other typeable (5%) *Haemophilus influenzae.* Blood cultures remain a highly specific but insensitive tool in ascertaining the etiology of community acquired bacterial pneumonia.[73] Non-bacteremic pneumonia is a major disease worldwide but proving its etiology is even more difficult and costly.[74]

Consideration must be given to 'probe' trials using SPn and Hib conjugate vaccines in the Northern Areas. Efforts are now underway to develop a site in Karachi for a potential pneumococcal conjugate vaccine trial possibly beginning in 2007 or 2008. In light of this new development in Karachi, the Northern Areas remains a strong candidate

site for the conduct of a Hib conjugate vaccine trial in Pakistan. Given the information available from Pakistan and the challenges of determining the etiologic agent in non-bacteremic pneumonia, a well designed and properly conducted individually randomized trial to measure the efficacy of the Hib conjugate vaccine on the rates of radiologically defined pneumonia with lobar consolidation will add considerably to our understanding of Hib disease in Pakistan.

The section that follows is a detailed literature review of the burden of Hib disease, the Hib conjugate vaccine and the results of Hib vaccine randomized control trials. Two key aspects of a Hib vaccine trial proposed for the Northern Areas of Pakistan are described in the appendix. The first is a statement of the study objectives and hypothesis. The second is the study design and methods, including a description of vaccine and control groups, outcome measures, eligibility criteria, selection of sites, unit of analysis, study power calculations, double blinding, enrollment procedures, and data analysis plan.

Burden of *Haemophilus Influenzae* type b (Hib) Disease

Haemophilus influenzae type b (Hib) infections are estimated to cause 3 million episodes of serious illness and between 400,000-700,000 deaths per year worldwide, the majority of which occur during the first two years of life.[75] In an extensive review of the literature available from Asian countries, Peltola has estimated an average incidence of 25 per 100,000 per year for Hib meningitis and of 40 per 100,000 per year for invasive Hib disease (including bacteremic pneumonia) in children less than 5 years old in Asia.[76] The incidence of the less-well described burden of non-bacteremic Hib pneumonia has

been conservatively estimated to be five-fold greater than that of the incidence of Hib meningitis around the world.[77]

Controversy still surrounds the burden of Hib disease in some Asian countries.[78,79] The evidence cited against a high burden of childhood Hib disease in Asia is based upon studies from South and Southeast Asia that did not find Hib to be a common cause of meningitis or pneumonia among children admitted to hospital.[80,81,82,83,84,85] A 1993 report from India found no Hib in 135 CSF cultures from children with meningitis.[86] The incidence of Hib meningitis among children under 5 years of age in Hong Kong has been reported to be less than 2 per 100,000 per year, a figure substantially lower than the reported rate among the same age group in many industrialized nations in the pre-vaccination era (e.g. 60 per 100,000 per year in the United States).[11] The low estimates of invasive Hib disease in some Asian countries are believed to be attributable to a combination of poor reporting, indiscriminate use of antibiotics, infrequent use of blood and cerebro-spinal fluid (CSF) cultures, inadequate laboratory diagnosis, and the low rates of bacteremia in Hib pneumonia.[2,87] A different explanation for these low disease incidence rates have been proposed by Puliyel et al.[88] Based on reports of high levels of antibodies to Hib polyribosylribitol phosphate (anti-PRP) in young infants prior to vaccination, Puliyel raises the possibility that these may reflect cross-reactive antibodies to other common infections in early infancy that provide cross-protection against invasive Hib disease. This opinion conflicts with the results of a prospective, multi-center study conducted by the Invasive Bacterial Infections Surveillance (IBIS) Group in 6 Indian cities between 1993 and 1997 that found Hib to be the most frequent cause of bacterial meningitis in children less than 5 years of age.[89] Almost 70% of all invasive Hib disease

identified and a quarter of all meningitis reported in children less than 5 years age occurred in infants, peaking between 6 to 9 months of age.

Burden of Hib Disease in Pakistan

Two studies conducted in the late 1980's in Islamabad and Rawalpindi demonstrated a substantial burden of *Haemophilus influenzae* disease among children with acute lower respiratory tract infections (ALRI).[90,91] Ghafoor and colleagues isolated *Haemophilus* species from 144 (11%) of 1,331 blood specimens collected from children under 5 of years of age in a mixed population of hospital inpatients and out-patients. (Table 15). A higher than expected proportion of the isolates characterized were non-typeable *Haemophilus influenzae* (36%); the remaining (64%) were due to Hib.[92] Mastro and colleagues enrolled 601 children 2-59 months old who presented with ALRI to two hospitals in Rawalpindi during a six month period between October 1989 and April 1990.[3] *Haemophilus* species were isolated from the blood of 100 (17%) children and only 3 (3%) of the 89 isolates subsequently characterized were Hib, the remainder being non-typeable (92%) or other typable (5%) *Haemophilus influenzae.* The large proportion of non-typeable *Haemophilus influenzae* is unlike that reported in other countries in the region where over 95% of the *Haemophilus influenzae* isolates from blood and CSF were type b, but non-typeables exceeding 30% of all *Haemophilus influenzae* isolates have been reported in Papua New Guinea and The Gambia (Table 16).[15,93,94] Qazi et al conducted a clinical trial during the early 1990s in Islamabad to measure the effect of dexamethasone therapy on children with suspected bacterial meningitis that showed 20 (22%) of 89 patients had *Haemophilus influenzae* infection (capsular types not specified),

indicating that a considerable burden of meningitis was attributable to *Haemophilus influenzae* (regardless of the serotype).[95]

Hib Conjugate Vaccines

The pure polysaccharide Hib vaccines that became available in the 1970s afforded variable protection to children older than 18 months of age and were neither immunogenic nor efficacious in younger children.[96] The capacity to mount protective immune responses to T cell-independent antigens is not usually developed until the second year of life, severely limiting the effectiveness of polysaccharide vaccines in controlling invasive Hib disease. The process of conjugating the polyribosylribitol phosphate (PRP) to a protein carrier, however, markedly improves the immunogenicity of the polysaccharide antigen in children less than 18 months, converting a T-cell independent immune response to a T-cell dependent one.[97,98] Four such Hib conjugate vaccines have become available since the late 1980s, differing from each other primarily in the use of protein carriers, but also in the way the protein carrier is linked to the polysaccharide and the size of the polysaccharide molecule.[99]

The first of these new Hib vaccines to become available was that of PRP conjugated to diphtheria toxoid (PRP-D). Both the efficacy and immunogenicity of this vaccine have been found to be less than optimal in some populations (Table 17), see following section) and it is currently not licensed for use in the primary series for infants in the US. Different vaccine companies also conjugated PRP to a modified diphtheria protein (PRP-CRM_{197}, also known as HbOC), to outer membrane protein complex of group B meningococcus (PRP-OMP), and to tetanus toxoid (PRP-T). All three of these

conjugate vaccines have been licensed for use in the primary series for infants and are administered simultaneously with DTaP (2, 4 and 6 months) in the US.

Hib Conjugate Vaccine Efficacy Trials in Industrialized Countries

Four Hib conjugate vaccine efficacy trials were carried out in Finland and the US during the late 1980s and their results were published within a short span of seven months (Table 17). The first two trials (published simultaneously) were both of the polyribosylribitol phosphate-diphtheria toxoid (PRP-D) conjugate vaccine. The Finnish trial in 114,000 infants demonstrated an efficacy of 94% (95% Confidence Interval, 83-98%) against invasive Hib disease, while the trial in 2,102 native Alaskan infants showed an efficacy of only 35% (95 CI, -57-73%).[100,101] The results from a trial of Hib oligosaccharide conjugate vaccine (HbOC, also known as PRP-CRM_{197}) in a heterogeneous population of 61,080 infants in California showed an efficacy of 100% (95% CI, 68-100%) against invasive Hib disease.[102] A Hib polysaccharide-*Neisseria meningitidis* outer-membrane protein (PRP-OMP) conjugate trial in 5,190 Native American infants demonstrated 93% efficacy (95% CI, 53-98%) against invasive disease.[103] A fifth trial conducted in the United Kingdom (published in 1994) enrolled 27,708 children and showed an efficacy of 95% (95% CI, 74-100%).[104] These initial trials laid the foundations for the inclusion of Hib conjugate vaccines in childhood immunization schedules in industrialized nations.

Impact of Hib Conjugate Vaccines in Industrialized Countries

Wide scale use of the (Hib) conjugate vaccines has resulted in the virtual elimination of invasive Hib disease in industrialized countries during the 1990s.[105,106] The annual incidence of Hib meningitis among children less than 5 years in the United States declined by 98% from between 50-60 per 100,000 to 1.6 following the licensure of the conjugate vaccine in 1991.[107,108] There is a lack of epidemiological data available from developing countries that would be needed to determine the potential benefit and cost effectiveness of introducing these vaccines before national decisions can be made. [3,35,36]

Randomized Hib Conjugate Vaccine Trials in Developing Countries

Randomized trials of conjugate Hib vaccines in The Gambia and Chile have demonstrated both a high efficacy against invasive Hib disease and a 20-25% reduction in the incidence of radiologically defined pneumonia among vaccine recipients, documenting the potential benefits of using Hib conjugate vaccines in developing countries (Table 17).[109,110]

In a double blind, randomized trial in the Western Region of the Gambia, approximately 43,000 infants were randomly allocated to receive the Hib PRP-T conjugate vaccine mixed with DTP or DTP alone at 2,3, and 4 months of age. Surveillance for invasive Hib disease was conducted at three main hospitals in the region among children 5 to 36 months of age. Fifty cases of invasive Hib disease were detected over a three year period, 17 of which were culture-positive Hib pneumonia. The efficacy of the vaccine to prevent Hib pneumonia was 100% (95% Confidence Interval; 55, 100). The trial also demonstrated a 21% (95% CI; 4.6, 34.9) reduction in the cases of

radiologically defined pneumonia (showing definite radiological changes) and a 25% (95% CI; 0.24, 44.1) reduction in pneumonia with lobar consolidation. Hospital based surveillance data from the same sites prior to the vaccine trial had suggested that 10-15% of all pneumonias were due to Hib.[111] The protection provided by the Hib conjugate vaccine at the same site during the vaccine trial suggests that the hospital based data substantially underestimated the true burden of Hib pneumonia in the population. [35]

In a randomized vaccine effectiveness trial in Santiago, Chile 36 of 71 vaccination centers were randomly assigned to provide the Hib PRP-T vaccine. Children presenting to control vaccination centers were not offered the vaccine. In an analysis of approximately 20,000 children enrolled into the trial by Levine et al, 608 cases of pneumonia hospitalizations were detected among children 4-23 months of age.[112] The incidence of pneumonia with radiologically defined consolidation or effusion was reduced by 22% (95% CI, -7 to 43) in the vaccine group. Both trials have documented potential benefits of the Hib conjugate vaccines and shown that its impact on pneumonia incidence in developing countries is likely to be many times greater than the impact on meningitis incidence. Mulholland, Levine and Peltola support the use of vaccine trials as 'probes' for estimating the true burden of Hib pneumonia in populations where good quality data on Hib disease are lacking. [3,35,36]

While there is a growing body of evidence that invasive Hib disease is a significant burden of early childhood disease in several Asian countries, there are inconsistencies in studies. In a hamlet-randomized, controlled, double-blind vaccine-probe study conducted by Gessner and colleagues in Lombok, Indonesia between 1998-2002, 28,147 children were assigned to receive DTP-PRP-T and 26,926 received the

control DTP vaccine.[113] The Hib vaccine in this setting showed no evidence of prevention of radiologically confirmed lobar pneumonia.

