ICDDRB: Centre for Health & Population Research RRC APPLICATION FORM

RESEARCH PROTOCOL

Protocol No.: 2002-006

FOR OFFICE USE ONLY

RRC Approval: Yes/No Date: 27/2/2002

ERC Approval: Yes/No Date:

AEEC Approval: Yes/No Date:

Project Title:
Community-based study of bronchial asthma among children in an urban slum in Dhaka, Bangladesh

Theme: *(Check all that apply)*

- ☐ Nutrition
- ☐ Emerging and Re-emerging Infectious Diseases
- ☐ Population Dynamics
- ☐ Reproductive Health
- ☐ Vaccine evaluation
- ☒ Environmental Health
- ☐ Health Services
- ☒ Child Health
- ☐ Clinical Case Management
- ☐ Social and Behavioural Sciences

Key words:
Bronchial asthma, childhood, Pneumonia, Slum, Bangladesh

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Co-Principal Investigator(s): Haruko Takeuchi
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Co-Investigator(s):
Iwata Tsutomu Takahashi Junnkichi Yasueda Hiroshi
Akiyama Kazuo Wakai Susumu Ito Naoki

Student Investigator/Intern:
Ito Naoki

Collaborating Institute(s):
The University of Tokyo

Population: Inclusion of special groups (*Check all that apply*):

Gender
- ☒ Male
- ☒ Females

Age
- ☒ 0 – 5 years
- ☐ 5 – 9 years
- ☐ 10 – 19 years
- ☐ 20 +
- ☐ > 65

- ☐ Pregnant Women
- ☐ Fetuses
- ☐ Prisoners
- ☐ Destitutes
- ☐ Service providers
- ☐ Cognitively Impaired
  - ☐ CSW
- ☐ Others (specify _____)
- ☐ Animal

Project / study Site (*Check all the apply*):

- ☐ Dhaka Hospital
- ☐ Matlab Hospital
- ☐ Matlab DSS area
- ☐ Matlab non-DSS area
- ☐ Mirzapur
- ☒ Dhaka Community
- ☐ Chakaria
- ☐ Abhoynagar
- ☐ Mirsarai
- ☐ Patyia
- ☐ Other areas in Bangladesh _____
- ☐ Outside Bangladesh
  name of country: _____
- ☐ Multi centre trial
  (Name other countries involved)
  _____

Type of Study *(Check all that apply)*:

- ☐ Case Control study
- ☐ Community based trial / intervention
- ☐ Program Project (Umbrella)
- ☐ Secondary Data Analysis
- ☐ Clinical Trial (Hospital/Clinic)
- ☐ Family follow-up study
- ☒ Cross sectional survey
- ☐ Longitudinal Study (cohort or follow-up)
- ☐ Record Review
- ☐ Prophylactic trial
- ☐ Surveillance / monitoring
- ☐ Others

Targeted Population *(Check all that apply)*:

- ☒ No ethnic selection (Bangladeshi)
- ☐ Bangalee
- ☐ Tribal groups
- ☐ Expatriates
- ☐ Immigrants
- ☐ Refugee

Consent Process *(Check all that apply)*:

- ☒ Written
- ☐ Oral
- ☐ None
- ☒ Bengali language
- ☐ English language

Proposed Sample size: Total sample size: 2000 ☐

Sub-group
3 years old - 1,000 ☐
Parents with children <12 months (questionnaire only) - 1,000 ☐
☐

Determination of Risk: Does the Research Involve *(Check all that apply)*:

- ☐ Human exposure to radioactive agents?
- ☐ Fetal tissue or abortus?
- ☐ Investigational new device?
  (specify_____)
- ☒ Existing data available from Co-investigator
- ☐ Human exposure to infectious agents?
- ☐ Investigational new drug
- ☐ Existing data available via public archives/source
- ☐ Pathological or diagnostic clinical specimen only
- ☐ Observation of public behaviour
- ☐ New treatment regime

Yes/No

☒ ☐ Is the information recorded in such a manner that subjects can be identified from information provided directly or through identifiers linked to the subjects?

☐ ☒ Does the research deal with sensitive aspects of the subject's behaviour; sexual behaviour, alcohol use or illegal conduct such as drug use?

Could the information recorded about the individual if it became known outside of the research:

☐ ☒ a. place the subject at risk of criminal or civil liability?

☐ ☒ b. damage the subject's financial standing, reputation or employability; social rejection, lead to stigma, divorce etc.

Do you consider this research *(Check one)*:

- ☐ greater than minimal risk
- ☐ no risk
- ☒ no more than minimal risk
- ☐ only part of the diagnostic test

Minimal Risk is "a risk where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical, psychological examinations or tests. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as a part of routine physical examination".

Yes/No

☒ ☐ Is the proposal funded?

If yes, sponsor Name: HEIWA NAKAJIMA FUNDS, JAPAN & NISSAN SCIENTIFIC FUNDS, JAPAN

Yes/No

☐ ☒ Is the proposal being submitted for funding ?

If yes, name of funding agency: (1)

(2) _____

Do any of the participating investigators and/or their immediate families have an equity relationship (e.g. stockholder) with the sponsor of the project or manufacturer and/or owner of the test product or device to be studied or serve as a consultant to any of the above?

No

IF YES, submit a written statement of disclosure to the Director.

Dates of Proposed Period of Support	**Cost Required for the Budget Period ($)**
(Day, Month, Year - DD/MM/YY)	***1st Year (12 months)***
Beginning date 10 / 03 / 02	US $ 30,000
End date 12 months from starting	***Direct Cost :*** **$ 24,000** ***Total Cost :*** **$ 30,000**

Approval of the Project by the Division Director of the Applicant

The above-mentioned project has been discussed and reviewed at the Division level as well by the external reviewers. The protocol has been revised according to the reviewer's comments and is approved.

Peter Kim Streatfield
Name of the Division Director
(Acting)

P. K. Streatfield
Signature

20-2-2002
Date of Approval

Certification by the Principal Investigator

I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

Signature of PI Yukiko Wagatsuma

Date: 20/02/02

Name of Contact Person (if applicable)

Yukiko Wagatsuma

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[X] Check here if appendix is included

PROJECT SUMMARY: Describe in concise terms, the hypothesis, objectives, and the relevant background of the project. Describe concisely the experimental design and research methods for achieving the objectives. This description will serve as a succinct and precise and accurate description of the proposed research is required. This summary must be understandable and interpretable when removed from the main application. **(TYPE TEXT WITHIN THE SPACE PROVIDED).**

Principal Investigator Yukiko Wagatsuma

Project Name:
Community-based study of bronchial asthma among children in an urban slum in Dhaka, Bangladesh

Total Budget US $ 30,000 Beginning Date 10/03/02 Ending Date 31/03/03

Background
Estimates of current and lifetime prevalence of wheeze and asthma of children in tropical countries in the 1990s showed an increasing trend and found an association between urbanization and prevalence of exercise-induced bronchospasm. The ICDDR,B Asthma Study Group is currently working on an epidemiological study in Matlab (rural area) using the children under the Health and Demographic Surveillance System. This new proposal will address more pertinent issues on the epidemiology of paediatric asthma in urban areas of Bangladesh. This study will focus the hypothesis testing on the relationship between infant pneumonia and paediatric bronchial asthma in later childhood. The study will also address the estimation of prevalence due to paediatric bronchial asthma in urban area of Bangladesh.

Main hypothesis
Pneumonia in infancy significantly increases bronchial asthma in later childhood (in this study, among children aged 3 years (36-47 months)) in an urban slum area of Bangladesh.

Methods
The study will be conducted in Kamalapur where ICDDR,B is maintaining the Urban Health and Demographic Surveillance System. The Kamalapur Study Team conducted active pneumonia surveillance among the children less than 2 years old in 1999-2000 as part of a study to reduce pneumonia incidence with zinc supplementation in the same age group. Our study will recruit subjects from this previous study who are currently 36-47 months old. All eligible children from that cohort who are 3 years old (36-47 months), and are currently living in the study area, will be asked about asthma attacks. Bronchial asthma will be diagnosed using the standard questionnaire of International Studies of Asthma and Allergies in Childhood (ISAAC).
Blood and stool samples will be collected from 250 children from each with and without pneumonia in infancy. House dust will also be collected from same sub-sample children's houses using the standard aspiration technique. The recurrent wheezing rates will be compared between the groups with and without pneumonia in infancy stratified by the level of atopic sensitisation. Associations with bronchial hyperresponsiveness, serum IgE, RAST IgE Score, house dust types and social and environmental factors will be tested.

Implications of the study
This study will identify the risk factors that are relevant to practical and effective case-management of bronchial asthma in Bangladesh by suggesting possible modifications in guideline and improvements through interventions.

KEY PERSONNEL (List names of all investigators including PI and their respective specialties)

Name	*Professional Discipline/ Specialty*	*Role in the Project*
1. Yukiko Wagatsuma	Medical Epidemiologist, ECPU/PHSD	Principal Investigator
2. Haruko Takeuchi	Paediatrician / wheeze control, Tokyo Univ.	Co-PI
3. Tahmeed Ahmed	Paediatrician, CHU/CSD	Co-PI
4. Abdullah Brooks	Paediatrician/Epidemiologist, IDVS/HSRD	Co-PI
5. Naoki Ito	Paediatrician, Graduate Student, Tokyo Univ.	Co-investigator

6. Tsutomu Iwata	Paediatrican / Asthma & Allergy, Tokyo Univ.	Co-investigator
7. Hiroshi Yasueda	Physician / Allergy, Clinical Institute of National Sagamihara Hospital	
8. Kazuo Akiyama	Physician / Allergy, Clinical Institute of National Sagamihara Hospital	
9. Junnkichi Takahashi	Wako Pure Chemical Co., Japan	Co-investigator
10. Susumu Wakai	Neurosurgeon & International Health, Tokyo Univ.	Co-investigator

DESCRIPTION OF THE RESEARCH PROJECT

Hypothesis to be tested:

Concisely list in order, in the space provided, the hypothesis to be tested and the Specific Aims of the proposed study. Provide the scientific basis of the hypothesis, critically examining the observations leading to the formulation of the hypothesis.

We hypothesize that there are identifiable factors that alter the risk of child-onset asthma among low socio-economic inhabitants of an urban area.

Based on previous studies and knowledge of the disease, we hypothesize that pneumonia in early period of life (e.g., infant period) is a risk factor for bronchial asthma among children aged 3 years (36 – 47 months) in an urban low socio-economic area.

Specific Aims:

Describe the specific aims of the proposed study. State the specific parameters, biological functions/ rates/ processes that will be assessed by specific methods (TYPE WITHIN LIMITS).

1. To estimate the prevalence of bronchial asthma (recurrent wheezing) among children aged 3 years old (36–47 months) in an urban slum area.
2. To test whether those who had pneumonia during the first year of life have higher risk to have bronchial asthma (recurrent wheezing) at 3 years old (36-47 months).
3. To test the relationship between bronchial hyperresponsiveness and pneumonia in infancy.
4. To identify individual and household level risk factors for bronchial asthma (i.e., pneumonia in infancy, house-dust specific IgE level, atopic dermatitis, bronchial hyperresponsiveness, environmental house-dust level, parasite infections, breast feeding, early weaning food introduction, etc.), and to assess epidemiologic and environmental dynamics among factors in urban slum area.
5. To test the field applicability of the Modified ISAAC Questionnaire for assessing infants to prepare the cohort to monitor paediatric asthma development in later childhood (10-15 years; integrated into the Kamalapur Health and Demographic Surveillance System).