There are many gaps in our knowledge and some unexpected observations that do not permit a conclusive statement regarding the burden of Hib disease in Pakistan. Many of the deficiencies are easily recognizable, such as the absence of surveillance systems for invasive Hib disease, the infrequent use of bacterial blood cultures in clinical practice and the inadequacy of laboratory methods utilized for Hib isolation at most centers in the country. The observations of the BOSTID studies in Islamabad and Rawalpindi on children with ALRI conducted were unusual with respect to the *Haemophilus influenzae* isolation rates from blood (11% and 17%), the proportion of *Haemophilus influenzae* isolated from blood that was not type b (34% and 92%) and the degree of clonal restriction among both type b and non-typeable isolates (two clonal types for Hib, nine for non-typeable *Haemophilus influenzae*).[16,17,18] The available data would compel us to conclude that the epidemiology of invasive *Haemophilus influenzae* disease in Pakistani children is very different from what is observed in all other countries (including neighboring India) and that the benefits of Hib conjugate vaccines will be limited in Pakistan.

An estimation of the potential benefits of preventing invasive Hib disease in Pakistan can not be made unless the evidence base is expanded. Surveillance systems designed to detect invasive Hib disease in young children by strengthening case identification and laboratory methods in hospitals (such as IBIS in India) will continue to play a major role in our understanding of Hib disease in Asia. Some of the limitations of these surveillance systems include the difficulty in (1) enumerating the proportion of all

cases from the catchment population that access health facilities, (2) determining the implications of antibiotics received prior to a hospital visit on bacterial isolation rates and (3) standardizing laboratory methods across multiple centers. These challenges apply whether the surveillance is conducted out of a group of large urban hospitals or out of all small health centers accessible to a cohort being tracked in the community (although a community based cohort is more likely to yield a better estimate of the proportion of all cases that access health care).

Blood cultures remain a highly specific but insensitive tool in ascertaining the etiology of community acquired pneumonia.[114] Non-bacteremic pneumonia is a major disease worldwide but proving its etiology is more difficult and costly.[3] While lung aspirates are a sensitive and specific method of determining the etiology of non-bacteremic pneumonias they are performed infrequently and include greater risks to the patient than blood cultures. Lower respiratory tract secretions are difficult to obtain from younger children and are often contaminated by resident flora. Identification of organisms from nasopharyngeal swabs is not a good predictor of the organism involved in invasive disease and the sensitivity and specificity of serum antibodies to type b capsular antigen are not well-defined. [2,42]

Table 15. Hospital and population based Haemophilus influenzae studies among Pakistani children, 1985-2001

Site	Date Published	Group studied	Number Studied	Case Definition Used	Culture Results					
					Specimen	Number	H	Hi	Hib	NTHi
Rawalpindi/ Islamabad	1989 Oct 1990 Nov	Inpatients/ outpatients < 5 years with ALRI	1,492	*Any one or more of the following:* RR > 50/min; chest retractions; stridor; cyanosis; wheezing; rales	Blood	1,331	144[1] (11%)	95/105[1]	61/95[1] (64%)	34/95 (36%)
	1990 Dec				Blood	NS	111[1]	99[1] (89%)	63/99 (64%)	36/99 (36%)
Rawalpindi/ Rural villages	1993 Oct	Outpatients 2-59 months	601	*Cough or difficulty breathing with one or more of the following:* RR > 50/min; tachypnea; chest indrawing; axillary temp >38°C	Blood	601	NS	100[1] (17%)	3/89[1] (3%)	82/89 (92%)
					NP	601	NS	220[1] (37%)	4/196[1] (2%)	179/196 (91%)
		Urban 2-59 months	133	Healthy	NP	133	NS	38[1] (29%)	0/28[1]	27/28 (96%)
		Rural 2-59 months	285	Healthy *or* with cough alone	NP	285	NS	123[1] (43%)	1/111[1] (<1%)	98/111 (88%)
Islamabad	1996 Oct	Inpatients with suspected bacterial meningitis 2 months - 12 years	103	*Either of the two:* CSF Gram stain +ve CSF Latex agglutination +ve *And at least two of the following: i*ncreased leucocytes cells; increased protein, decreased glucose	CSF	89	NS	20/89 (22%)	NS	NS

ALRI**: acute lower respiratory tract infection,** NP**: nasopharyngeal,** CSF**: cerebrospinal fluid,** RR**: respiratory rate,** NS**: not specified;** [1] **Isolation and identification of the species were done in Pakistan, sero-typing and genotyping at the University of Washington. Losses were reported during transportation of specimens from Pakistan to the United States resulting in the variations in denominators reported.**

Table 16. Serotypes of invasive H. influenzae isolates in cases of lower respiratory tract infections.
(Adapted from Berman S. Epidemiology of Acute Respiratory Infections in Children of Developing Countries. Rev Inf Dis. 1991;13 (Suppl 6):S454-S462)

Site	Source	No. of strains	Percent of indicated serotype		
			Type b	Non-type b	Non-typeable
Papua New Guinea Shann F et al[115]	Lung Aspirate Blood	32	19%	25%	56%
The Gambia Wall RA et al[116]	Lung Aspirate Blood	13	54%	15%	31%
Pakistan Weinberg GA et al[18]	Blood	95	64%	0	36%
Mastro TD et al[17]	Blood	89	3%	5%	92%

Table 17. Demonstrated efficacies of Haemophilus influenzae type b conjugate vaccines against invasive Hib disease, 1985-2002

Site	Date Published	Double Blind, Individually Randomized Trial	Vaccine Group (schedule)	Control Group (schedule)	Number of Children in Vaccine Group	Enrollment Start/End Dates	Follow-up Period	Vaccine Efficacy Point Estimate (95%CI)
Finland Eskola et al	1990 Nov	No	PRP-D 3,4,6,14-18	PRP-D 24	58,000	1985 Oct / 1987 Aug	7-24m	94% (83-98)
Alaska Ward et al	1990 Nov	Yes	PRP-D 2,4,6	Saline 2,4,6	1,054	1984 Oct/ 1988 Jan	1-45 m	35% (-57-73)
Northern California Black et al	1991 Feb	No	HbOC 2,4,6	Vaccine not offered	20,800	1988 Feb / 1990 June	1 week after 3rd dose-18m	100% (68-100)
Navajo Indian Reservation Santosham et al	1991 June	Yes	PRP-OMPC 42-90d, 70-146d	Lactose 42-90d, 70-146d	2,588	1988 July / 1990 Aug	1st dose-18m	93% (53-98)
United Kingdom Booy et al	1994 Aug	No	PRP-T 2,3,4	Vaccine not offered	27,860	1991 May/ 1993 Nov	5m – 1993 Nov	95% (75-100)
Chile Levine et al	1996 Mar	No	PRP-T 2,4,6	Vaccine not offered	35,264	1992 Nov / 1993 Oct	4-23m	92% (75-100)
Gambia Mulholland et al	1997 Apr	Yes	PRP-T 2,3,4	Dextrose 2,3,4	21,490	1993 Mar / 1995 Aug	5-36m	95% (67-100)

Appendix

A. Survey Consent Form

The Johns Hopkins University
School of Hygiene and Public Health
Committee on Human Research

CONSENT FORM B

Title of Research Project: **CHR# H.22.00.07.05.A**
Surveillance for Invasive Disease Due to H. *Influenza* type b and *S. Pneumonia* in Pakistani Children

Explanation of Research Project:

PURPOSE OF STUDY
Doctors and Health Workers here are working with the following organizations:

1. Government of Pakistan
2. Aga Khan Health Service, Pakistan
3. The Aga Khan University
4. The Johns Hopkins University

Researchers want to find out the rate of pneumonia, meningitis and measles in Pakistani children less than three years of age. Meningitis is the infection of the outer covering of brain and spinal cord.

PROCEDURES
If you agree for your child to be in this study we will ask you some questions about the following:

1. Your child's past and present illnesses.
2. Vaccines your child received. We will check the information with the records of Aga Khan Health Services.
3. The costs to you for travel and medical care

If your child is seriously ill the doctor may take some blood or other tests to see what caused the infection. We will collect the results of these tests. The samples will be destroyed if negative. Your doctor will be informed of the test results to help in the treatment. We will not provide the costs of treatment or vaccines for your child.

We would also like to store your child's blood sample to test for other infections that might look like pneumonias and measles. The blood sample may be stored for up to 10 years. The samples will be stored in a manner that will not identify your child. The results from these future tests may not be available to you.

Do you agree to let the blood sample be stored for up to 10 years for future research? Yes ____; No _____

The information will be kept at the project office in Gilgit. It will be available only to people working on the study. We will keep the study information private to the extent possible by the laws of Pakistan. People responsible for making sure that the research is done properly may review your study records. This might include people from Johns Hopkins University and the Aga Khan Health Service, Pakistan. All of these people are required to keep your identity confidential.

RISKS AND DISCOMFORTS
The tests that the doctor may perform include needle sticks that cause some discomfort and bruising. The information that you share about your family could cause embarrassment if it were made public.

BENEFITS
We will share the test results with your doctor so as to help guide therapy. The doctors will benefit by finding out what are the different germs that cause pneumonia and measles in Pakistan. This information will help the Ministry of Health in planning for the use of new vaccines. You will not receive any payment for participating in this study.

You are not forced to be in this study. You may quit at any time. If you decide not to be in the study, your care or relations with your doctors will not be changed in any way. You should ask the project coordinator any questions you may have about this study. You may ask him/her questions in the future if you do not understand anything. The researchers will tell you any new information that they may find out while you are in this study.

If you think being in the study has hurt you, you have not been treated fairly you can call Dr. Aamir Khan. Phone number: 92-572-55158, 92-572-55735 (Gilgit, Pakistan). You can also call the Principal Investigator Dr. Neal Halsey. Phone number 410-955-6964 (United States). You can also call the Office for Research Subjects. Phone number 410-614-1856 / Fax 410-955-0258 (United States).

If you agree to participate in this study please sing your name below.

_____
Signature of Parent of Guardian (when applicable)

_____
*Witness to Consent Procedures**

_____
Signature of Investigator

NOT VALID WITHOUT THE COMMITTEE OR IRB STAMP OF CERTIFICATION

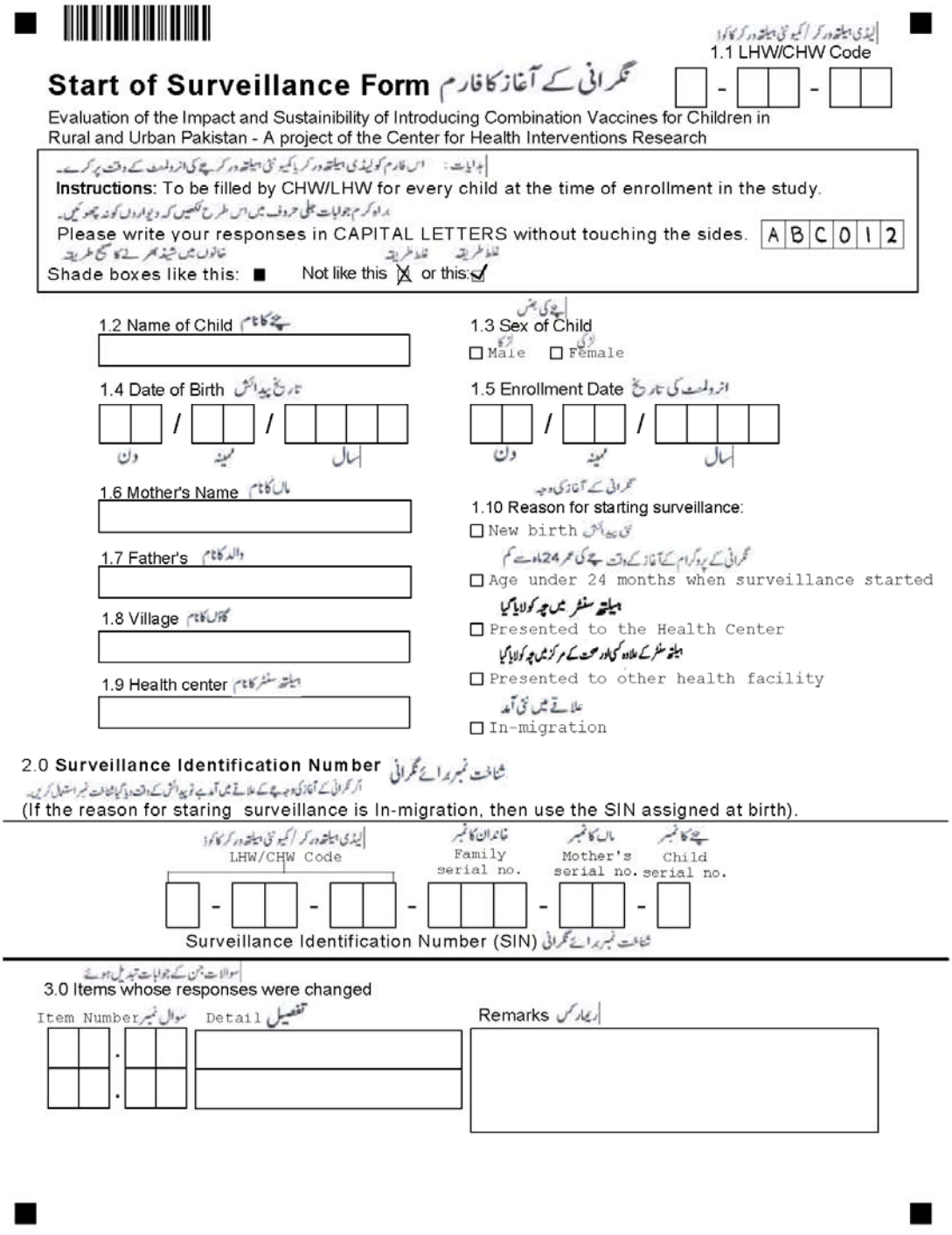
Void One Year From Above Date
CHR
No. _____
Approved From _____ to _____

_____
Date

**Optional unless subject is illiterate, or unable to sign*

***Note:** Signed copies of this form must be a) retained in file by the Principal Investigator, b) given to the participant and c) put in the patient's medical record (when applicable).*

B. Questionnaire: Start of Surveillance Form



1.1 LHW/CHW Code (ایذی ہیلتھ ورکر/کیہ نئی ہیلتھ ورکر کا کوڈ)

Start of Surveillance Form نگرانی کے آغاز کا فارم

Evaluation of the Impact and Sustainibility of Introducing Combination Vaccines for Children in Rural and Urban Pakistan - A project of the Center for Health Interventions Research

ہدایات: اس فارم کو لیڈی ہیلتھ ورکر یا کیہ نئی ہیلتھ ورکر بچے کی انرولمنٹ کے وقت پر کرے۔

Instructions: To be filled by CHW/LHW for every child at the time of enrollment in the study.

براہ کرم جوابات بلی حروف میں اس طرح لکھیں کہ دیواروں کو نہ چھوئیں۔

Please write your responses in CAPITAL LETTERS without touching the sides. A B C 0 1 2

خانوں میں شیڈ لگانے کا صحیح طریقہ — غلط طریقہ — غلط طریقہ

Shade boxes like this: ■ Not like this ☒ or this: ☑

1.2 Name of Child بچے کا نام

1.3 Sex of Child بچے کی جنس
☐ Male لڑکا ☐ Female لڑکی

1.4 Date of Birth تاریخ پیدائش
__ / __ / ____
دن مہینہ سال

1.5 Enrollment Date انرولمنٹ کی تاریخ
__ / __ / ____
دن مہینہ سال

1.6 Mother's Name ماں کا نام

1.7 Father's والد کا نام

1.8 Village گاؤں کا نام

1.9 Health center ہیلتھ سنٹر کا نام

1.10 Reason for starting surveillance: نگرانی کے آغاز کی وجہ
☐ New birth نئی پیدائش
☐ Age under 24 months when surveillance started نگرانی کے پروگرام کے آغاز کے وقت بچے کی عمر 24 ماہ سے کم
☐ Presented to the Health Center ہیلتھ سنٹر میں بچہ کو لایا گیا
☐ Presented to other health facility ہیلتھ سنٹر کے علاوہ کسی اور صحت کے مرکز میں بچہ کو لایا گیا
☐ In-migration علاقے میں نئی آمد

2.0 **Surveillance Identification Number** شناخت نمبر برائے نگرانی
اگر نگرانی کے آغاز کی وجہ بچے کے علاقے میں آمد ہے تو پیدائش کے وقت دیا گیا شناخت نمبر استعمال کریں۔
(If the reason for staring surveillance is In-migration, then use the SIN assigned at birth).

LHW/CHW Code (ایذی ہیلتھ ورکر/کیہ نئی ہیلتھ ورکر کا کوڈ) — Family serial no. (خاندان کا نمبر) — Mother's serial no. (ماں کا نمبر) — Child serial no. (بچے کا نمبر)

__ - __ - __ - ___ - __ - __

Surveillance Identification Number (SIN) شناخت نمبر برائے نگرانی

3.0 Items whose responses were changed سوالات جن کے جوابات تبدیل ہوئے

Item Number سوال نمبر	Detail تفصیل	Remarks ریمارکس
__ . __		
__ . __		

C. Questionnaire: Home Visit Form

Home Visit Form گھر گھر وزٹ فارم

A Project of the Center for Health Interventions Research

1.1 Surveillance Identification Number (SIN) شناخت نمبر برائے نگرانی

[ ] - [ ][ ] - [ ][ ] - [ ][ ][ ] - [ ][ ] - [ ]

ہدایات: اس فارم کو ہیلتھ ورکرز کی نگرانی میں شامل ہر بچے کیلئے پُر کریں

Instructions: To be filled by LHWs every two weeks for every child enrolled in the study.

براہ کرم جواب بڑے (کیپٹل) حروف میں لکھیں اور اس طرح لکھیں کہ خانوں کی دیواروں کو نہ چھوئیں

Please write your responses in CAPITAL LETTERS without touching the sides. A B C 0 1 2

خانوں میں شیڈ بھرنے کا صحیح طریقہ — غلط طریقہ — غلط طریقہ

Shade boxes like this: ■ Not like this ☒ or this: ☑

1.2 LHW Code لیڈی ہیلتھ ورکر کوڈ

[ ] - [ ][ ] - [ ][ ]

1.3 Visit Date وزٹ کی تاریخ

[ ][ ] / [ ][ ] / [ ][ ][ ][ ]

دن | مہینہ | سال

1.4 Information provider: معلومات دینے والا

☐ Mother ماں ☐ Father والد ☐ Grandmother نانی ردادی ☐ Grandfather نانا ردادا ☐ Aunt خالہ رچچی ☐ Uncle چچا رماموں ☐ Neighbour پڑوسی ☐ Sibling بہن ربھائی ☐ None کوئی نہیں ☐ Other دیگر

اگر بچہ نگرانی کے لیے موجود نہ ہو تو مندرجہ ذیل میں سے ایک وجہ پُر کریں بقیہ فارم پُر نہ کریں

1.5 If the child is not available for surveillance, choose one of the following reasons and do not fill out rest of the form:

☐ Child not at home بچہ گھر پر نہیں ☐ Child died بچہ فوت ہو گیا ہے ☐ Out migration علاقہ چھوڑ کر گیا ہے ☐ Visit not conducted وزٹ نہیں ہوا ☐ Other دیگر

کیا بچے کو حالیہ اور گزشتہ وزٹ کے دوران مندرجہ ذیل میں سے کوئی علامات ہوئی ہے

1.6 Has the child had ANY of the following symptoms between this and the previous visit?

☐ Unable to breastfeed بچہ ماں کا دودھ نہیں پی سکتا ہے رتھا
☐ Difficulty in breathing سانس لینے میں دشواری
☐ Vomits everything ہر چیز قے (الٹی) کرنا
☐ Fever بخار
☐ Convulsions جھٹکے لگنا
☐ Generalized rash of measles جسم پر خسرہ کے دانے
☐ Cough کھانسی

اگر ہاں تو پھر اس فارم کے علاوہ بیماری کے متعلق معلومات کا فارم پُر کریں

If yes to 1.6, then fill out Disease Information Form in addition to this form

Immunization Update ٹیکوں کی موجودہ صورت حال

کیا بچے کو حالیہ اور گزشتہ ملاقات کے دوران کوئی ٹیکہ لگا ہے؟

2.1 Did the child recieve any vaccines during the time between this and the previous visit?

☐ Yes ہاں ☐ No نہیں

اگر ہاں تو 2.2 پُر کریں ورنہ 3.0 پُر کریں

If yes to 2.1, go to item 2.2, otherwise go to item 3.0

شناخت نمبر برائے نگرانی
Surveillance Identification Number (SIN) ☐☐ - ☐☐ - ☐☐ - ☐☐☐ - ☐☐ - ☐