Background of the Project including Preliminary Observations

Describe the relevant background of the proposed study. Discuss the previous related works on the subject by citing specific references. Describe logically how the present hypothesis is supported by the relevant background observations including any preliminary results that may be available. Critically analyze available knowledge in the field of the proposed study and discuss the questions and gaps in the knowledge that need to be fulfilled to achieve the proposed goals. Provide scientific validity of the hypothesis on the basis of background information. If there is no sufficient information on the subject, indicate the need to develop new knowledge. Also include the **significance and rationale** of the proposed work by specifically discussing how these accomplishments will bring benefit to human health in relation to biomedical, social, and environmental perspectives. **(DO NOT EXCEED 5 PAGES, USE CONTINUATION SHEETS).**

The increasing trend of asthma has been reported from many countries, especially in industrialised countries (Peat et al, 1999). Although asthma is highly associated with hereditary characteristics of individuals, the wide variation in the prevalence observed from areas to areas shows that some environmental factors contribute to this increase (ISAAC Steering Committee, 1998; von Mutius et al, 1999). In developing countries, the urbanization has been suggested to link with this increasing trend of asthma (Yemaneberhan et al, 1997). Studies of current and lifetime prevalence of wheeze and asthma of children in tropical countries in the 1990s found an association between urbanization and exercise-induced bronchospasm (Brabin et al, 1998).

Several epidemiological observations show that microbial burden during early infancy is protective against atopic sensitisation (Flynn et al, 1994; Martinez et al, 1999). Asthma is more common in higher socio-economic societies and in people who experienced less respiratory infections during infancy (von Mutius et al, 1994). A Bangladesh study, however, reported a higher asthma prevalence in rural and lower socio-economic populations (Asthma Association, Bangladesh, 2001).

In Bangladesh, asthma was reported as the third leading cause of death in 1996, consisting 5.20% of deaths of the whole nation. In contrast to previous publications, the percentage was higher in rural areas than in urban areas, 5.70% and 3.82% respectively (Bangladesh Bureau of Statistics, 1999). Since there are many factors associated with higher risk of asthma, many of which may have greater importance in specific settings, public health interventions should emphasise those most relevant to the local situation. A nation wide survey in 1999 in Bangladesh showed higher than expected prevalence of asthma, particularly among younger age groups (Asthma Association, Bangladesh, 2001). In November 1999, we conducted a survey in a rural area of Mymensingh, Bangladesh and found that the prevalence of asthma among children was 8.5%, and that a history of pneumonia in infancy was a significant risk factor (Takeuchi et al, 2000).

Pneumonia is a leading cause of death among children in Bangladesh. The infant mortality rate in 1997 was 60 / 1000 live births (Bangladesh Bureau of Statistics, 1999). About one third was due to pneumonia in 1989 (Spika et al, 1989). Mortality rate due to pneumonia among infants younger than 6 months was 139 / 1000 live births in 1985 and 16 / 1000 live births among children less than 5 years old (Baqui et al, 1998). A prospective study conducted in a rural area in 1989 showed that the incidence of pneumonia among infants less than 6 months old and 6 months to 1 year old was 0.51 and 0.25 times/year/person respectively (Zaman et al, 1997). The main bacterial causes of pneumonia are *S. pneumoniae* and *H. influenzae*, while a principal non-bacterial cause is Respiratory Syncytial Virus (RSV) (Huq et al, 1990; Utsunomiya et al, 1998). Not only RSV pneumonia (Sigurs N, 1995; Hogg et al, 1999) but also bacterial pneumonia has been associated with wheezing among young children in developing countries (von Mutius E et al, 1996; Stein et al, 1999).

There have been only a few recent publications on paediatric asthma in Bangladesh (Asthma Association, Bangladesh, 2001). Currently, an epidemiological study among children focusing on pneumonia as a risk factor is carrying out in a rural area of Bangladesh (Matlab). As far as pneumonia during infancy is concerned, however, it may be more common and serious in urban slums than in rural areas. A community-based study in Kamalapur area employing weekly home surveillance showed that

the crude incidence of pneumonia among children aged less than 2 years was 1.9 episodes/child per year (Brooks A, personal communication). In non-slum areas in Dhaka, where the standard of living is higher, asthma incidence may be relatively high while pneumonia incidence may be low. It would be useful to study in these two types of urban population to determine whether early pneumonia morbidity is associated with an increased likelihood of asthma in later childhood. In this study we propose to focus on the risk factors related to paediatric asthma among the urban population with low socio-economic status in Kamalapur area of Dhaka City. Kamalapur has been assigned as one of the health and demographic surveillance areas in the urban slum setting for ICDDR,B. The ICDDR,B is presently conducting health and demographic surveillance system and various interventions for diseases of major public health importance, such as diarrhoea, acute respiratory infections and their pathogens, vector-borne diseases like dengue and dengue haemorrhagic fever, and emerging problems like paediatric asthma.

The standard set of indicators to monitor for the morbidity/burden of diseases due to asthma has been prepared and currently been tested in more than 50 countries (Asher et al., 1995). The study proposes to include these standard questionnaires for Kamalapur surveillance system.

Diagnosing infant asthma for preventing paediatric asthma

Diagnosis of infant asthma is not always easy, thus it is required to develop better instruments for diagnosis. However, the diagnosis is likely to be delayed because of the diversity of the signs and symptoms. In addition to the difficulty in obtaining the objective evidence of reversible lower airway obstruction, age-specific complaints from the patients are seldom specific for asthma, and may be only infrequently brought to physician's attention. The principal respiratory function tests, like spirometry or measurement of peak flow, cannot be performed by infants. Information about family history of asthma is important, but the positive rate for atopic antigens is rather low during infancy. Recently recurrent dry cough especially which worsens during the night, or with infection is considered an important clinical sign in infants and young children (NIH, 1998). Although there are diseases with this type of cough to be differentiated, such as congenital malformations, foreign bodies or congenital heart diseases, recurrent dry cough is important both for diagnosis and better lifetime control of asthma (Furusho et al, 2000). To find an association between infant wheezing and later asthma, we will develop and test a questionnaire focusing on recurrent cough and will add it to the ISAAC standard questionnaire. The final outcome of paediatric asthma to test the association with recurrent cough at infancy will be monitored through the Kamalapur Surveillance System.

Research Design and Methods

Describe in detail the methods and procedures that will be used to accomplish the objectives and specific aims of the project. Discuss the alternative methods that are available and justify the use of the method proposed in the study. Justify the scientific validity of the methodological approach (biomedical, social, or environmental) as an investigation tool to achieve the specific aims. Discuss the limitations and difficulties of the proposed procedures and sufficiently justify the use of them. Discuss the ethical issues related to biomedical and social research for employing special procedures, such as invasive procedures in sick children, use of isotopes or any other hazardous materials, or social questionnaires relating to individual privacy. Point out safety procedures to be observed for protection of individuals during any situations or materials that may be injurious to human health. The methodology section should be sufficiently descriptive to allow the reviewers to make valid and unambiguous assessment of the project. **(DO NOT EXCEED TEN PAGES, USE CONTINUATION SHEETS).**

Study area

The Study Site and Population

Kamalapur is an impoverished urban area located in the southeastern sector of Dhaka (approximately 30 – 40 minutes drive from ICDDR,B). The surveillance area is spread over 4.0 sq Km (1.5 sq mile or 988 acres). It is located between a train terminal and a bus station, thus serving as a major point of population ingress and egress. There are 32,339 households in the community, all of which have been entered into an electronic database maintained at ICDDR,B. (We will plan on representationally enrolling approximately 20,000 individuals from 4,000-6,000 households [see below] in the dengue surveillance system.)

There are currently five ongoing activities at the study site that make it ideal for both cross-sectional and longitudinal surveillance. These have been in operation since 1998 and are being used to survey for pneumonia, diarrhoea and dysentery, as well other diseases of high prevalence in impoverished urban areas. In December 2000, we adapted the system to accommodate surveillance for dengue and dengue haemorrhagic fever.

Mapping and Enumeration: The entire community has been mapped twice at two-yearly intervals. Small cluster maps are drawn to scale that emphasise epidemiological parameters, including houses, industry, schools, other gathering places, and natural features such as water and flora. To facilitate surveillance and intervention activities, the community has been organised into seven strata that roughly follow geographical landmarks in the community. The seven strata have been organised into 380 clusters. The mean number of clusters per stratum is 63, and the mean number of households per cluster is 87. Each house is assigned a 7-digit unique identification number corresponding to its stratum, cluster, and structure number. This serves as a digital address that is location-specific. Enumeration occurs at the same time. Every household is interviewed and all members are counted, and basic demographic data, including name, age, gender, and name of the household head, are recorded and stored electronically.

Active Surveillance: Field Research Assistants (FRAs) collect data from all households under surveillance once weekly, by using a standardised calendar questionnaire administered to a key informant, and asking about occurrence of specific symptoms and signs for each day of the week since the last visit. If the criteria for any disease under study are present, or if any household member has danger signs, the FRA refers the individual to the field office clinic. In addition to routine weekly visits to all surveillance households, the FRA also follows up on all participants who have been placed on antibiotics within the last 48 hours and/or who should be followed up according to treatment protocols. The number of FRAs varies according to the surveillance requirements. All are under the direct daily supervision of a Field Research Officer (FRO). The FRO submits daily reports to our office, giving performance indicators for surveillance activities (thus allowing for daily monitoring of the system). Additionally, the FRO submits monthly summary reports that permits cross checks. Verbal autopsies are performed on death cases. This active surveillance core system permits the addition of new data collection activities, such as cross-sectional surveys and the addition of new diseases for surveillance. Such additions are commonly performed for specific studies.

Clinical Management: The field office is comprised of a field clinic staffed by medical officers, nurses, and health assistants who are organised into teams. The clinic operates six days weekly from 08:30 to 17:00. The teams attend patients that are FRA-referred and self-referred. The teams use a triage algorithm based on disease severity and whether a disease is under study (reportable) to prioritise patients. Patients referred by the FRA for a reportable disease are interviewed using standardised questionnaires. Samples are collected from these patients and are sent to the lab at ICDDR,B. Disease treatment is standardised according to protocol. Indications for referral to hospital are based on an algorithm by disease. The clinic also collects surveillance data. It submits weekly reports on the numbers of patients seen and disease distribution.

Training: Before a new surveillance activity or intervention takes place, all project staff undergo an average of two weeks' of training pertinent to all the new activity/disease.

Monitoring and Evaluation: A 2% sample of the surveillance interviews are repeated and compared for inter-observer agreement. Additionally, spot checks are performed for the clinic to determine sample collection, case diagnosis, and management. Additionally, the daily and monthly field surveillance reports, and the weekly clinic reports provide performance indicators used in monitoring. Feedback is provided to the staff at weekly staff meetings in the field.

Features of the Study Population

The total population as of 30 November 2000 was 118,654. The outmigration rate averages < 2%; however, the population of the community has doubled since 1997, largely as a result of immigration from rural areas. Population density is 29,663 individuals per square kilometre (191 persons per acre or 77,048/sq mile). The population is relatively young. In our 1998 census, the mean age of males was 32.8 years, the mean age of females was 24.2 years, and 11.2% of the population was younger than five years old. There is a mixture of squatter settlements and formal permanent structures. The mean household number is 4.0, but ranges from 1 – 20 persons per household. The educational level in the community among adults is low; however, the majority of children less than 12 years attend school. Mean level of schooling for men above 18 years old is 4.5 years, and for women is 3.1 years. Unemployment is relatively low. Most men less than 60 years are employed at least part time, resulting in total unemployment of only 1.6%. Among occupations, the most common for men are merchant (24.2%), office worker (21.6%), rickshaw puller (17.0%), and skilled labourers (12.3%). Day labourers and unskilled workers comprise only 7.7%. The mean family income is TK 3,000 or about US $60/month.

Thus, the surveillance community demonstrates potential risk factors of low income and overcrowding. Other data show that there is also an absence of adequate sanitation, appropriate waste management, and other services that may affect vector prevalence, and a high disease burden of other infectious diseases (such as diarrhoea and pneumonia), all of which may combine to make this urban area a potentially high risk area for dengue transmission.

Study subjects & sampling

Specific Aim 1: To estimate the prevalence of bronchial asthma among children aged 36-47 months old.

All recruited infants at the age of 2-11 months old in 1999 for the pneumonia surveillance study (originally recruited number: approximately 1,800) will be followed up to find the prevalence of current wheezing at the age of 3 years old (36-47 months) in 2002, among those who remain in the study area (estimated number: 1,000). We will determine what proportion of them developed bronchial asthma using the standard questionnaire of International Studies of Asthma and Allergies in Childhood (ISAAC Phase II Study Protocol) (Asher et al, 1995).

Specific Aim 2: To test the relationship between pneumonia in infancy and later development of bronchial asthma at 3 years old.

The study will assess the relationship between recurrent wheezing at 3 years old (36-47 months; diagnosed by ISAAC Standardised Questionnaire) and infant pneumonia using among the same children described above (Table 3). Using the records from the previous pneumonia study in Kamalapur, we will identify which of the study children were diagnosed with pneumonia in infancy (< 12 months). The data on respiratory morbidity in the clinic record book will be entered into the computer for the analysis between observed respiratory illness in the first and second year of life and current wheezing at 3 years of age. We will examine the skin of all children for atopic dermatitis. The operational definition of atopic dermatitis should follow the criteria of ISAAC.

For stratification analyses using the blood, stool and housedust results, 250 children will be matched by age (within 2-3 month) with 250 non-pneumonia children. The estimated distribution is shown in Table 3 (see sample size calculation).

Specific Aim 3: To test the relationship between bronchial hyperresponsiveness and pneumonia in infancy.

Hypertonic saline challenge test will be used to test the relationship between detected airway hyperresponsiveness at the age of 36-47 months (BHR; followed by ISAAC Phase II Study Protocol) and pneumonia during infancy. Bronchial hyper responsiveness (BHR) is one of the major physiological and pathological characteristics of asthmatic patients and causes asthmatic attack. As described before it has been suggested that pneumonia or lower respiratory infection would be one of the strong risk factors for developing childhood asthma. The objective of this study is to test the relationship between infantile pneumonia and BHR at the age of 3 years old. 200 sub-samples of study children will be randomly chosen (age-matched) from each group with and without infant pneumonia (Table 4).

Specific Aim 4: To identify individual and household level risk factors for bronchial asthma, and to assess epidemiologic and environmental dynamics among factors in urban slum area.

250 infant pneumonia cases will be matched by age (within 2-3 months) with non-pneumonia 250 children, and these children will be asked for blood, stool and housedust sample collection (estimated sample size: 500; Table 3). This is to identify individual and household level risk factors for bronchial asthma (i.e., pneumonia in infancy, total serum IgE, house-dust specific IgE level, atopic dermatitis, bronchial hyperresponsiveness, environmental house-dust level, parasite infections, breast feeding, early weaning food introduction, etc.), and to assess epidemiologic and environmental dynamics among factors in urban slum area.

Specific Aim 5: To test the field applicability of the Modified ISAAC Questionnaire for assessing infants to prepare the cohort to monitor paediatric asthma development in later childhood (10-15 years; integrated into the Kamalapur Health and Demographic Surveillance System) (Descriptive study to pretest infant questionnaire for Reactive Airways Disease [RAD]).

All the children (estimated number 1,000) aged 2-11 months old presently under active surveillance will be asked questions about asthma using a standardised questionnaire for infant asthma and will be routinely followed thereafter, as part of ongoing morbidity surveillance. Questions about asthma will be incorporated into the Kamalapur field clinic's standardised clinic questionnaire. Thus, we will capture data on all children in the age group who present to the clinic with respiratory complaints and these can be followed longitudinally through time until they reach 15 years old. Among those who come with age 2-11 months infants to the Centre's Kamalapur clinic referred by the community health workers with any respiratory ill conditions will be asked with questions for reactive airway disease (RAD).

The idea will be total integration of some selected questions specific for bronchial asthma into the Kamalapur Health and Demographic System in the near future. Point estimates for the year-specific cohort might not be sufficient to make a conclusion due to the attrition over time. Time-trend analysis

and survival analysis, however, will be extremely useful using total surveillance population over the years (e.g. 10-15 years).

Sample size calculation

The study assume that about 30% children aged 36-47months would have wheeze in this population at the time of survey. This estimate was made from the value of Matlab study among 5 years (17%) and with the consideration of younger age for this proposed study (Asthma Association, Bangladesh, 2001). To estimate this level of prevalence with ± 3% precision with 95% confidence limit, we need a minimum population of 900. With estimated refusal of 10%, the study will aim to recruit all the children of 3 years (36-47 months) who participated in the previous pneumonia surveillance study and currently live in Kamalapur surveillance area for questionnaire (estimated available number will be 1000).

Given the assumption of 70% of children with pneumonia in infancy and 50% excess in recurrent wheezing rates over Matlab study data (justified by younger age than Matlab), 35% and 21% of wheezing cases among those who had and who did not have pneumonia in infancy might be observed in this Kamalapur study. Table 1 shows estimated distribution for all 1,000 children.

Table 1: Recurrent wheezing by pneumonia in infancy (estimated distribution of total 1,000 subjects)

Pneumonia in infancy	Recurrent wheezing at 3 years old (36-47 months)		Total
	+	-	
+	245(35%)[1]	455(65%)	700(100%) (70%)
-	63(21%)[1]	237(79%)	300(100%)(30%)
Total	308(31.0%)	692(69%)	1,000 (100%)

1 The percentages were estimated (Matlab value x 1.5) from the previous asthma study in Matlab.

Sample size calculations for risk factor analysis are difficult because there has been only one previous study of this sort in Matlab and laboratory assays have not been completed yet. It is unclear to what extent we can generalise Matlab results to the different age group (5 years old for Matlab study) of the very different setting in urban slum population. Bronchial hyperresponsiveness test was not included in previous study in Matlab. There are no data on which to base sample size calculations for risk factors; nevertheless, as an assumption, if 30% of this study population has high level of house dust-specific IgE (IgE RAST), then the distribution stratified by RAST Score might be assumed as in Table 2. The detectable minimum difference in proportions having recurrent wheezing for the cells with and without pneumonia in infancy assumed to be 0.11% for RAST negative group. Given the sampled population with above assumption (proportion distribution as in Table 2), for detecting the difference in proportions with the significance level of 5% (1-sided) and 80% power, using the formula of power calculation (Marascuilo and McSweeney, 1977), the necessary sample size for equal size will be 250 per group. Therefore, we would like to collect blood samples for RAST Score measurements from 250 age-matched (e.g., within 2-3 months) subjects with and without pneumonia in infancy (total number: 500; Table 3). It is important to have adequate number for each cell as well as margins after stratified by RAST level so that we can test the hypothesis of independent increment effect on the risk of recurrent wheezing after controlling the atopic sensitisation level. With the assumption of 30% houses have above cut-off housedust level and similar recurrent wheezing rates as calculated above, having a power above 80%, the study requires to collect housedust from all the houses of the same children whose blood samples are

collected. To facilitate the analysis of confounding variable of parasite infection, the study will collect stool sample from the same children.

Table2: RAST Score level by recurrent wheezing and pneumonia in infancy (estimated distribution of total 1,000 subjects)

Recurrent wheezing at 3 years old (36-47 months)		RAST Score above cut-off level		Total
		+	-	
+	+ Pneumonia in infancy	123(50%)	122(50%)	245(100%)
	- Pneumonia in infancy	38(60%)	25(40%)	63(100%)
-	+ Pneumonia in infancy	68(15%)	387(85%)	455(100%)
	- Pneumonia in infancy	71(30%)	166(70%)	237(100%)
Total		300(30%)	700(70%)	1,000(100%)

Table 3: RAST Score level by recurrent wheezing and pneumonia in infancy (estimated distribution of 500 sub-samples)

Recurrent wheezing At 3 years old (36-47 months)		RAST Score above cut-off level		Total
		+	-	
+	+ Pneumonia in infancy	44(50%)	44(50%)	88(100%)
	- Pneumonia in infancy	32(60%)	21(40%)	53(100%)
-	+ Pneumonia in infancy	24(15%)	138(85%)	162(100%)
	- Pneumonia in infancy	59(30%)	138(70%)	197(100%)
Total		159(32%)	341(68%)	500(100%)

For hyperresponsiveness test, given the assumption of hyperresponsiveness in 30% and 15% for those with and without pneumonia in infancy respectively, minimum sample size required for equal samples will be 130. With the consideration of stratification strategy, but with the logistical limitation of total test numbers within the proposed study period, the study will have 200 age-matched samples for each group with and without pneumonia in infancy (Table 4).

Table 4: Hyperresponsiveness by pneumonia in infancy

	Hyperresponsiveness +	Hyperresponsiveness -	Total
+ Pneumonia in infancy	210 (30%) => 60	490 (70%) => 140	700 (100%) => 200
- Pneumonia in infancy	45 (15%) => 30	255 (85%) => 170	300 (100%) => 200
Total	255 (25%) => 90	745 (75%) => 310	1,000 => 400

=> shows sub-sample (200 samples each with and without pneumonia in infancy) for hyperresponsiveness test.

Measurement

Measurement in the field

1. Questionnaire

- **Modified ISAAC Questionnaire, parent interview**

The questionnaire contains items about wheezing, allergic rhinitis, eczema and risk factors for bronchial asthma. A questionnaire adopted from ISAAC will be used for diagnosing asthma and allergy. Risk factors include artificial feeding, introduction of eggs as weaning food, living circumstances such as carpets or cooking fuel, household smoking and crowdedness, family history, socio-economic status of families and demographic characteristics. It will be translated into Bangla confirmed with back translation. Answers will be obtained by in-person interview from guardians mainly mothers, otherwise fathers, grandparents, aunts, sisters or other adult people who know the child and can answer the questions.

The diagnosis of bronchial asthma (recurrent wheezing) during the fourth year of life will be determined based on the interview result of positive wheezing episode during the past one year period from the interview date. This is the accepted standard practice for the asthma specialists in the international board, thus this study follows this criteria.

- **Questionnaire for infant asthma, parent interview**

We have added questions about recurrent cough at night, during infection and at exercise. This is because we have to depend early diagnosis of infant asthma on observation of clinical signs and symptoms.