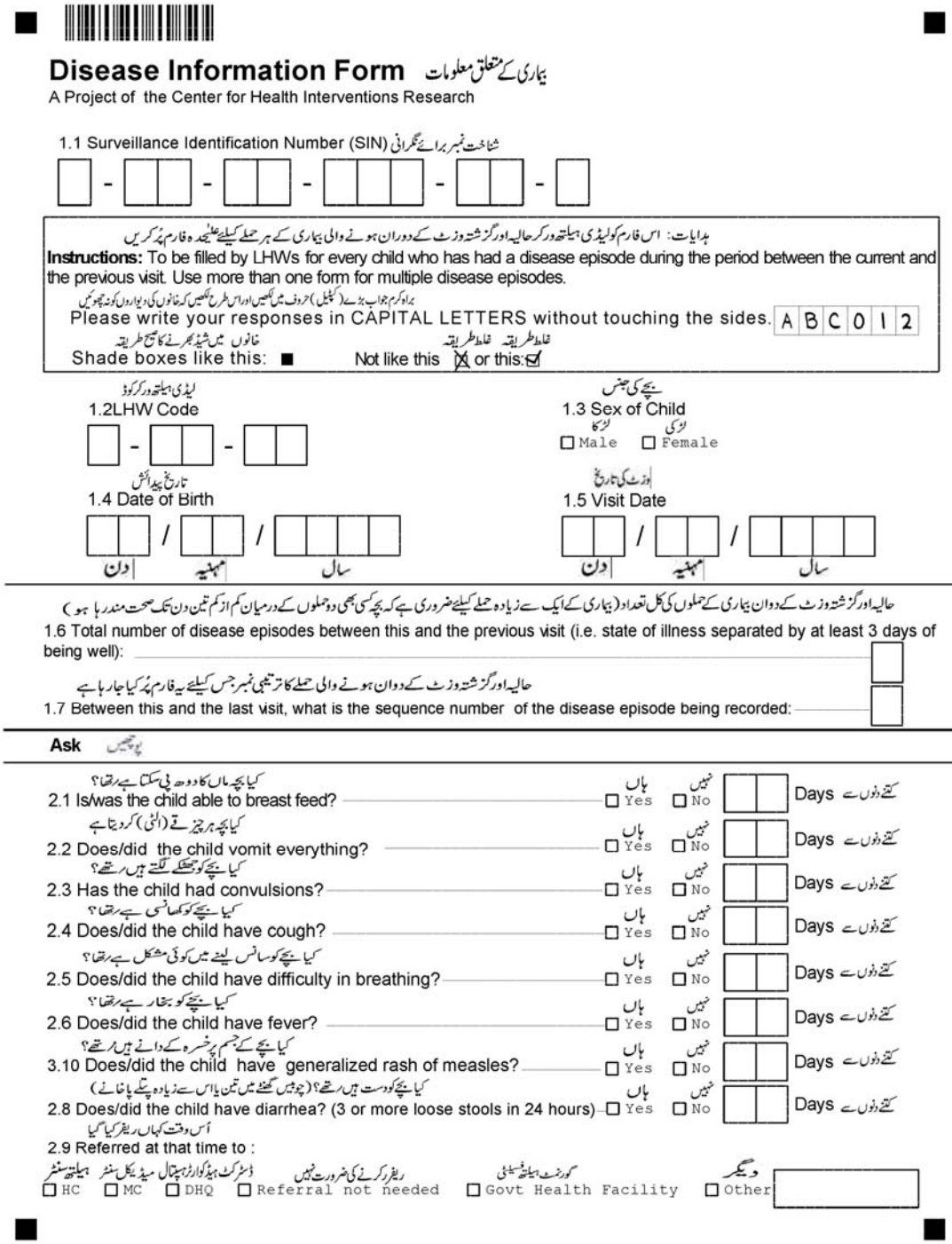
2.2 Vaccine(s) recieved between this and the previous visit: حالیہ اور گذشتہ وزٹ کے درمیان لگنے والے ٹیکے

☐ BCG بی سی جی	☐☐ دن /	☐☐ مہینہ /	☐☐☐☐ سال
☐ OPV-0 پولیو0	☐☐ دن /	☐☐ مہینہ /	☐☐☐☐ سال
☐ Hep B-0 ہیپاٹائٹس بی0	☐☐ دن /	☐☐ مہینہ /	☐☐☐☐ سال
☐ DPT-1 ڈی پی ٹی1	☐☐ دن /	☐☐ مہینہ /	☐☐☐☐ سال
☐ OPV-1 پولیو1	☐☐ دن /	☐☐ مہینہ /	☐☐☐☐ سال
☐ Hep B-1 ہیپاٹائٹس بی1	☐☐ دن /	☐☐ مہینہ /	☐☐☐☐ سال
☐ DPT-2 ڈی پی ٹی2	☐☐ دن /	☐☐ مہینہ /	☐☐☐☐ سال
☐ OPV-2 پولیو2	☐☐ دن /	☐☐ مہینہ /	☐☐☐☐ سال
☐ DPT-3 ڈی پی ٹی3	☐☐ دن /	☐☐ مہینہ /	☐☐☐☐ سال
☐ OPV-3 پولیو3	☐☐ دن /	☐☐ مہینہ /	☐☐☐☐ سال
☐ Hep B-3 ہیپاٹائٹس بی3	☐☐ دن /	☐☐ مہینہ /	☐☐☐☐ سال
☐ Measles خسرہ	☐☐ دن /	☐☐ مہینہ /	☐☐☐☐ سال
☐ Other دیگر	☐☐ دن /	☐☐ مہینہ /	☐☐☐☐ سال

سوالات جن کے جوابات تبدیل ہوئے
3.0 Items whose responses were changed

Item Number سوال نمبر	Details تفصیل	Remarks ریمارکس
☐☐.☐☐		
☐☐.☐☐		

D. Questionnaire: Disease Information Form



Disease Information Form بیماری کے متعلق معلومات

A Project of the Center for Health Interventions Research

1.1 Surveillance Identification Number (SIN) شناخت نمبر برائے نگرانی

☐ - ☐☐ - ☐☐ - ☐☐☐ - ☐☐ - ☐

ہدایات: اس فارم کو لیڈی ہیلتھ ورکر حالیہ اور گزشتہ وزٹ کے دوران ہونے والی بیماری کے ہر حملے کیلئے علیٰحدہ فارم پُر کریں

Instructions: To be filled by LHWs for every child who has had a disease episode during the period between the current and the previous visit. Use more than one form for multiple disease episodes.

براہ کرم جواب بڑے (کیپٹل) حروف میں لکھیں اور اس طرح لکھیں کہ خانوں کی دیواروں کو نہ چھوئیں

Please write your responses in CAPITAL LETTERS without touching the sides. A B C 0 1 2

خانوں میں شیڈ بھرنے کا صحیح طریقہ — غلط طریقہ — غلط طریقہ

Shade boxes like this: ■ Not like this ☒ or this: ☑

لیڈی ہیلتھ ورکر کوڈ
1.2LHW Code

☐ - ☐☐ - ☐☐

بچے کی جنس
1.3 Sex of Child

☐ Male لڑکا ☐ Female لڑکی

تاریخ پیدائش
1.4 Date of Birth

☐☐ / ☐☐ / ☐☐☐☐ (دن / مہینہ / سال)

وزٹ کی تاریخ
1.5 Visit Date

☐☐ / ☐☐ / ☐☐☐☐ (دن / مہینہ / سال)

حالیہ اور گزشتہ وزٹ کے دوان بیماری کے حملوں کی کل تعداد (بیماری کے ایک سے زیادہ حملے کیلئے ضروری ہے کہ بچہ کسی بھی دو حملوں کے درمیان کم از کم تین دن تک صحت مند رہا ہو)

1.6 Total number of disease episodes between this and the previous visit (i.e. state of illness separated by at least 3 days of being well): ☐

حالیہ اور گزشتہ وزٹ کے دوان ہونے والی حملے کا ترتیبی نمبر جس کیلئے یہ فارم پُر کیا جا رہا ہے

1.7 Between this and the last visit, what is the sequence number of the disease episode being recorded: ☐

Ask پوچھیں

2.1 Is/was the child able to breast feed? کیا بچہ ماں کا دودھ پی سکتا ہے/رہا تھا؟	☐ Yes ہاں	☐ No نہیں	☐☐ Days کتنے دنوں سے
2.2 Does/did the child vomit everything? کیا بچہ ہر چیز قے (الٹی) کر دیتا ہے	☐ Yes ہاں	☐ No نہیں	☐☐ Days کتنے دنوں سے
2.3 Has the child had convulsions? کیا بچے کو جھٹکے لگتے ہیں/رہے تھے؟	☐ Yes ہاں	☐ No نہیں	☐☐ Days کتنے دنوں سے
2.4 Does/did the child have cough? کیا بچے کو کھانسی ہے/رہا تھا؟	☐ Yes ہاں	☐ No نہیں	☐☐ Days کتنے دنوں سے
2.5 Does/did the child have difficulty in breathing? کیا بچے کو سانس لینے میں کوئی مشکل ہے/رہا تھا؟	☐ Yes ہاں	☐ No نہیں	☐☐ Days کتنے دنوں سے
2.6 Does/did the child have fever? کیا بچے کو بخار ہے/رہا تھا؟	☐ Yes ہاں	☐ No نہیں	☐☐ Days کتنے دنوں سے
3.10 Does/did the child have generalized rash of measles? کیا بچے کے جسم پر خسرہ کے دانے ہیں/رہے تھے؟	☐ Yes ہاں	☐ No نہیں	☐☐ Days کتنے دنوں سے
2.8 Does/did the child have diarrhea? (3 or more loose stools in 24 hours) کیا بچے کو دست ہیں/رہے تھے؟ (چوبیس گھنٹے میں تین یا اس سے زیادہ پتلے پاخانے)	☐ Yes ہاں	☐ No نہیں	☐☐ Days کتنے دنوں سے

2.9 Referred at that time to : اُس وقت کہاں ریفر کیا گیا

☐ HC ہیلتھ سنٹر ☐ MC ☐ DHQ ڈسٹرکٹ ہیڈکوارٹر ہسپتال میڈیکل سنٹر ☐ Referral not needed ریفر کرنے کی ضرورت نہیں ☐ Govt Health Facility گورنمنٹ ہیلتھ فیسلٹی ☐ Other دیگر ☐

شناخت نمبر برائے نگرانی
Surveillance Identification Number (SIN) ☐ - ☐☐ - ☐☐ - ☐☐☐ - ☐☐ - ☐

کیا بچہ اس وقت بیمار ہے؟
2.10 Is the child currently sick? ☐ Yes ہاں ☐ No نہیں

If no, then go to item 4.0, otherwise proceed to the next question اگر نہیں تو 4.0 پر جائیں ورنہ اگلا سوال پُر کریں