2. Information on past morbidity

Data on pneumonia and other infectious diseases, such as diarrhoea, measles or whooping cough, and records of immunization is obtained from the records of Kamalapur. The previous pneumonia study in Kamalapur recorded for the study subjects for the above information up to 24 months old.

Sample collection

1. Blood and stool samples collection

Three (3) ml of venous blood and small amount of stool (the size of thumb) samples will be collected from study children. Blood samples will be collected into two vials; one for eosinophil counting; and one for separating serum. Separated serum will be kept at –70 degrees C and sent to Tokyo for IgE RIST (serum total IgE), IgE RAST (house dust-specific IgE) tests and cytokine measurements (Sporic et al, 1990). Stool samples will be examined for intestinal parasites by formalin concentration technique at parasitology Unit, ICDDR,B (Johanessen, 1998).

2. Housedust collection from bedding materials

House dust will be collected from the same children's' houses as blood and stool collection using the standard aspiration technique. The study will collect the house dust to test the mite allergen contents. A vacuum cleaner of 1500 W equipped with a paper bag to filter the dust will be used for house dust collection (Johanessen, 1998).

Site and time of collection

Sampling sites will be the bedding material of the child and the carpet of the house (at least 2 sites from each house). The standard sampling technique will be used and the duration of aspiration will be 2 minutes/m^2 for 4 minutes (Platts-Mills et al, 1995). From the collected dust in the paper bag, lighter upper part of dust will be removed and heavier part like the sandy dust at the bottom will only be used for mite allergen test and endotoxin test.

Measurement on children

1. Measurement for bronchial hyperresponsiveness (4.5% Saline challenge test measured by Pulse-oximetor)

Hypertonic saline challenge test will be used to test the relationship between detected airway hyperresponsiveness at 36-47 months old (BHR; followed by ISAAC Phase II Study Protocol) and pneumonia during infancy. Besides taking history of asthma or wheezing by questionnaire, the study will examine bronchial hyperresponsiveness (BHR), which is one of the major physiological and pathological characteristics of asthmatic patients (i.e., BHR causes asthmatic attack). As described before, it has been suggested that pneumonia or lower respiratory infection could be one of the major risk factors for developing childhood asthma. The objective of this study is to test the relationship between infantile pneumonia and BHR at the age of 36-47 months old. We will recruit subjects from the children who will cooperate to collect blood samples and cooperate with this challenge test. We have been keeping their record whether they have the history of infantile pneumonia or not. BHR will be measured for sub-sample of study children 200 (random sample) each from with and without pneumonia in infancy.

In many epidemiological surveys of asthma in children, bronchial hyperresponsiveness (BHR) to inhaled pharmacological agents has been used as an objective measure of asthma. Bronchial provocation tests using hyperosmolar aerosols are, however, practical to use in the identification and assessment of BHR as non-pharmacological agents (Schoeffel et al 1981). Bronchial challenge by inhaling aerosols of hyperosmolar saline has obvious appeal from an ethical standpoint and provides an attractive and much less costly alternative to pharmacological agents. There may be an advantage in using hyperosmolar challenges that provoke airway narrowing indirectly by causing endogenous release of mediators to which the subject is sensitive. In the field these challenges have sensitivity for current asthma in the order of 47% and specificity in the order of 92% (Riedler et al, 1994b). For the evaluation of BHR, aiming at measuring the baseline airflow obstruction, in this challenge we will measure oxygen saturation fall with pulse oximeter (SpO_2) monitoring instead of measuring FEV1 (Forced Expiratory Volume at the first second) or respiratory resistance change with spirometer, because of the study subjects are 3 years old who could not manage to handle spirometer (Nicola et al, 1991).

Safety of Saline challenge test

As with any other bronchial provocation tests, non-isotonic aerosols leads to airway narrowing that can be of sudden onset and cause a marked reduction in arterial oxygen tension. We do not recommend a challenge in children with their asthmatic attack within 48 hours or resting SpO_2 less than 95% (exclusion criteria). For the reverse of an acute attack, inhaled bronchodilators and if in need oxygen should be at hand in case of emergency. The study will set up oxygen and drip infusion with steroids i.v. as bronchodilators. Only trained personnel should administer these challenges and immediate access to medical assistance should be available at the clinic. Children should never leave the clinic before the reversion to their baseline SpO_2 level. The initial challenge period should be limited to 30 seconds.

Another exclusion criteria will be medications. Some medications for the treatment of asthma can inhibit the response to hyperosmolar saline, thus subjects will be excluded or should withhold certain asthma medications prior to the challenge test; anti-histamines for 48 hrs, theophylline and long acting beta2 adrenorceptor agonists for 24 hrs.

Site for the test
Hyperresponsiveness test will be conducted in ICDDR,B Kamalapur clinic. For the safety procedure assurance, the test for initial 50 patients will be conducted in ICDDR,B Dhaka Hospital with close supervision of physicians and a clinical scientist (Dr. Tahmeed Ahmed; Co-PI). This helps the physicians who ultimately conduct the test in clinic setting, gaining skills and confidence in conducting the test.

Procedure
Nebulizers will be used to generate non-isotonic aerosols. We will measure the output of the nebulae by weighing the canister and tubing prior to and on completion of each challenge test, to ensure that the output is adequate for each challenge.
The subject will be measured stable (in normal breathing) baseline SpO_2. If this is less than 95%, no saline will be given; an inhaled bronchodilator is administered, confirming SpO_2 elevation above 95%. The time of inhalation of the saline aerosol is progressively increased. The initial exposure time to the aerosol is 30 seconds. One minute later the next measurement of SpO_2 will be made. The next challenge period should follow within three minutes of the end of the previous one. If delta SpO_2 (calculated by baseline SpO_2 value minus post-hypertonic saline inhalation value) is 0 or minus value the exposure time is doubled. If delta SpO_2 is between 1 and 3%, the exposure time should be repeated. After two repetitions of the exposure time, if SpO_2 value is still 1 to 3% below the baseline value, the duration of the inhalation period should be doubled again according to the protocol. If delta SpO_2 is more than 4% or SpO_2 is less than 92% the bronchial challenge will be stopped (Sole et al, 1999). The inhalation periods are 30 seconds, 1 minutes, 2 minutes, 4 minutes and 8 minutes, when repetitions are not needed (Sole et al, 1999). In any case, the inhalation of hypertonic saline will be stopped after a maximum inhalation period of 15.5 minutes. The canister and tubing will be weighed before the first and after the final challenge period to measure the total dose of aerosol delivered. To obtain the rate of nebulizer output in ml per minute, the total output will be divided by the total time of exposure.

The hypertonic saline challenge has been performed widely in the laboratory and in epidemiological studies in the field, and has been found to be safe and well tolerated (Riedler et al 1994a). The degree of expected bronchoconstriction would not result in clinically apparent symptoms and can be readily reversed with the inhalation of a bronchodilator. The challenge is designed in dose-response fashion so that only a very small dose is delivered initially, ensuring a safe challenge even for those subjects with very sensitive airways.

Expression of the response
Firstly, the dose delivered in each challenge period is calculated by multiplying the output in ml per minute by the time of the challenge period. A dose-response curve is constructed by plotting the delta SpO_2, against the cumulative dose of aerosol delivered, expressed in ml on a log scale for each inhalation period.

2. Examination for atopic dermatitis

We will examine the skin of all study children with questionnaire by inspection for eczema to find association between pneumonia during infancy and atopic sensitisation. The operational definition of atopic dermatitis should be followed by ISAAC definition (ISAAC Phase II Study Protocol). The visible flexural dermatitis is a key feature in diagnosing atopic dermatitis. The field research assistants will be able to correctly ascertain this physical sign after training with a standard set of photographic prints. The photographic protocol of ISAAC on its use will be provided in the field. This protocol was developed using a standard set of photographs and accompanying instructions, that terms flexural dermatitis. There was a study for the assessment of this protocol, which revealed excellent agreement between trained nurses and a dermatologist with regard to the presence or absence of the skin sign (case definition) with 97% agreement (chance corrected index 0.90 (95%CI 0.77-0.99; Williams HC, et al., 1994). This protocol is known as the U.K. working party's criteria for atopic dermatitis (Williams HC et al., 1994; 1995; 1996). An individual must have itchy skin condition plus three or more of the followings: history of asthma/hay fever, a history of generalized dry skin, onset under the age of 2 years, or visible flexural

dermatitis. The protocol is easy to perform and takes only one minute per patient to ascertain. The quality control will be conducted by comparing each observer's assessment of these standard photographs with ISAAC's protocol. This centralized approach will achieve a degree of standardization among field workers during field studies.

3. Nutrition status of children

Body weight and height will be measured for study children of 36-47 months (500 sub-sample children as blood sampling) at the Kamalapur ICDDR,B Clinic. Body weight will be measured with a digital scale (100g precision) and height will be measured by a vertical height board with 0.1 cm accuracy (made at ICDDR,B workshop).

Laboratory tests

1. **Serum IgE (IgE RIST)**

Total serum IgE levels will be measured by commercially available ImmunoCAP System IgE FEIA (Fluoroimmunoassay; Pharmacia K.K., Tokyo) (Zetterstrom et al., 1981, Johanessen, 1988).

2. **Serum specific IgE (IgE RAST)**

Serum IgE antibodies specific to house dust, mite and egg white will be measured by commercially available ImmunoCAP System RAST (radioallergosorbent test) FEIA (Pharmacia K.K., Tokyo) (Okundira et al., 1991).

3. Eosinophil count

Collected blood will be sent to Clinical Service Laboratory, ICDDR,B for eosinophil counting.

4. Cytokine measurements

Serum will be examined for cytokine (IL-4, IL-5, etc.) level in Tokyo (Methodology will be specified after confirming with collaborative laboratories in Tokyo).

5. **Intestinal parasite infection**

Intestinal parasites will be examined by the standardized formalin concentration technique (collaboration with Dr. Rashidul Haque, Head, Parasitology Unit, ICDDR,B).

6. **Limulus test (endotoxin measurement)**

House dust collection paper will be frozen at –20 degrees and sent to Tokyo to test the content of endotoxin in house dust by Limulus test (Limulus Colour KY Test Wako; Wako Pure Chemicals Industries Ltd., Osaka, Japan).

Limulus test uses the characteristic of lysate of hemolymph of horseshoe crab, *Limulus polyphemus,* to form gel-clot by activation of endotoxin. HS-test Wako is either a quantitative method detecting increment of turbidity due to gel-formation (turbidimetric kinetic assay), with specific computerized toxinometer, or a semiquantitative visual gel-clot formation test (Wako Pure Chemical Co., Tokyo, Japan).

7. **ELISA test (house dust measurement)**

There are three ways to estimate mite allergen: 1) direct count of mites; 2) semi-quantification of mite body and feces (Acarex test); and 3) Enzyme-linked Immuno Sorbant Assay (ELISA) of *D. pteronyssinus* antigen. This study will use ELISA since this is the most reliable method, although Acarex test was used for the pervious Matlab study. The samples will be examined at National Sagamihara Hospital Clinical Institute, Kanagawa, Japan.

Quality control

All questionnaire and data collection instruments will be pretested. The questionnaire will be administered in Bangla. A Field Research Officer, along with the PIs will be responsible for quality control of data through spot-checking and checking of the completed forms. The supervisor will repeat the questionnaire with some mothers (around 10%) selected at random, and the results will be checked against the field worker's form. There will be regular meetings at Kamalapur with PIs, supervisors and field workers to resolve any issues.

Data quality of the laboratory procedures will be assured by making appropriate labelling system of samples, by preparing proper flow system of the samples, by establishing good checking system and standardization of the equipment.

Treatment

Children will be given treatment for bronchial asthma and for intestinal parasites. The children will be referred to the Kamalapur ICDDR,B Clinic and will be examined by the study physician. If necessary, patients will be referred to other NGO clinics or hospitals for the treatment.

The treatment of asthma at the Kamalapur ICDDR,B clinic will be as follows (Mollah et al, 2000):

Mild acute asthma:

Salbutamol inhaler 1-2 puffs every 3-4 hours for 12-24 hours or oral salbutamol 0.2-0.4mg/kg/day every 8 hours.

Moderate acute asthma:

Salbutamol inhaler with spacer 2 puffs every 20 minutes for 3 times. If no improvement, nebulized salbutamol 0.15 to 0.3 mg/kg. Then to continue salbutamol inhaler 2 puffs 2-4 hourly for 24-36 hours. Oral prednisolone1-2 mg/kg/day in 3 divided doses for 3 days is to be added.

Severe asthma:

Needs immediate hospitalisation. In addition to oxygen inhalation the patient is to be given nebulized salbutamol 0.15 to 0.3 mg/kg/dose every 20 minutes for 3 times or continuously. At the same time inj. hydrocortisone 3-4 mg/kg 4-6 hourly or oral prednisolone 2 mg/kg/starting dose and then 1mg/kg 6-12 hourly will be given. If improvement is observed, salbutamol 2 puffs will be given 2-4 hourly for 3-5 days and oral prednisolone 1-2 mg/kg/day for 3-10 days. According to the severity of asthma long-term management should be given at least for 3 months. The choices of drugs are oral salbutamol, sodium cromoglycate, aldesine and long-acting beta2 agonist (salmeterol).

Treatment of intestinal parasites:

Treatment should be given with oral mebendazol 100 mg/ twice daily for 3 days.

Facilities Available

Describe the availability of physical facilities at the place where the study will be carried out. For clinical and laboratory-based studies, indicate the provision of hospital and other types of patient's care facilities and adequate laboratory support. Point out the laboratory facilities and major equipments that will be required for the study. For field studies, describe the field area including its size, population, and means of communications. **(TYPE WITHIN THE PROVIDED SPACE).**

The International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) has large multi-disciplinary international and national scientific research staff. This study will be conducted in urban Dhaka. ICDDR,B has been maintaining a field research area at Kamalapur for almost four years. Given the presence of ongoing health and demographic surveillance system, effective referral facilities, well-established infrastructure at ICDDR,B laboratories and data-management system, it offers excellent research facilities for this study.

Data Analysis

Describe plans for data analysis. Indicate whether data will be analysed by the investigators themselves or by other professionals. Specify what statistical software packages will be used and if the study is blinded, when the code will be opened. For clinical trials, indicate if interim data analysis will be required to monitor further progress of the study. **(TYPE WITHIN THE PROVIDED SPACE).**

Data will be analysed by investigators in Epi-Info, SPSS, SAS and STATA software packages. Initial exploratory data analysis will be conducted to examine the distribution of the variables.

Specific Aim 1: To estimate the prevalence of bronchial asthma among the children aged 36-47 months

Recurrent wheezing rates will be estimated and expressed with 95% confidence interval. Overall and categorized estimates (e.g., by sex and socio-economic status, etc.) will be calculated.

Specific Aim 2: To test the relationship between pneumonia in infancy and bronchial asthma among the children aged 3 years old

We will compare the recurrent wheezing rates between the children with and without pneumonia in infancy and calculate the odds ratios with confidence intervals. Other individual and environment related factors will be assessed through appropriate stratification analyses.

Specific Aim 3: To test the association between bronchial hyperresponsiveness and infant pneumonia.

The analysis will use the value of SpO2 fall (delta SpO2) or the final SpO2 value for the inhaled aerosol volume per minutes. The former will use the categorical statistics (e.g., chi-square, non-parametric methods, etc.) and the latter will use t-test, F-test, ANOVA, etc. The identifiable confounding factors will be analysed by appropriate stratifications.

Specific Aim 4: To identify individual and household level risk factors for bronchial asthma, and to assess epidemiologic and environmental dynamics among factors in urban slum area.

Associations with IgE RIST, IgE RAST Score, house dust types & level, family history of asthma and social and environmental factors will be assessed with appropriate statistics (e.g., t test, F test, chi-square test, Exact test, ANOVA, etc.). We will use logistic regression models incorporating Generalized Estimating Equations (GEE) to assess both individual and household level risk factors, and, if necessary, to account for household clustering.

Specific Aim 5: To test the field applicability of the Modified ISAAC Questionnaire for assessing infants to prepare the cohort to monitor paediatric asthma development in later childhood

This component will be a descriptive study. Reported symptoms possibly related to the development of paediatric asthma will be described with estimated proportions. The study will assist to develop a database to monitor the surveillance population on paediatric asthma integrated into the Kamalapur Health and Demographic Surveillance System.

Ethical Assurance for Protection of Human Rights

Describe in the space provided the justifications for conducting this research in human subjects. If the study needs observations on sick individuals, provide sufficient reasons for using them. Indicate how subject's rights are protected and if there is any benefit or risk to each subject of the study.

1. Requirements for study population: The required study population is the inhabitants of Kamalapur ICDDR,B Urban Health and Demographic Surveillance area. The study will identify the study subjects who participated pneumonia active surveillance study in 1999 (when they were 2-11 months infants). They have become 3 years old (36-47 months) in 2002 and they will comprise the study population. Although 1,800 children participated in the previous study, we estimate approximately 1,000 children are still living in the surveillance area. Because of the necessary sample size with expected precision for the recurrent wheezing prevalence estimate, we require to contact with all 1,000 children to participate for the interview (home questionnaire). For the analysis with controlling the atopic sensitisation measured from IgE RAST Score, we require to take blood sample from 250 children with pneumonia in infancy matched by age (e.g., within 2-3 months) with 250 children without pneumonia in infancy (estimated number 250 in each group). We will exclude subjects whose parents/guardian cannot give informed consent because of impaired understanding or consciousness. Hypersensitiveness test will require 400 sub-sample subjects; 200 each from with and without pneumonia in infancy. Infants (2-11months old in 2002; estimated number 1,000) in Kamalapur Weekly Surveillance Area will be asked for a questionnaire only (integrated into the surveillance system).

2-3. Risks and measures taken to minimize them: The risks to subjects are minimal and consist primarily of the discomfort of blood sampling and hyperresponsiveness test, and positive reactions to this test. In addition, there will be the inconvenience of answering a questionnaire and atopic dermatitis checking at home, stool sample collection (size of thumb), brief physical examination and weight and height measurements at ICDDR,B Kamalapur Clinic.
Blood sampling will cause transient pain at the site of the needle entry. Participants (3 years old; 36-47 months) will be asked to allow the study team to draw a venous blood specimen of 3 ml (parents of infants are only asked to answer to the infant questionnaire at home, but not for any other procedures (i.e., no blood and stool sampling and no physical examination)). Rarely, venipuncture may cause bruising, or theoretically, infection, but normal clinical procedures will be used to prevent them.

4.5% saline challenge test for bronchial hyperresponsiveness (It is written in the consent form as " lung function test.")
As with any other bronchial provocation tests, non-isotonic aerosols leads to airway narrowing that can be of sudden onset and cause a marked reduction in arterial oxygen tension. We do not challenge for children with an asthmatic attack within 48 hours or resting SpO_2 less than 95% (exclusion criteria). For the reverse of an acute attack, inhaled bronchodilators and oxygen should be at hand in case of emergency. The study will always set up oxygen and drip infusion with steroids i.v. as bronchodilators. Only trained personnel should administer these challenges and immediate access to medical assistance should be available at the ICDDR,B Kamalapur Clinic. Children should never allow to leave the clinic before the reversion to their baseline SpO_2 level.
Hyperresponsiveness test will be conducted at the ICDDR,B Kamalapur clinic. For the safety procedure assurance, the test for initial 50 patients will be conducted in ICDDR,B Dhaka Hospital with close supervision of physicians and a clinical scientist (Dr. Tahmeed Ahmed; Co-PI). This helps the physicians who ultimately conduct the test in clinic setting, gaining skills and confidence in conducting the test.

4. Methods for safeguarding confidentiality: Code numbers unique for each study subject will be used for labeling specimen containers, consent form and questionnaire. The names of participants will be marked into the Kamalapur Health and Demographic Surveillance database to provide the key to the ID code numbers; all other databases will use ID code numbers only. The surveillance database and all other databases will be accessible only to the study investigators and will be kept on the PI's computer and one

computer at the ICDDR,B that will be dedicated to this study. Both computers will be secured through password access only by study co-investigators. The hard copy questionnaires will be kept in a locked file cabinet accessible only by the study investigators.

5. Consent procedures: The study will be explained to all potential participants and obtain a signed informed consent statement from the subject's parents/guardian. For participants unable to read, the consent form will be read aloud and explained in detail, and consent will be recorded by a fingerprint on the consent form. No information will be withheld from participants. The consent forms include an explanation of the risks and discomforts involved in the study, and methods used to minimize them. For participants, such as infants, who participate only in the infant questionnaire component of the study, a separate consent form will be used.

6. Interviews and other procedures: The interview will occur in the home. The only exception is the component of physical examination and venous blood sampling of subjects, which will take place in the Kamalapur ICDDR,B Clinic. The interview will take about 20 minutes. Physical examination and blood sampling will take about 20 minutes. Hyperresponsiveness test will take between 30 minutes to 1 hour, depending on their responses.

7. Benefits: The benefits to study subjects include detection of undiagnosed bronchial asthma cases with referral for treatment, which may be life saving. We also provide the initial treatment for a month for study subjects. For future asthma patients, these data should allow the implementation of better diagnostic algorithms for early referral for appropriate care. For the community as a whole, we hope that this study will lead to better asthma prevention strategies in the future. Bronchial asthma causes a heavy burden of disease in the community. The treatment is long and expensive. The disease is often lethal if untreated. The benefits to study subjects also include detection of undiagnosed intestinal helminth infections as we treat them.

8. Records: We will review the previous Kamalapur pneumonia surveillance database and look for the subjects who are still living in Kamalapur surveillance area and who had pneumonia in infancy. Other morbidity and treatment records in the past two years will be reviewed by looking at the Kamalapur clinic records. This is included in the consent form.

The statement to the subject included information specified in item 2, 3, 4, 5, 7, 8 as well as indicating the approximate time required for participation in the study activities.

Use of Animals

Describe in the space provided the type and species of animal that will be used in the study. Justify with reasons the use of particular animal species in the experiment and the compliance of the animal ethical guidelines for conducting the proposed procedures.

No use of animals

Literature Cited

Identify all cited references to published literature in the text by number in parentheses. List all cited references sequentially as they appear in the text. For unpublished references, provide complete information in the text and do not include them in the list of Literature Cited. There is no page limit for this section, however exercise judgment in assessing the "standard" length.