Look, Listen, Feel دیکھیں سنیں اور محسوس کریں

بچہ سُست یا بے ہوش ہے
3.1 Child lethargic or unconscious ☐ Yes ہاں ☐ No نہیں

ناک بہنا
3.2 Runny nose ☐ Yes ہاں ☐ No نہیں

سرخ آنکھیں
3.3 Red eyes ☐ Yes ہاں ☐ No نہیں

سانس کی رفتار فی منٹ
3.4 Breaths/min ☐☐☐ breaths/min

پسلی چلنا
3.5 Chest indrawing ☐ Yes ہاں ☐ No نہیں

سانس میں غراہٹ
3.6 Stridor ☐ Yes ہاں ☐ No نہیں

پانی کی کمی
3.7 Dehydration ☐ Yes ہاں ☐ No نہیں

گردن کی سختی
3.8 Stiff neck ☐ Yes ہاں ☐ No نہیں

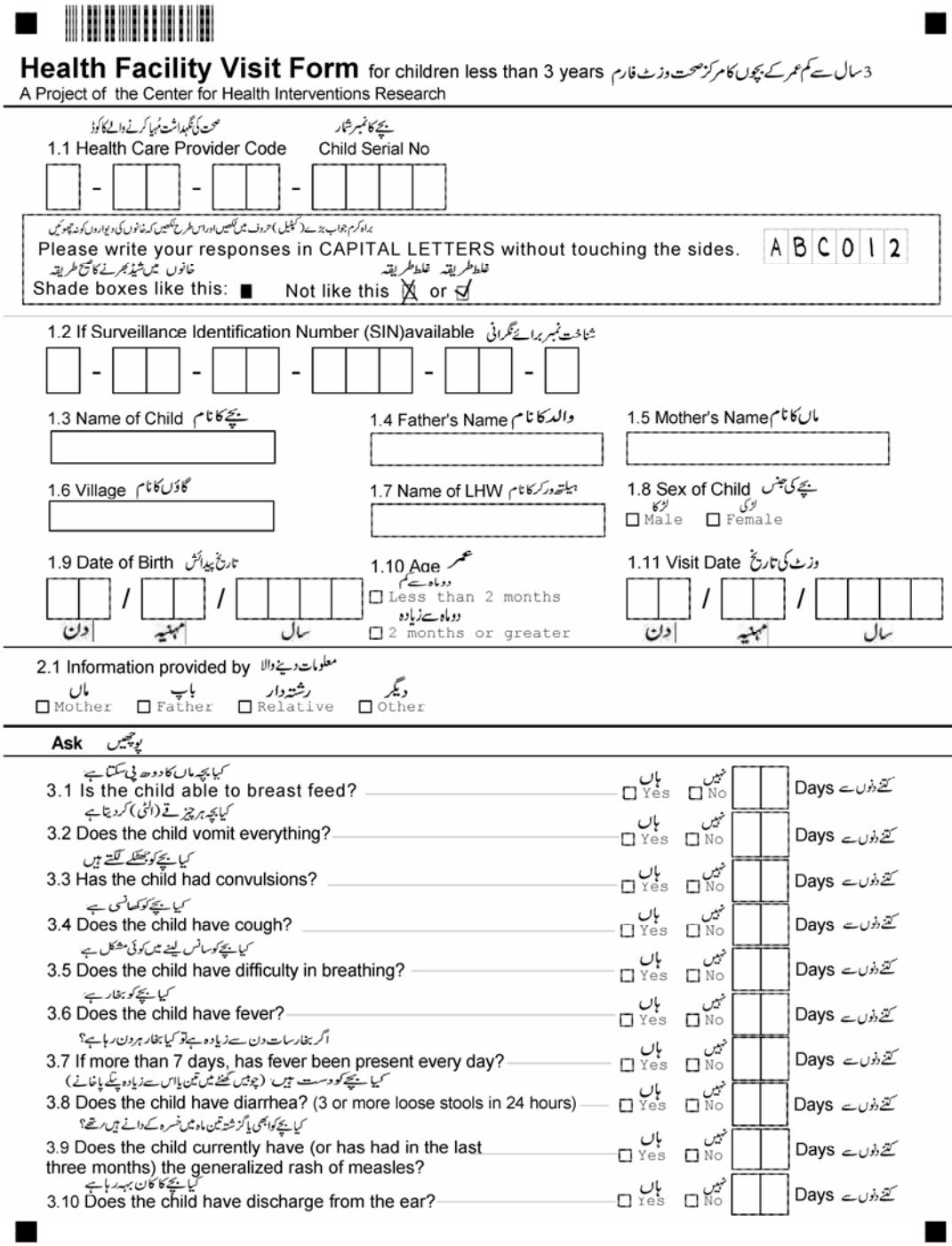
ریفر کیا گیا
3.9 Referred to :

☐ HC ہیلتھ سنٹر ☐ MC میڈیکل سنٹر ☐ DHQ ڈسٹرکٹ ہیڈکوارٹر ہسپتال ☐ Govt Health Facility گورنمنٹ ہیلتھ فیسلٹی ☐ Referral not needed ریفر کرنے کی ضرورت نہیں ☐ Other دیگر ☐

سوالات جن کے جوابات تبدیل ہوئے
4.0 Items whose responses were changed

Item Number سوال نمبر		Details تفصیل	Remarks ریمارکس
☐☐	☐☐		
☐☐	☐☐		

E. Questionnaire: Health Facility Visit Form



Health Facility Visit Form for children less than 3 years 3 سال سے کم عمر کے بچوں کا مرکز صحت وزٹ فارم

A Project of the Center for Health Interventions Research

1.1 Health Care Provider Code صحت کی نگہداشت مہیا کرنے والے کا کوڈ — Child Serial No بچے کا نمبر شمار

_ - __ - __ - ____

Please write your responses in CAPITAL LETTERS without touching the sides. براہ کرم جواب بڑے (کیپٹل) حروف میں لکھیں اور اس طرح لکھیں کہ خانوں کی دیواروں کو نہ چھوئیں — A B C 0 1 2

Shade boxes like this: ■ Not like this ☒ or ☑ — خانوں میں شیڈ بھرنے کا صحیح طریقہ — غلط طریقہ غلط طریقہ

1.2 If Surveillance Identification Number (SIN)available شناخت نمبر برائے نگرانی

_ - __ - __ - ___ - __ - _

1.3 Name of Child بچے کا نام

1.4 Father's Name والد کا نام

1.5 Mother's Name ماں کا نام

1.6 Village گاؤں کا نام

1.7 Name of LHW ہیلتھ ورکر کا نام

1.8 Sex of Child بچے کی جنس — ☐ Male لڑکا ☐ Female لڑکی

1.9 Date of Birth تاریخ پیدائش — __ / __ / ____ (دن / مہینہ / سال)

1.10 Age عمر — ☐ Less than 2 months دو ماہ سے کم ☐ 2 months or greater دو ماہ سے زیادہ

1.11 Visit Date وزٹ کی تاریخ — __ / __ / ____ (دن / مہینہ / سال)

2.1 Information provided by معلومات دینے والا — ☐ Mother ماں ☐ Father باپ ☐ Relative رشتہ دار ☐ Other دیگر

Ask پوچھیں

3.1 Is the child able to breast feed? کیا بچہ ماں کا دودھ پی سکتا ہے	☐ Yes ہاں	☐ No نہیں	__ Days کتنے دنوں سے
3.2 Does the child vomit everything? کیا بچہ ہر چیز قے (اُلٹی) کر دیتا ہے	☐ Yes ہاں	☐ No نہیں	__ Days کتنے دنوں سے
3.3 Has the child had convulsions? کیا بچے کو جھٹکے لگتے ہیں	☐ Yes ہاں	☐ No نہیں	__ Days کتنے دنوں سے
3.4 Does the child have cough? کیا بچے کو کھانسی ہے	☐ Yes ہاں	☐ No نہیں	__ Days کتنے دنوں سے
3.5 Does the child have difficulty in breathing? کیا بچے کو سانس لینے میں کوئی مشکل ہے	☐ Yes ہاں	☐ No نہیں	__ Days کتنے دنوں سے
3.6 Does the child have fever? کیا بچے کو بخار ہے	☐ Yes ہاں	☐ No نہیں	__ Days کتنے دنوں سے
3.7 If more than 7 days, has fever been present every day? اگر بخار سات دن سے زیادہ ہے تو کیا بخار ہر دن رہا ہے؟	☐ Yes ہاں	☐ No نہیں	__ Days کتنے دنوں سے
3.8 Does the child have diarrhea? (3 or more loose stools in 24 hours) کیا بچے کو دست ہیں (چوبیس گھنٹے میں تین یا اس سے زیادہ پتلے پاخانے)	☐ Yes ہاں	☐ No نہیں	__ Days کتنے دنوں سے
3.9 Does the child currently have (or has had in the last three months) the generalized rash of measles? کیا بچے کو ابھی یا گزشتہ تین ماہ میں خسرہ کے دانے ہیں رہے؟	☐ Yes ہاں	☐ No نہیں	__ Days کتنے دنوں سے
3.10 Does the child have discharge from the ear? کیا بچے کا کان بہہ رہا ہے	☐ Yes ہاں	☐ No نہیں	__ Days کتنے دنوں سے

صحت کی نگہداشت مہیا کرنے والے کا کوڈ
Health care provider code ☐☐ - ☐☐ - ☐☐ - ☐☐☐☐

Look, Listen, Feel دیکھیں سنیں اور محسوس کریں

4.1 Child lethargic or unconscious بچہ سست یا بے ہوش ہے	☐ Yes ہاں	☐ No نہیں
4.2 Temperature ٹمپریچر ☐☐.☐	°c	
4.3 Weight وزن ☐☐.☐	Kg	
4.4 Respiratory rate سانس کی رفتار فی منٹ ☐☐☐	breaths/min	
4.5 Stiff neck گردن کی سختی	☐ Yes ہاں	☐ No نہیں
4.6 Chest indrawing پسلی چلنا	☐ Yes ہاں	☐ No نہیں
4.7 Stridor سانس میں خرابہ	☐ Yes ہاں	☐ No نہیں
4.8 Dehydration پانی کی کمی	☐ Yes ہاں	☐ No نہیں
4.9 Runny nose ناک بہنا	☐ Yes ہاں	☐ No نہیں
4.10 Red eyes سرخ آنکھیں	☐ Yes ہاں	☐ No نہیں
4.11 Generalized rash of measles. خسرے کے دانے	☐ Yes ہاں	☐ No نہیں
4.12 Pus draining from eyes آنکھوں سے پیپ کا اخراج	☐ Yes ہاں	☐ No نہیں
4.13 Clouding of cornea کورنیا کی دھندلاہٹ	☐ Yes ہاں	☐ No نہیں
4.14 Mouth ulcer منہ کا السر	☐ Extensive شدید	☐ Superficial سطحی ☐ None کوئی نہیں

نوٹ: اگر عمر دو ماہ سے کم ہے تو یہ حصہ پُر کرنا ہوگا
NOTE: if age is less then 2 months fill this part also

4.15 Nasal flaring نتھنوں کا پھولنا	☐ Yes ہاں	☐ No نہیں
4.16 Bulging Fontanelle تالو آ بھرنا	☐ Yes ہاں	☐ No نہیں
4.17 Umbilical redness extending to the skin ناف کی سرخی جو کہ ناف تک جاتی ہو	☐ Yes ہاں	☐ No نہیں
4.18 Skin Pustule جسم پر دانے	☐ None کوئی نہیں	☐ Few/mild چند/معمولی ☐ Many/severe بہت زیادہ/شدید
4.19 Movements حرکات	☐ Normal نارمل	☐ Decreased کم ہونا
4.20 Muscle stiffness / spasm پٹھوں کی سختی	☐ Normal نارمل	☐ Increased زیادہ ہونا

5.0 Classification of the child بچے کی درجہ بندی

- ☐ Pneumonia نمونیہ
- ☐ Severe peeumonia شدید نمونیہ
- ☐ Very severe febrile disease بہت شدید بخار والی بیماری
- ☐ Measles خسرہ
- ☐ Measles with eye/mouth complications آنکھ اور منہ کی پیچیدگیوں کے ساتھ خسرہ
- ☐ Severe complicated measles شدید پیچیدہ خسرہ
- ☐ Possible serious bacterial infection ممکنہ شدید بیکٹیریائی انفیکشن
- ☐ Possible neonatal tetanus ممکنہ نوزائیدہ ٹیٹنس
- ☐ other دیگر ☐☐☐☐☐☐☐☐☐☐

6.0 Antibiotic received prior to current visit: موجودہ وزٹ سے پہلے کوئی اینٹی بائیوٹک دی گئی

	Days کتنے دن	Doses کتنی خوراک	Last dose آخری خوراک
☐ Septran (Co-trimoxozole) سپٹران (کوٹرائی میکسازول)	☐☐	☐☐	☐☐ days ago دنوں پہلے
☐ Amoxicillin ایماکسلین	☐☐	☐☐	☐☐ days ago دنوں پہلے
☐ Other 1 دیگر ☐☐☐☐☐☐☐☐☐☐☐☐☐☐	☐☐	☐☐	☐☐ days ago دنوں پہلے
☐ Other 2 دیگر ☐☐☐☐☐☐☐☐☐☐☐☐☐☐	☐☐	☐☐	☐☐ days ago دنوں پہلے

☐ No antibiotic given کوئی اینٹی بائیوٹک نہیں دی

7.1 Culture specimen obtained

☐ Blood ☐ CSF ☐ Other ☐ Not obtained

7.2 X ray chest obtained

☐ Yes ☐ No ☐ Not known

8.0 Referred to ریفر کیا گیا

☐ AKHSP facility اے کے ایچ ایس پی فیسلٹی ☐ Govt health facility گورنمنٹ ہیلتھ فیسلٹی ☐ DHQ ڈی ایچ کیو

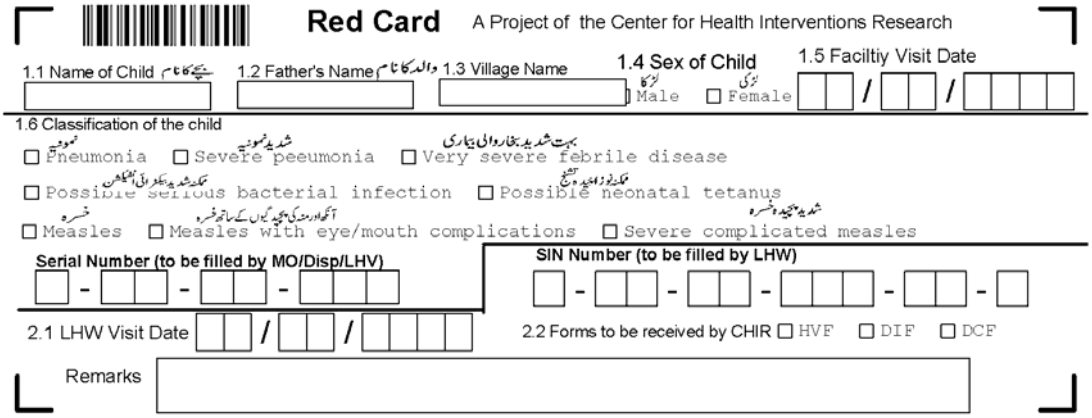
☐ Treated at facility فیسلٹی میں علاج کیا گیا ☐ Sent Home گھر بھیجا ☐ MC میڈیکل سنٹر

☐ Other دیگر ☐☐☐☐☐☐☐☐☐☐

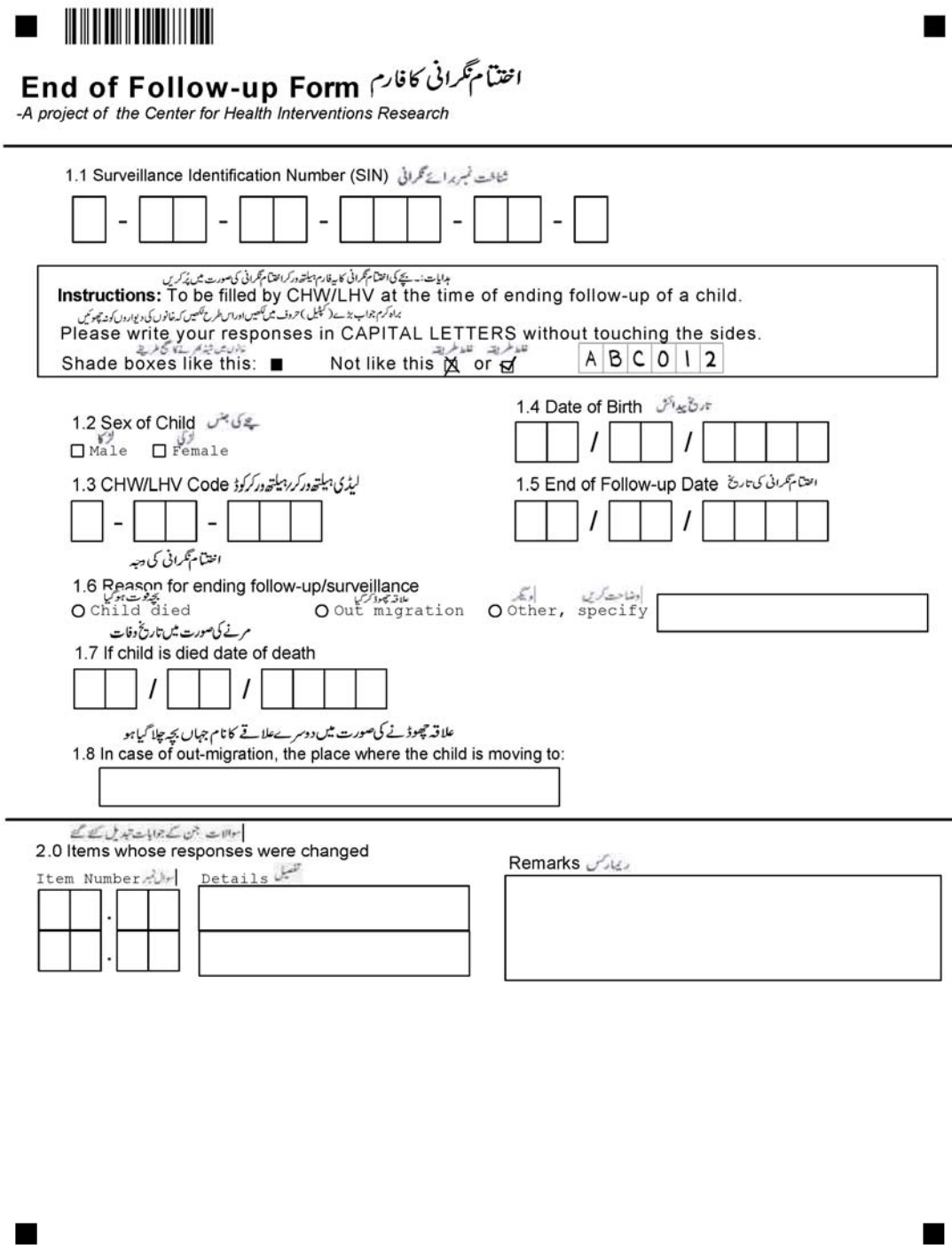
9.0 Items whose responses were changed سوالات جن کے جوابات تبدیل ہوئے

Item Number سوال نمبر	Details تفصیل	Remarks ریمارکس
☐☐.☐☐		
☐☐.☐☐		

F. Questionnaire: Red Card



G. Questionnaire: End of Follow Form



End of Follow-up Form اختتام نگرانی کا فارم

-A project of the Center for Health Interventions Research

1.1 Surveillance Identification Number (SIN) شناخت نمبر برائے نگرانی

☐ - ☐☐ - ☐☐ - ☐☐☐ - ☐☐ - ☐

ہدایات:۔ بچے کی اختتام نگرانی کا یہ فارم ہیلتھ ورکر اختتام نگرانی کی صورت میں پُر کریں

Instructions: To be filled by CHW/LHV at the time of ending follow-up of a child.

براہ کرم جواب بڑے (کیپٹل) حروف میں لکھیں اور اس طرح لکھیں کہ خانوں کی دیواروں کو نہ چھوئیں

Please write your responses in CAPITAL LETTERS without touching the sides.

Shade boxes like this: ■ Not like this ☒ or ☑ A B C 0 1 2

1.2 Sex of Child بچے کی جنس

☐ Male لڑکا ☐ Female لڑکی

1.3 CHW/LHV Code لیڈی ہیلتھ ورکر/ہیلتھ ورکر کوڈ

☐ - ☐☐ - ☐☐☐

1.4 Date of Birth تاریخ پیدائش

☐☐ / ☐☐ / ☐☐☐☐

1.5 End of Follow-up Date اختتام نگرانی کی تاریخ

☐☐ / ☐☐ / ☐☐☐☐

1.6 Reason for ending follow-up/surveillance اختتام نگرانی کی وجہ

○ Child died بچہ فوت ہو گیا ○ Out migration علاقہ چھوڑ گیا ○ Other, specify دیگر، وضاحت کریں

1.7 If child is died date of death مرنے کی صورت میں تاریخ وفات

☐☐ / ☐☐ / ☐☐☐☐

1.8 In case of out-migration, the place where the child is moving to: علاقہ چھوڑنے کی صورت میں دوسرے علاقے کا نام جہاں بچہ چلا گیا ہو

2.0 Items whose responses were changed سوالات جن کے جوابات تبدیل کئے گئے

Item Number سوال نمبر	Details تفصیل
☐☐.☐☐	
☐☐.☐☐	

Remarks ریمارکس

H. Questionnaire: LHW Quality Management Form

LHW Quality Management Form

A project of the Center for Health Interventions Research

1.1 Surveillance Identification Number (SIN)

☐ - ☐☐ - ☐☐ - ☐☐☐ - ☐☐ - ☐

Instructions: To be filled by LHV conducting a home visit along with an LHW. (SIN randomly generated)
Please write your responses in CAPITAL LETTERS without touching the sides. A B C 0 1 2
Shade boxes like this: ■ Not like this ☒ or ☑

1.2 LHV Code ☐ - ☐☐ - ☐☐

1.3 LHW Code ☐ - ☐☐ - ☐☐

1.4 Visit Date ☐☐ / ☐☐ / ☐☐☐☐

Review Home Visits with Parent or Guardian

2.0 Information porvider:
☐ Mother ☐ Father ☐ Grandmother ☐ Aunt ☐ Other

2.1 Is the parent or guardian aware that this child is under surveillance?
☐ Yes ☐ No

2.2 Did the parent or legal guardian provide written consent for enrolling this child?
☐ Yes ☐ No

2.3 Is the parent or guardian aware that the LHW must conduct a Home Visit for this child every 2 weeks?
☐ Yes ☐ No

2.4 Is the parent or guardian aware that the LHW must ask at every Home Visit whether the child has been ill or is currently ill?
☐ Yes ☐ No

2.5 Is the parent or guardian aware that the LHW must ask at every Home Visit if the child has received any new vaccinations?
☐ Yes ☐ No