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Dissemination and Use of Findings

Describe explicitly the plans for disseminating the accomplished results. Describe what type of publication is anticipated: working papers, internal (institutional) publication, international publications, international conferences and agencies, workshops etc. Mention if the project is linked to the Government of Bangladesh through a training programme.

The findings will be disseminated through presentations in the seminars/conferences. It must be helpful to have a joint dissemination seminar at the end of study with the Bangladesh ISAAC study group. The findings will be published in national and international peer review journals.

Collaborative Arrangements

Describe briefly if this study involves any scientific, administrative, fiscal, or programmatic arrangements with other national or international organizations or individuals. Indicate the nature and extent of collaboration and include a letter of agreement between the applicant or his/her organization and the collaborating organization. **(DO NOT EXCEED ONE PAGE)**

- Department of Paediatrics, The University of Tokyo

  Tsutomu IWATA, Associate Professor

  Responsible for organizing and analysis of involved tests.

- Department of International Health

  Susumu Wakai, Professor

  Responsible for supervising the implementation and analysis of hyper responsiveness test

- Wako Pure Chemical, Tokyo, Japan

  Responsible for measurement of endotoxin

- Allergy Section, Clinical Institute, National Sagamihara Hospital, Kanagawa, Japan

  Responsible for the measurement of mite antigen for housedust

Biography of the Investigators

Give biographical data in the following table for key personnel including the Principal Investigator. Use a photocopy of this page for each investigator.

1 Name: Yukiko Wagatsuma

2 Present position: Scientist, Public Health Sciences Division, ICDDR, B
Assistant Scientist, Division of Disease Control, Department of International Health, Johns Hopkins University School of Hygiene and Public Health

3 Educational background (last degree and diploma & training relevant to the present research proposal)
M.D., University of Tsukuba, Japan, 1987
D.T.M., Tropical Medicine, University of Tokyo, Japan, 1987
M.P.H., International Health, Johns Hopkins University, USA, 1990
Dr. P.H., International Health, Johns Hopkins University, 1996
Certificate in Health Economics, Joint Programme of London School of Economics and London School of Hygiene and Tropical Medicine, 1999

4. List of ongoing research protocols (start and end dates; and percentage of time):

2000-023: Emergency research programme to enhance dengue prevention and control programs in Bangladesh; vector surveillance and control component.
#2000-025: Combined interventions to promote maternal and infant health.
#2000-026: Drug resistance monitoring and community-based case-management using dipstick for malaria diagnosis in Bangladesh.
#2000-028: Population-based evaluation of *Shigella* infection in an urban area of Dhaka, Bangladesh.
#2001-021: Community-based epidemiologic study of visceral leishmaniasis in Bangladesh.

4.1. As Principal Investigator

Protocol Number	Starting date	End date	Percentage of time
#2000-023	16/08/2000	31/12/2001	20%
#2000-026	3 years after starting (not yet started)		30%
#2001-021	01/12/01	30/12/05	3%

4.2. As Co-Investigator

Protocol Number	Starting date	Ending date	Percentage of time
#2000-025	01/11/2000	30/10/20005	30%
#2000-028	01/07/2001	30/06/2003	5%

5 Publications

Types of publications	Numbers
a) Original scientific papers in peer-review journals	12
b) Peer reviewed articles and book chapters	2
c) Papers in conference proceedings	9
d) Letters, editorials, annotations, and abstracts in peer-reviewed journals	2
e) Working papers	6
f) Monographs	1

6 Five recent publications including publications relevant to the present research protocol

1) Richter J, Wagatsuma Y, Aryeetey ME. Feldmeier H. Sonographic screening for urinary tract abnormalities in patients with *Schistosoma haematobium* infection; pitfalls in examining pregnant women. *Bull World Health Org* 1996;74(2):217-221.

2) Abdel-Wahab MF, Campagne G, Doehring E, Garba A, Hammou A, Hatz C, Homeida MMA, Kardorff R, Magak PW, Mbaye A, Olveda RM, Qurashi MA, Ramarokoto CE, Richter J, Traore M, Wagatsuma Y, Zhongdao W. WHO Niamey Working Group. Ultrasound in schistosomiasis: A practical guide to the standardized use of ultrasonography for the assessment of schistosomiasis-related morbidity. *World Health Organization* TDR/STR/SCH/00.1.

3) Wagatsuma Y, Aryeetey ME, Sack DA, Morrow RH, Hatz C, Kojima S. Resolution and resurgence of *S. haematobium*-induced pathology following community-based chemotherapy in Ghana as detected by ultrasound. *J Inf Dis* 1999;179(6):1515-1522.

4) Aryeetey ME, Aholu C, Wagatsuma Y, Bentil G, Nkrumah FK. Health education and community participation in the control of urinary schistosomiasis in Ghana. *East African Medical J* 1999; 76(6): 324-329.

5) Nsowah-Nuamah NNN, Mensah G, Asryeetey ME, Wagatsuma Y, Bentil G. Urinary schistosomiasis in southern Ghana: a logistic regression approach to data from a community-based integrated control program. *Am J Trop Med Hyg* 2001; 65(5):484-490.

Biography of the Investigators

Give biographical data in the following table for key personnel including the Principal Investigator. Use a photocopy of this page for each investigator.

1 Name: Takeuchi Haruko

2 Present position: Visiting researcher, The University of Tokyo

3 Educational & professional background
(last degree and diploma & training relevant to present research proposal)

M.D., The University of Tokyo, Japan, 1973
Pediatrician, Department of Pediatrics, University of Tokyo, Japan, 1973
Pediatrician, Tsukiji Maternal and Child Hospital, 1974-82
Instructor, Department of Pediatrics, University of Tokyo, Japan, 1975
Pediatrician, Toranomon Hospital, 1983-98
Post-graduate program, International Community Health, University of Tokyo, Japan, 1998-99

4. List of ongoing research protocols (start and end dates; and percentage of time):

2000-038: Epidemiology of bronchial asthma among children in Bangladesh at Matlab.

4.1. As Principal Investigator

Protocol Number	Starting date	End date	Percentage of time
#2000-038	11/03/2001	30/4/2002	100%

4.2. As Co-Investigator

Protocol Number	Starting date	Ending date	Percentage of time

5 Publications

Types of publications	Numbers
a) Original scientific papers in peer-review journals	5
b) Peer reviewed articles and book chapters	3
c) Papers in conference proceedings	
d) Letters, editorials, annotations, and abstracts in peer-reviewed journals	
e) Working papers	
f) Monographs	

6 Five recent publications including publications relevant to the present research protocol

General Treatment Practice in Cebu and Negros Oriental, the Philippines. In: Mori T, et al, editors. *Tuberculosis Control Development and NGO Collaboration: Report of the survey under the Japan International Cooperation Agency.* Tokyo: The Research Institute of Tuberculosis Japan Anti-Tuberculosis Association; 1999. p. 95-97, 112-125.

Merits and Demerits of Women Doctors. In: Yanagisawa M, editor. *A Practical Guide for Pediatric Training.* Tokyo: Shindan to Chiryou Sha; 1998. p. 146-147.

Takeuchi H, Haque R, Wakai S, Iwata T. Childhood asthma prevalence in rural Bangladesh. *J of Japan Association for International Health* 2000; **15**: S113.(In Japanese)

Biography of the Investigators

Give biographical data in the following table for key personnel including the Principal Investigator. Use a photocopy of this page for each investigator.

Name: W. Abdullah Brooks, MD, MPH

POSITION TITLE

Health & Child Survival Advisor, Health & Child Survival Fellows Program, ICDDR,B
Research Associate , Department of International Health, Johns Hopkins University School of Hygiene and Public Health

EDUCATION

Institution/Location	Degree	Year Conferred	Field of Study
Stanford University	MD	1991	Medicine
The New York Hospital / Cornell Medical Center	Diploma	1994	Pediatrics
Johns Hopkins University	MPH	1995	International Health
Johns Hopkins University	Diploma	1996	Preventive Medicine

EXPERIENCE AND APPOINTMENTS

Year	Activity
1985-1986	Principal Investigator: Identification of heat-shock proteins in *F.hepatica*, Stanford University
1986	Investigator: Isolation of *L. major* attachment proteins, National Institutes of Health
1990	Epidemiology Intelligence Service Medical Student Clerkship, Enteric Branch, Centers for Disease Control and Prevention
1992	Investigator: Community-based dysentery intervention for urban slum children, Salvador, Bahia, Brazil
1995	Multicentre Study on Lower Osmolar ORS, International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B)
1994 – 1997	Paediatric On-Call Physician, Kennedy-Krieger Institute, Johns Hopkins
1995 – 1997	Paediatric consultant: Urban school-based clinics for Baltimore County
1995 – 1997	Paediatric Emergency Room Attending, St. Joseph's Hospital, Baltimore
1996	Epidemiologist: Consultants in Epidemiology and Occupational Health, Washington, DC
1996	EPI Technical Advisor: National measles vaccination campaign children 12 - 59 months, PAHO, EPI/SVI, Georgetown, Guyana
1996 – 1997	Chief Resident Preventive Medicine Program, Johns Hopkins University
1997 – Present	Paediatric Consultant, US Embassy, Dhaka
1997 – Present	Regional Medical Consultant: AEA International, Singapore
1997 – Present	Principal Investigator: Hospital-based study to test efficacy of zinc in acute watery diarrhoea in children less than 6 months old
1998 – Present	Principal Investigator: Community-based study to prevent pneumonia/diarrhoea with zinc in children less than 2 years old
1999 – Present	Principal Investigator: Hospital-based study of efficacy of zinc as adjuvant therapy in management of severe pneumonia, hospitalised children less than 2 years old

PROTOCALS UNDER DEVELOPMENT

Projected Start Date	Intervention	Stage of Development
2000	Identification of primary bacterial and non-bacterial pathogens of pneumonia and their patterns of antimicrobial resistance among urban slum children 2 – 59 months of age through community-based active surveillance	Proposal, possible donor
2000	Comparison of antimicrobial outpatient management regimens for pneumonia and their effects on antimicrobial resistance among urban slum children less than 5 years old	Proposal, possible donor

PUBLICATIONS RELATED TO PRESENT WORK

Brooks WA, Fuchs G. Recent advances in research on zinc and child health in developing countries. *J Int Pediatr* 1998;35:1173-76.

Budget Justifications

Please provide one page statement justifying the budgeted amount for each major item. Justify use of manpower, major equipment, and laboratory services.

Personnel

In addition to the investigators, we require six Field Research Assistants (FRAs), a medical officer, a data management officer and a research officer for 4 months and four porters for 2.5 months. A nurse/paramedic and field research assistants will be required for 5 months.

We plan to obtain 2,000 questionnaire interviews and 1,000 blood and stool samples. Each FRA will obtain 10 questionnaires per day, thus 4 FRAs will complete 2,000 questionnaires for 2-3 months. At the same time in the clinic 20 children a day will be asked to come for samples and physiological test. 3 months will be required to complete 1,000 children for sample collection and further 1-2 months will require for completing hyperresponsive test (400 subjects). 1,000 housedust samples will be collected by home visits with two teams (1 FRA and 2 porters in a team) for 2.5 months.

FRA is GS-3 level, a nurse/paramedic and a data management officer are GS-4 level. Medical officer is NO-A and research officer is GS-5 level.

Equipment

Puls-oximetor, nebulizer and treatment drugs were procured from the previous study funds (Matlab Asthma Study). Additional treatment drug costs are estimated $1,500.

For local travel cost is estimated $3,000.

Laboratory services

Laboratory costs for processing stool and blood are estimated $ 3,770.

Incentives for participants (e.g., public transportation cost payment, lunch at clinic, treatment cost for general PHC service at clinic, etc.) will be covered from other operational cost and drug cost.

Other Support

Describe sources, amount, duration, and grant number of all other research funding currently granted to PI or under consideration. (DO NOT EXCEED ONE PAGE FOR EACH INVESTIGATOR)

Wagatsuma, Y

ACTIVE

1. USAID/W/ID — Jan 2000–Dec 2003 — 50% effort
   Responsible: Coordination, Infectious Disease Initiatives — $150,000

2. Japan Government — Apr 2000-Mar 2003 — 30% effort

   Low Birth Weight Study
   Fetal ultrasound component (PI: Y Wagatsuma) was integrated into the umbrella protocol of "Combined Interventions to Promote Maternal and Infant Health" funded by UNICEF and NIH.
   $2,582,389

3. IVI — July 2001-June 2003 — 5% effort

   DOMI-Shigellosis: Population-based evaluation of *Shigella* infection in an urban area of Dhaka, Bangladesh — $940,246

4. CDC — Dec 2001-Sep 2004 — 3% effort
   Community-based epidemiologic study of visceral leishmaniasis in Bangladesh
   $103,913

PENDING

1. Chakaria Community Health Research — 30% effort
   Drug resistance monitoring and community-based case-management using dipstick for malaria diagnosis in Bangladesh — $700,000

OVERLAP
None

APPENDIX

International Centre for Diarrhoeal Disease Research, Bangladesh
Voluntary Consent Form

Title of the Research Project:
Community-based study of bronchial asthma among children in an urban slum in Dhaka, Bangladesh

Principal Investigator: Haruko Takeuchi Yukiko Wagatsuma

Before recruiting into the study, the study subject must be informed about the objectives, procedures, and potential benefits and risks involved in the study. Details of all procedures must be provided including their risks, utility, duration, frequencies, and severity. All questions of the subject must be answered to his/ her satisfaction, indicating that the participation is purely voluntary. For children, consents must be obtained from their parents or legal guardians. The subject must indicate his/ her acceptance of participation by signing or thumb printing on this form.

Asthma is a major problem among children in Bangladesh. To know the scale of asthma problem is helpful to understand how to control and prevent asthma among children. ICDDR,B is conducting a study to learn about bronchial asthma in your community and related environmental and personal risk factors. We are interested to know if any of your family members aged 3 years old have any symptoms of bronchial asthma. If you agree to participate, we will ask you some questions regarding the illness of your child and socio-economic conditions. It will take you about 20 minutes to answer the questions. We will refer your child to the ICDDR,B Kamalapur Clinic for collection of blood (3 ml, about 1 teaspoonful) and stool samples. A medical doctor will check your child and skin will be inspected to know if your child has any symptoms suggestive of bronchial asthma. These examinations will help us to understand the mechanism of asthma. We will also look at the Kamalapur ICDDR,B Clinic records to know what kind of respiratory related illness your child had in the past. This information may help us to understand the possible association for developing asthma later.

In addition to the tests described above, we will ask you to participate in lung function test. We can know asthma tendency by inhaling saline. It does not involve the inhalation of chemicals or drugs. Your child will be asked to inhale a fine mist of concentrated saline solution (similar to sea water). The test will be supervised by our study doctors. During the test, breathing pattern will be monitored for any changes. The test is positive when there is a small reduction of normal breathing. The test is usually not great enough to cause symptoms and returns to normal within a few minutes after completion of the test. If your child has asthmatic attack within 48 hours or initial low lung function, they will be excluded for this test. If an acute attack is observed, the study doctor will provide the child a medicine to help breathing (medicines and oxygen will be ready at the examination room). Only trained physician will administer this test and immediate access to medical help will be available at the clinic.

There are minimal risks involved for participating in the study. You may decide not to participate in the study at all and this will not affect your child's treatment. You are at liberty to withdraw your child from the study at anytime without any obligations and jeopardizing medical care and treatment. Your child may benefit by early detection of asthmatic symptoms for advice and treatment. The study will provide detected bronchial asthma patients with treatment according to the national guideline.

If you allow your child to participate in the study, please sign your name or give left thumb impression below.

Consent: The study described above has been explained to me and I voluntarily consent to allow my child participating in this study

Signature of Investigator/ or agents **Signature of Subject/ Guardian**

Date: **Date:**

International Centre for Diarrhoeal Disease Research, Bangladesh
Voluntary Consent Form for Infant Questionnaire

Title of the Research Project:
Community-based study of bronchial asthma among children in an urban slum in Dhaka, Bangladesh

Principal Investigator: **Haruko Takeuchi**
Yukiko Wagatsuma

Before recruiting into the study, the study subject must be informed about the objectives, procedures, and potential benefits and risks involved in the study. Details of all procedures must be provided including their risks, utility, duration, frequencies, and severity. All questions of the subject must be answered to his/ her satisfaction, indicating that the participation is purely voluntary. For children, consents must be obtained from their parents or legal guardians. The subject must indicate his/ her acceptance of participation by signing or thumb printing on this form.

Asthma is a major problem among children in Bangladesh. To know the scale of asthma problem is helpful to understand how to control and prevent asthma among children. ICDDR,B is conducting a study to know how prevalent the problem is, to know related risk factors and its association with environmental and personal factors. We are interested to know if any of your family members aged less than 1 year old have any symptoms of bronchial asthma. If you agree to participate, we will ask you some questions regarding the illness of your baby and your socio-economic conditions. It will take you about 20 minutes to answer the questions.

There is no risk involved in participating in the study. You may decide not to participate in the study at all and this will not affect your baby's treatment. You are at liberty to withdraw your baby from the study at anytime without any obligations and jeopardizing medical care and treatment. Your baby may benefit by early detection of asthmatic symptoms for advice and treatment. The study will provide detected bronchial asthma patients with treatment according to the national guideline.

If you allow your child to participate in the study, please sign your name or give left thumb impression below.

Consent: The study described above has been explained to me and I voluntarily consent my child to participate in your study.

Signature of Investigator/ or agents

Date:

Signature of Subject/ Guardian

Date:

Check List

After completing the protocol, please check that the following selected items have been included.

1. Face Sheet Included ☐
2. Approval of the Division Director on Face Sheet ☐
3. Certification and Signature of PI on Face Sheet, #9 and #10 ☐
4. Table on Contents ☐
5. Project Summary ☐
6. Literature Cited ☐
7. Biography of Investigators ☐
8. Ethical Assurance ☐
9. Consent Forms ☐
10. Detailed Budget ☐

QUESTIONNAIRE FOR 3-YEARS-OLD CHILDREN

IDENTIFICATION SHEET

Interview Blood & House dust & Stool

RECORD NUMBER: |_|_|_|_|_| |_|_|_|_|

CHILD'S NAME: _____

CHILD'S PID: |_|_|_|_|_|_|_|_|_|_|

DATE OF BIRTH: |_|_| |_|_| |_|_|
D M Yr

NAME of HOUSEHOLD HEAD: _____

PID of HOUSEHOLD HEAD: |_|_|_|_|_|_|_|_|_|_|

RESPONDENT'S NAME: _____

RESPONDENT'S PID: |_|_|_|_|_|_|_|_|_|_|

RELATION of the RESPONDENT to the child

1. Mother
2. Father
3. Others _____

INTERVIEWER'S NAME: _____

INTERVIEWER'S NUMBER: |_|_|

DATE OF INTERVIEW |_|_| |_|_| |_|_|
D M Yr

Date blood sample taken |_|_| |_|_| |_|_|
D M Yr

Date stool sample taken |_|_| |_|_| |_|_|
D M Yr

1. RECORD NUMBER 1. |__|__|__|__|

2. SAMPLE NUMBER 2. |__|__|__|

3. CHILD'S PID 3. |__|__|__|__|__|__|__|__|__|__|

4. Sex of child? 4. 1. Male 2. Female

5. Was the child born within 3 weeks of the calculated date? 5. 1. Yes
2. No, more than 3 weeks early
3. No, more than 3 weeks late
4. Unknown

6. Height and weight of the child? 6. |__|__|__| cm

7. |__|__|.|__| kg

8. In what city or area was the child's mother living when this child was born? 8. _____

9. Please list all places where the child lived for 6 months or longer, from birth to the present. 9. _____

_____

Years at current address |__|__| years

FAMILY MEMBERS

10. Number of family members? 10. |__|__| persons

11. Number of older siblings? 11. |__|__| persons

12. Number of younger siblings? 12. |__|__| persons

PAST HISTORY

History of illnesses

13. Measles

Age |__|__| Years |__|__| Months

14. Whooping cough

|__|__| Years |__|__| Months

15. Tuberculosis

|__|__| Years |__|__| Months

16. Acute diarrhea (o) & 17. Persistent diarrhea (x)

0 year old

|__| __| 0 1 2 3 4 5 6 7 8 9 10 11

1 years old

|__| __| 0 1 2 3 4 5 6 7 8 9 10 11

2 years old

|__| __| 0 1 2 3 4 5 6 7 8 9 10 11

3 years old

|__| __| 0 1 2 3 4 5 6 7 8 9 10 11

4 years old

|__| __| 0 1 2 3 4 5 6 7 8 9 10 11

History of pneumonia

18. (o)

0 year old

|__| 0 1 2 3 4 5 6 7 8 9 10 11

1 year old

|__| 0 1 2 3 4 5 6 7 8 9 10 11

2years old

|__| 0 1 2 3 4 5 6 7 8 9 10 11

3 years old

|__| 0 1 2 3 4 5 6 7 8 9 10 11

4 years old

|__| 0 1 2 3 4 5 6 7 8 9 10 11

Record of immunization

19. BCG |__|__| __|__| __|__|
D M Yr

20.

DPT 1 |__|__| __|__| __|__|
D M Yr

DPT 2 |__|__| __|__| __|__|
D M Yr

DPT 3 |__|__| __|__| __|__|
D M Yr

DTP 4 |__|__| __|__| __|__|
D M Yr

21.

Polio 1 |__|__| __|__| __|__|
D M Yr

Polio 2 |__|__| __|__| __|__|
D M Yr

Polio 3 |__|__| __|__| __|__|
D M Yr

Polio 4 |__|__| __|__| __|__|
D M Yr

22.

Measles |__|__| __|__| __|__|
D M Yr

These questions pertain mainly to your child's chest.

WHEEZING

23. Has your child ever had wheezing or whistling in the chest at any time in the past?

    1. Yes 2. No

    IF YOU ANSWERED "NO" PLEASE SKIP TO QUESTION 28

---

24. Has your child had wheezing or whistling in chest in the last 12 months?

    1. Yes 2. No

    IF YOU ANSWERED "NO" PLEASE SKIP TO QUESTION 28

---

25. How many attacks of wheezing has your child had in the last 12 months?

    1. None 2. 1 to 3 3. 4 to 12 4. More than 12

26. In the last 12 months, how often, on average, has your child's sleep been disturbed due to wheezing?

    1. None 2. Less than one night per week
    3. One or more nights per week

27. In the last 12 months, has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breaths?

    1. Yes 2. No

---

28. Has your child ever had asthma?

    1. Yes 2. No

29. In the last 12 months, has your child's chest sounded wheezy during or after exercise?

    1. Yes 2. No

30. In the last 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or a chest infection?

    1. Yes 2. No

All questions are about problems which occur when your child DO NOT have a cold or the flu.