2.6 What is this child's date of birth?
☐☐ / ☐☐ / ☐☐☐☐

2.7 Have you ever refused vaccination for this child?
☐ Yes ☐ No

2.8 How many Home Visits has the LHW conducted for this child during the last 30 days? ☐ Home Visit(s)

2.8.1 Last Visit Date
☐☐ / ☐☐ / ☐☐☐☐

Time of visit: ☐☐ : ☐☐ ☐ am ☐ pm
☐ Child ill between this and last visit
☐ Child ill and at home at time of visit
☐ Child was not at home

2.8.2 Visit Date Prior to 2.8.1
☐☐ / ☐☐ / ☐☐☐☐

Time of visit: ☐☐ : ☐☐ ☐ am ☐ pm
☐ Child ill between this and last visit
☐ Child ill and at home at time of visit
☐ Child was not at home

2.6 How many other children in this household are less than 24 months of age? ☐

2.6 How many are enrolled? ☐

Observe the LHW fill the Home Visit Form

3.1 Fill the box for each sign or symptom that was reviewed:
☐ Unable to breastfeed ☐ Difficulty in breathing
☐ Vomits everything ☐ Fever
☐ Convulsions ☐ Generalized rash
☐ Cough

Ask the LHW to count the respiratory rate of this child for exactly 1 minute

3.2 Did the CHW count the respiratory rate correctly? (verify by counting yourself)
☐ Yes ☐ No

LHW Quality Management Form

Ask

4.1 Ask the LHW to tell you the definition of fast breathing in a child who is:

4.1.1 Less than 2 months of age ☐☐☐ breaths/minutes

4.1.2 From 2 months up to 12 months of age ☐☐☐ breaths/minutes

4.1.3 Twelve months up to 5 years of age ☐☐☐ breaths/minutes

Recognizing signs and symptoms in the sick child

5.0 Complete the following table by asking the LHW to identify the signs and symptoms in the sick child for the following conditions under IMCI. Mark only those signs or symptoms that the LHW identifies without prompting.

	Sick Child				
Signs	No Pneumonia. Cough or Cold	Pneumonia	Severe Pneumonia	Very Severe Febrile Disease	Measles
Child unable to drink/breastfeed	☐	☐	☐	☐	☐
Child vomits everything	☐	☐	☐	☐	☐
Convulsions	☐	☐	☐	☐	☐
Lethargic or unconscious	☐	☐	☐	☐	☐
Chest Indraw ing	☐	☐	☐	☐	☐
Stridor in calm child	☐	☐	☐	☐	☐
Fast breathing	☐	☐	☐	☐	☐
Cough	☐	☐	☐	☐	☐
Nasal flaring	☐	☐	☐	☐	☐
Grunting	☐	☐	☐	☐	☐
Stiff neck	☐	☐	☐	☐	☐
Bulging fontanelle	☐	☐	☐	☐	☐
Fever	☐	☐	☐	☐	☐
Generalized rash of measles	☐	☐	☐	☐	☐
Runny nose	☐	☐	☐	☐	☐
Red eyes	☐	☐	☐	☐	☐

Referral Criteria

6.0 Complete the following table by asking the LHW to identify the appropriate referral facility for each of the following conditions:

	Referral Facility				
Classification	HC	MC	DHQ	Other	No referral required
No pneumonia. Cough or Cold	☐	☐	☐	☐	☐
Pneumonia	☐	☐	☐	☐	☐
Very severe pneumonia	☐	☐	☐	☐	☐
Very severe febrile disease	☐	☐	☐	☐	☐
Measles	☐	☐	☐	☐	☐

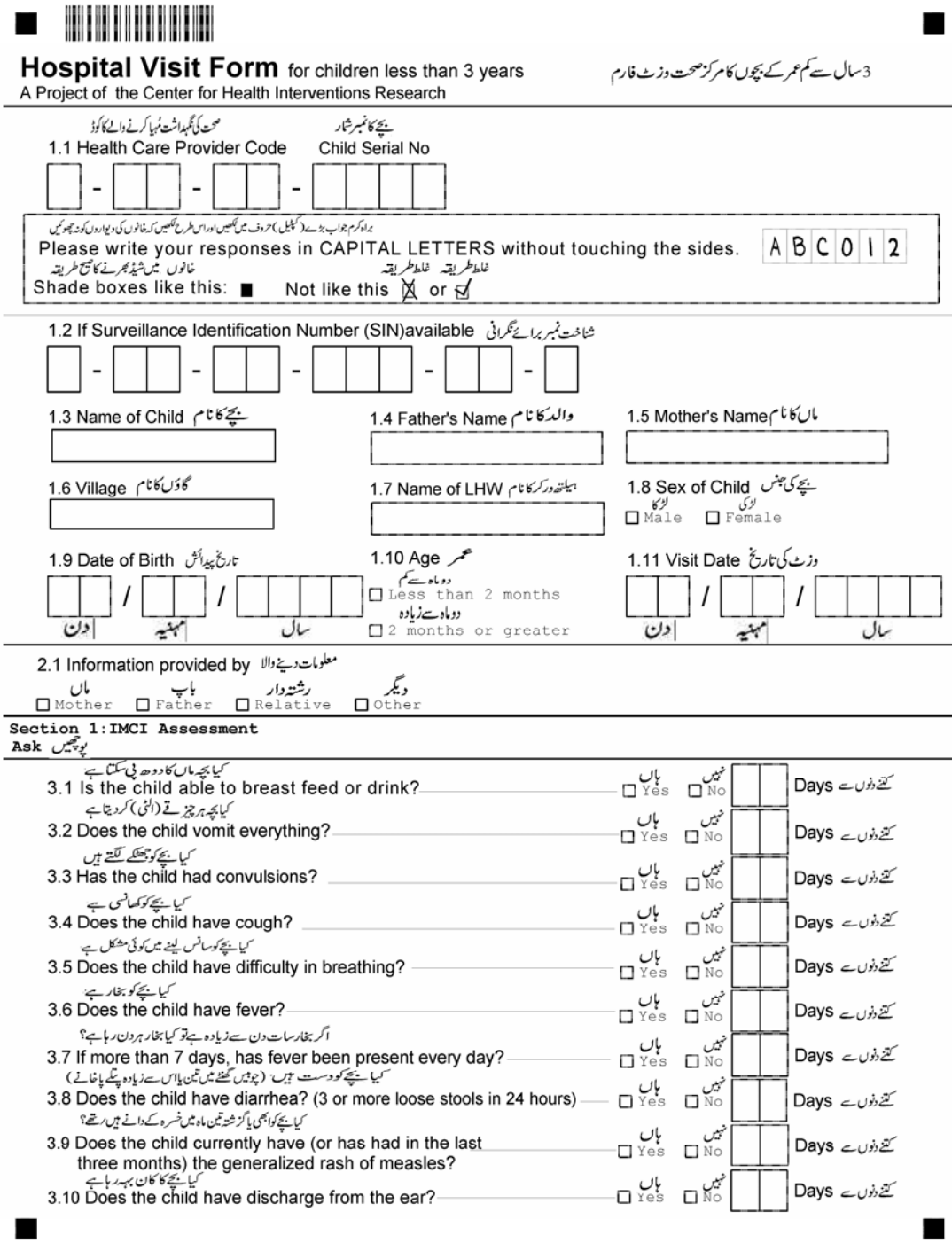
7.0 Items whose responses were changed

Item Number ☐☐.☐☐ ☐☐.☐☐

Details

Remarks

I. Questionnaire: Hospital Visit Form



Hospital Visit Form for children less than 3 years
3 سال سے کم عمر کے بچوں کا مرکز صحت وزٹ فارم
A Project of the Center for Health Interventions Research

1.1 Health Care Provider Code (صحت کی نگہداشت مہیا کرنے والے کا کوڈ) — Child Serial No (بچے کا نمبر شمار)

Please write your responses in CAPITAL LETTERS without touching the sides. (براہ کرم جواب بڑے (کیپٹل) حروف میں لکھیں اور اس طرح لکھیں کہ خانوں کی دیواروں کو نہ چھوئیں) A B C 0 1 2

Shade boxes like this: ■ (خانوں میں شیڈ بھرنے کا صحیح طریقہ) Not like this ☒ (غلط طریقہ) or ☑ (غلط طریقہ)

1.2 If Surveillance Identification Number (SIN)available (شناخت نمبر برائے نگرانی)

1.3 Name of Child (بچے کا نام) | 1.4 Father's Name (والد کا نام) | 1.5 Mother's Name (ماں کا نام)

1.6 Village (گاؤں کا نام) | 1.7 Name of LHW (ہیلتھ ورکر کا نام) | 1.8 Sex of Child (بچے کی جنس) ☐ Male (لڑکا) ☐ Female (لڑکی)

1.9 Date of Birth (تاریخ پیدائش) (دن / مہینہ / سال) | 1.10 Age (عمر) ☐ Less than 2 months (دو ماہ سے کم) ☐ 2 months or greater (دو ماہ سے زیادہ) | 1.11 Visit Date (وزٹ کی تاریخ) (دن / مہینہ / سال)

2.1 Information provided by (معلومات دینے والا) ☐ Mother (ماں) ☐ Father (باپ) ☐ Relative (رشتہ دار) ☐ Other (دیگر)

Section 1: IMCI Assessment
Ask (پوچھیں)

3.1 Is the child able to breast feed or drink? (کیا بچہ ماں کا دودھ پی سکتا ہے)	☐ Yes (ہاں)	☐ No (نہیں)	Days (کتنے دنوں سے)
3.2 Does the child vomit everything? (کیا بچہ ہر چیز قے (الٹی) کر دیتا ہے)	☐ Yes (ہاں)	☐ No (نہیں)	Days (کتنے دنوں سے)
3.3 Has the child had convulsions? (کیا بچے کو جھٹکے لگتے ہیں)	☐ Yes (ہاں)	☐ No (نہیں)	Days (کتنے دنوں سے)
3.4 Does the child have cough? (کیا بچے کو کھانسی ہے)	☐ Yes (ہاں)	☐ No (نہیں)	Days (کتنے دنوں سے)
3.5 Does the child have difficulty in breathing? (کیا بچے کو سانس لینے میں کوئی مشکل ہے)	☐ Yes (ہاں)	☐ No (نہیں)	Days (کتنے دنوں سے)
3.6 Does the child have fever? (کیا بچے کو بخار ہے)	☐ Yes (ہاں)	☐ No (نہیں)	Days (کتنے دنوں سے)
3.7 If more than 7 days, has fever been present every day? (اگر بخار سات دن سے زیادہ ہے تو کیا بخار ہر دن رہا ہے؟)	☐ Yes (ہاں)	☐ No (نہیں)	Days (کتنے دنوں سے)
3.8 Does the child have diarrhea? (3 or more loose stools in 24 hours) (کیا بچے کو دست ہیں (چوبیس گھنٹے میں تین یا اس سے زیادہ پتلے پاخانے))	☐ Yes (ہاں)	☐ No (نہیں)	Days (کتنے دنوں سے)
3.9 Does the child currently have (or has had in the last three months) the generalized rash of measles? (کیا بچے کو ابھی یا گزشتہ تین ماہ میں خسرہ کے دانے ہیں رہے؟)	☐ Yes (ہاں)	☐ No (نہیں)	Days (کتنے دنوں سے)
3.10 Does the child have discharge from the ear? (کیا بچے کا کان بہہ رہا ہے)	☐ Yes (ہاں)	☐ No (نہیں)	Days (کتنے دنوں سے)

صحت کی نگہداشت مہیا کرنے والے کا کوڈ
Health care provider code ☐ - ☐☐ - ☐☐ - ☐☐☐☐

Look, Listen, Feel دیکھیں سُنیں اور محسوس کریں

	ہاں	نہیں
4.1 Child lethargic or unconscious بچہ سُست یا بے ہوش ہے	☐ Yes	☐ No
4.2 Temperature ٹمپریچر ☐☐.☐ °c		
4.3 Weight وزن ☐☐.☐ Kg		
4.4 Respiratory rate سانس کی رفتار فی منٹ ☐☐☐ breaths/min		
4.5 Stiff neck گردن کی سختی	☐ Yes	☐ No
4.6 Chest indrawing پسلی چلنا	☐ Yes	☐ No
4.7 Stridor سانس میں غرغراہٹ	☐ Yes	☐ No
4.8 Dehydration پانی کی کمی	☐ Yes	☐ No
4.9 Runny nose ناک بہنا	☐ Yes	☐ No
4.10 Red eyes سرخ آنکھیں	☐ Yes	☐ No
4.11 Generalized rash of measles. خسرے کے دانے	☐ Yes	☐ No
4.12 Pus draining from eyes آنکھوں سے پیپ کا اخراج	☐ Yes	☐ No
4.13 Clouding of cornea کورنیا کی دھندلاہٹ	☐ Yes	☐ No
4.14 Mouth ulcer منہ کا السر ☐ Extensive شدید ☐ Superficial سطحی		☐ None کوئی نہیں

نوٹ: اگر عمر دو ماہ سے کم ہے تو یہ حصہ پُر کرنا ہوگا
NOTE: if age is less then 2 months fill this part also

	ہاں	نہیں
4.15 Nasal flaring نتھنوں کا پھولنا	☐ Yes	☐ No
4.16 Bulging Fontanelle تالوا بھرنا	☐ Yes	☐ No
4.17 Umbilical redness extending to the skin ناف کی سرخی جو کھال تک جاتی ہو	☐ Yes	☐ No

4.18 Skin Pustule جسم پر دانے ☐ None کوئی نہیں ☐ Few/mild چند/معمولی ☐ Many/severe بہت زیادہ/شدید

4.19 Movements حرکات ☐ Normal نارمل ☐ Decreased کم ہونا

4.20 Muscle stiffness / spasm پٹھوں کی سختی ☐ Normal نارمل ☐ Increased زیادہ ہونا

5.0 Classification of the child بچے کی درجہ بندی

- ☐ Pneumonia نمونیہ
- ☐ Severe pneumonia شدید نمونیہ
- ☐ Very severe febrile disease بہت شدید بخار والی بیماری
- ☐ Measles خسرہ
- ☐ Measles with eye/mouth complications آنکھ اور منہ کی پیچیدگیوں کے ساتھ خسرہ
- ☐ Severe complicated measles شدید پیچیدہ خسرہ
- ☐ Possible serious bacterial infection ممکنہ شدید بیکٹریائی انفیکشن
- ☐ Possible neonatal tetanus ممکنہ نوزائیدہ تشنج
- ☐ other دیگر ☐☐☐☐☐☐☐☐☐☐

Section 2:Clinical Assessment
To be filled by Medical Officer

5.1 General Appearance
☐ Alert ☐ Drowsy
☐ Restless ☐ Comatose

5.2 Anemia ☐ Yes ☐ No

5.3 Jaundice ☐ Yes ☐ No

5.4 Cyanosis ☐ Yes ☐ No

5.5 Dehydration ☐ Yes ☐ No

5.6 Edema ☐ Yes ☐ No

5.7 Pulse/min ☐☐☐

5.8 Temprature ☐☐☐.☐ °C

5.9 Respiratory rate ☐☐☐ breaths/min

صحت کی نگہداشت مہیا کرنے والے کا کوڈ
Health care provider code ☐ - ☐☐ - ☐☐ - ☐☐☐☐

Physical Examination contd.

5.10 Ear
- ☐ Normal
- ☐ Inflamed drum
- ☐ Discharge
- ☐ Other

5.11 Skin rash
- ☐ None
- ☐ Pustular
- ☐ Macular
- ☐ Patechae
- ☐ Papular
- ☐ Purpura
- ☐ Maculopapular
- ☐ Other
- ☐ Vesicular

5.12 Fontanelle
- ☐ Normal
- ☐ Full
- ☐ Depressed
- ☐ Bulged

5.13 Tonsils
- ☐ Normal
- ☐ Inflamed
- ☐ Pus

5.14 Enlarged lymph nodes
- ☐ None
- ☐ Axillary
- ☐ Cervical
- ☐ Generalized
- ☐ Inguinal

5.15 Chest indrawing
- ☐ Yes
- ☐ No

5.16 Percussion
- ☐ Normal
- ☐ Abnormal dullness
- ☐ Increased resonance

5.17 Breath sounds
- ☐ Vesicular
- ☐ Bronchial
- ☐ Harsh vesicular/prolonged exp
- ☐ Diminished
- ☐ Absent
- ☐ Other

5.18 Wheeze ☐ Yes ☐ No

5.19 Rales ☐ No ☐ Fine ☐ Coarse

5.20 Ronchi ☐ Yes ☐ No

5.21 Stridor ☐ Yes ☐ No

5.22 Musle tone
☐ Normal ☐ Low ☐ High

5.23 Convulsions ☐ Yes ☐ No

5.24 Neck rigidity ☐ Yes ☐ No

5.25 Kernig sign
- ☐ Positive
- ☐ Negative

(inability to extend the leg with the hip flexed)

5.26 Brudzinski sign
- ☐ Positive
- ☐ Negative

(flexing the neck with resultant flexion of hip or knee)

6.0 Antibiotic received prior to current visit:

	Days	Doses given (per day)	Last dose (01 if last dose given today)	
☐ Septran (Co-trimoxozole)	☐☐	☐☐	☐☐	days ago
☐ Amoxicillin	☐☐	☐☐	☐☐	days ago
☐ Other 1 ☐☐☐☐☐☐☐☐☐☐	☐☐	☐☐	☐☐	days ago
☐ Other 2 ☐☐☐☐☐☐☐☐☐☐	☐☐	☐☐	☐☐	days ago

☐ No antibiotic received

7.1 Clinical diagnosis
☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

7.2 Any other concurrent Illness 1
☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

7.3 Any other concurrent Illness 2
☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

7.4 Culture specimen obtained
☐ Blood ☐ CSF ☐ Other ☐ Not obtained

7.5 X ray chest obtained
☐ Yes ☐ No ☐ Not known

سوالات جن کے جوابات تبدیل کیے گئے
8.0 Items whose responses were changed
Item Number سوال نمبر | Details تفصیل
☐☐.☐☐
☐☐.☐☐

Remarks ریمارکس

J. Hib Probe Trial: Study Objectives and Hypothesis

Objectives

1. To estimate the efficacy of a Hib conjugate vaccine to reduce the incidence of pneumonia with lobar consolidation and all radiologically defined pneumonias in vaccinated children in comparison to a control group

2. To determine the burden of community acquired pneumonia attributable to Hib among children less than 3 years of age in Pakistan

Hypothesis

Ho: The difference in the rates of incidence of radiologically defined lobar pneumonia in the vaccine and control groups will be less than 15%

Ha: There will a 15% or greater reduction in the incidence of radiologically defined lobar pneumonia between the vaccine and control groups

K. Hib Probe Trial: Study Design and Methods

Description of Study Design

The proposed study will be a double blind, individually randomized vaccine efficacy trial.

Outcome measure

Incidence of pneumonia with lobar consolidation; incidence of radiologically defined pneumonia.

Description of Vaccine and Control Groups

Children randomized to the vaccine group will be offered the licensed Hib PRP-T vaccine in addition to DTP vaccine at 6, 10 and 14 weeks. Children randomized to the control group will be offered a licensed meningococcal serogroup C polysaccharide-protein conjugate vaccine in addition to DTP vaccine at 6, 10 and 14 weeks.

Eligibility Criteria

Infants between 6 to 12 weeks of age will be eligible for enrollment on their first visit to an EPI center at their scheduled DPT visit. The second and third doses will be scheduled 4 and 8 weeks after the first dose. Children who are lagging in their immunization schedule will be eligible for their second or third dose up till their first birthday.

Exclusion Criteria

Infants will not be excluded if they have had a prior episode of disease that might have been caused by Hib. Infants who have previously received Hib vaccine, are immuno-compromised (primary or acquired), or are on immunosuppressive therapy will not be eligible to participate in this trial. Laboratory screening for these disorders will not be performed; we will screen these conditions through a brief medical history at the time of enrollment.

Unit of Analysis

The unit of analysis will be a case with (1) pneumonia with lobar consolidation and (2) radiologically defined pneumonia presenting to any health facility in the surveillance area.

Radiology

The 4-wheel drive vehicles organized by the LHB will be utilized by health staff at participating centers to refer all patients with severe pneumonia to a secondary or tertiary care facility with IV antibiotics and X-ray facilities. Every patient diagnosed with severe pneumonia will be offered free return transport at project cost to and from a center with an X-ray machine. The LHB will additionally be compensated if it is required to make alternative vehicle arrangements in medical emergencies while the primary vehicle is transporting a child with severe pneumonia. We expect to procure chest radiographs on 80% of severe pneumonia cases presenting to participating health facilities. Chest radiographs will also be taken of all children who present with IMCI classified pneumonia to a health center with X-ray facilities.

High levels of inter- and intra-observer agreement are preferred for the sake of diagnostic accuracy in chest radiographs when one or more radiologists are conducting the review.[117] Pleural effusion and the presence of multi-lobar infiltrates have been shown to have acceptable inter-observer reliability.[118] We will procure digital pictures of all radiographs using a camera focused on the radiograph set vertically on an illuminator. The digital images will be read by two independent radiologists, one in Gilgit and the other in Karachi using standardized imaging software, graphics card and computer monitor.

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Curriculum Vita

Aamir Javed Khan was born in Lahore, Pakistan on June 7, 1969. He is a graduate of the Aga Khan University Medical School and has worked there as a Research Officer in Epidemiology. Aamir joined the faculty at Johns Hopkins as a Research Associate in 1998, where he now has a part-time faculty appointment. While based out of Johns Hopkins, Aamir coordinated research on persistent excretion of poliovirus in 7 countries, including Pakistan. His current work with Johns Hopkins includes serving as the Co-Principal Investigator on the GAVI PneumoADIP Asian Field Site Development grant for urban Karachi and a Co-Investigator on the Karachi measles surveillance project.

Aamir is the Director of Interactive R&D, a contract research organization (CRO) based in Karachi. This CRO was established in March 2004 and conducts work in the areas of epidemiology, clinical trials and geographical information systems. The company currently employs 44 full-time staff members.