RHINITIS

37. Has your child ever had a problem with sneezing, or a runny, or a blocked nose when he/she DID NOT have a cold or the flu?

    1. Yes 2. No

    IF YOU ANSWERED " NO" PLEASE SKIP TO QUESTION 36

---

38. In the past 12 months, has your child had a problem with sneezing, or a runny, or a blocked nose when he/she DID NOT have a cold or the flu?

    1. Yes 2. No

    IF YOU ANSWERED " NO" PLEASE SKIP TO QUESTION 36

---

39. In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?

    1. Yes 2. No

40. In which of the past 12 months, did this nose problem occur? (Tick any which apply)

    1. January 2. February 3. March 4. April 5. May
    6. June 7. July 8. August 9. September
    10. October 11. November 12. December

41. In the past 12 months, how much did this nose problem interfere with your child's daily activities?

    1. Not at all 2. A little 3. A moderate amount 4. A lot

---

42. Has your child ever had allergic rhinitis?

    1. Yes 2. No

These questions pertain mainly to your child's skin.

ECZEMA SCABIES

43. Has your child ever had itchy rash which was coming and going for at least 6 months?

    1. Yes 2. No

    IF YOU ANSWERED "NO" PLEASE SKIP TO QUESTION 43

---

44. Has your child had this itchy rash at any time in the last 12 months?

    1. Yes 2. No

    IF YOU ANSWERED "NO" PLEASE SKIP TO QUESTION 43

---

45. Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?

    1. Yes 2. No

46. At what age did this itchy rash first occur?

    1. Under 1 year 2. Age 1 – 2 3. Age 3 – 4 4. Age 5 or more

47. Has this rash cleared completely at any time during the last 12 months?

    1. Yes 2. No

48. In the last 12 months, how often, on average, has your child been kept awake at night by this itchy rash?

    1. Never in the last 12 months 2. Less than one night per week
    3. One or more nights per week

---

49. Has your child ever had eczema?

    1. Yes 2. No

DIET

A. 0 to 3 months of age

50. What was the main food of your child when he/she was younger than 3 months of age?

50.
1. Breast milk
2. Cow's milk
3. Powder milk
4. Bananas
5. Rice
6. Others

(Specify_____)

51. What did you use for additional food during this period?

51.
1. Breast milk
2. Cow's milk
3. Powder milk
4. Bananas
5. Rice
6. Others

(Specify_____)

B. Weaning food

52. At what age was your child first given semisolid weaning food?

52. |__|__| months

53. What was your child's first weaning food?

53.
1. Rice
2. Fruit
3. Suji
4. Vegetables
5. Others

(Specify_____)

54. What was the main food for your child at the first birthday?
(Choose any answer which apply.)

54.
1. Breast milk
2. Rice
3. Suji
4. Powder milk
5. cow's milk
6. Fruit
7. Others

(Specify_____)

BEDDING

55. What kind of bedding does your child use?

55. 1. Cotton cloth
2. Synthetic quilt
3. Blankets
4. Other ( )

56. What kind of pillow does the child use?

56. 1. Cotton
2. Synthetics
3. Feather
4. Others ( )
5. Does not use a pillow

FAMILY HISTORY

We would like to obtain information about the natural parents of the child.
(Even if he or she passed away.)

A. Female parent

57. Has the child's natural mother ever said to have:

A.	Asthma?	1. Yes	2. No
B.	Allergic rhinitis?	1. Yes	2. No
C.	Eczema?	1. Yes	2. No

58. Did the child's mother smoke?

	Yes	No
During the child's first year of life	( )	( )
During her pregnancy of this child	( )	( )

B. Male parent

59. Has the child's natural father ever had:

A.	Asthma	1. Yes	2. No
B.	Allergic rhinitis	1. Yes	2. No
C.	Eczema	1. Yes	2. No

Next we would like to obtain some information about the present guardians of the child.

C. Female parent or guardian

60. Please indicate whether the female guardian is:

60. 1. Natural mother
2. Stepmother
3. Other

61. What is the highest grade of education she completed?

61. Total years |__|__| years

62. What is her present job?

62. 1. Housewife
2. Others_____

63. How many years has the child been with her?

63. |__| years

D. Male parent or guardian

64. Please indicate whether the male guardian is:

64. 1. Natural father
2. Stepfather
3. Other

65. What is the highest grade of education he completed?

65. Total years |__|__| years

66. What is his present job?

66. 1. Service
2. Fisherman
3. Rickshaw or van puller / boatman
4. Business
5. Laborer
6. Student
7. Other _____

67. How many years has the child been with him?

67. |__| years

HOME ENVIRONMENT

A. Household Affaires

68. How many rooms (not counting bathrooms) are there in your house? Number of rooms — 68. |__|

69. How many people sleep in the same room as the child?

69. What is your economic status? — 69.
1. Surplus
2. Balance
3. Deficit
4. Do not know

Amount of income, please. _____ Tk/month

71. How many children under 5 sleep in the same room as the child?

70. Does anybody in the household, at present, smoke? — 70. 1. Yes. 2. No

B. Household Smoking & Others

71. How many in total are smoked per day in the child's home? — 71.

1. Cigarettes ( )
2. Cigars ( )
3. Biri ( )
4. Pipe ( )
5. Hukka ( )
6. Tobacco ( )
7. Other ( )

72. Where do you usually cook? — 72.
1. In the separated kitchen in the house
2. In the kitchen outside of the house
3. In the kitchen area in the house
4. Outside
5. Others
(Specify _____)

73. Where does the child stay when meals are cooked?

73. What fuel is used most for cooking in your house?

73. 1. Wood
2. Coal
3. Gas
4. Electricity
5. Kerosene
6. Dry leaves

74. How many windows are there in your house?

75. Do you have a fan at your home?

74. What is the main source of your drinking water?

74. 1. Piped into residence
2. Piped outside residence
3. Tube well
4. Surface water
5. Others
(Specify _____)

75. What is your sanitation facility?

75. 1. Open latrine
2. Pit latrine
3. Water sealed / slab latrine
4. Septic tank, modern
5. No facility / bush
6. Others
(Specify _____)

76. Do you have electricity at your house?

76. 1. Yes 2. No

77. What is the roof of your house made of?

77. 1. Thatched
2. Tin
3. Cement / concrete
4. Others
(Specify _____)

78. What is the wall of your house made of?

78. 1. Jute / bamboo / mud
2. Wood
3. Brick/concrete
4. Tin
5. Others
(Specify _____)

79. What is the floor of your house made of?

79. 1. Earth
2. Wood
3. Cement / concrete
4. Carpet
5. Others
(Specify _____)

Thank you very much for your cooperation.

QUESTIONNAIRE FOR INFANTS

IDENTIFICATION SHEET

Interview Blood & House dust & Stool

RECORD NUMBER: |__|__|__|__| |__|__|__|

CHILD'S NAME: _____

CHILD'S PID: |__|__|__|__|__|__|__|__|__|__|

DATE OF BIRTH: |__|__| |__|__| |__|__|
D M Yr

NAME of HOUSEHOLD HEAD: _____

PID of HOUSEHOLD HEAD: |__|__|__|__|__|__|__|__|__|__|

RESPONDENT'S NAME: _____

RESPONDENT'S PID: |__|__|__|__|__|__|__|__|__|__|

RELATION of the RESPONDENT to the child

1. Mother
2. Father
3. Others _____

INTERVIEWER'S NAME: _____

INTERVIEWER'S NUMBER: |__|

DATE OF INTERVIEW |__|__| |__|__| |__|__|
D M Yr

Date blood sample taken |__|__| |__|__| |__|__|
D M Yr

Date stool sample taken |__|__| |__|__| |__|__|
D M Yr

Date house dust sample taken |__|__| |__|__| |__|__|
D M Yr

1. RECORD NUMBER 1. |__|__|__|__|

2. SAMPLE NUMBER 2. |__|__|__|

3. CHILD'S PID 3. |__|__|__|__|__|__|__|__|__|__|

4. Sex of child? 4. 1. Male 2. Female

5. Was the child born within 3 weeks of the calculated date? 5. 1. Yes
2. No, more than 3 weeks early
3. No, more than 3 weeks late
4. Unknown

6. Height and weight of the child? 6. |__|__|__| cm

7. |__|__|.|__| kg

8. In what city or area was the child's mother living when this child was born? 8. _____

9. Please list all places where the child lived for 6 months or longer, from birth to the present. 9. _____

_____

Years at current address |__|__| years

FAMILY MEMBERS

10. Number of family members? 10. |__|__| persons

11. Number of older siblings? 11. |__|__| persons

12. Number of younger siblings? 12. |__|__| persons

PAST HISTORY

History of illnesses

13. Measles 14. Whooping cough 15. Tuberculosis

Age

|__|__| Years |__|__| Months

|__|__| Years |__|__| Months

|__|__| Years |__|__| Months

16. Acute diarrhea (o) & 17. Persistent diarrhea (x)

0 year old

|___| ___| 0 1 2 3 4 5 6 7 8 9 10 11

1 years old

|___| ___| 0 1 2 3 4 5 6 7 8 9 10 11

2 years old

|___| ___| 0 1 2 3 4 5 6 7 8 9 10 11

3 years old

|___| ___| 0 1 2 3 4 5 6 7 8 9 10 11

4 years old

|___| ___| 0 1 2 3 4 5 6 7 8 9 10 11

History of pneumonia

18. (o)

0 year old

|___| 0 1 2 3 4 5 6 7 8 9 10 11

1 year old

|___| 0 1 2 3 4 5 6 7 8 9 10 11

2years old

|___| 0 1 2 3 4 5 6 7 8 9 10 11

3 years old

|___| 0 1 2 3 4 5 6 7 8 9 10 11

4 years old

|___| 0 1 2 3 4 5 6 7 8 9 10 11

Record of immunization

19. BCG |__|__| __|__| __|__|
D M Yr

20.

DPT 1 |__|__| __|__| __|__|
D M Yr

DPT 2 |__|__| __|__| __|__|
D M Yr

DPT 3 |__|__| __|__| __|__|
D M Yr

DTP 4 |__|__| __|__| __|__|
D M Yr

21.

Polio 1 |__|__| __|__| __|__|
D M Yr

Polio 2 |__|__| __|__| __|__|
D M Yr

Polio 3 |__|__| __|__| __|__|
D M Yr

Polio 4 |__|__| __|__| __|__|
D M Yr

22.

Measles |__|__| __|__| __|__|
D M Yr

These questions pertain mainly to your child's chest.

WHEEZING

23. Has your child ever had wheezing or whistling in the chest at any time in the past?

    1. Yes 2. No

    IF YOU ANSWERED "NO" PLEASE SKIP TO QUESTION 28

---

24. Has your child had wheezing or whistling in chest in the last 12 months?

    1. Yes 2. No

    IF YOU ANSWERED "NO" PLEASE SKIP TO QUESTION 28

---

25. How many attacks of wheezing has your child had in the last 12 months?

    1. None 2. 1 to 3 3. 4 to 12 4. More than 12

26. In the last 12 months, how often, on average, has your child's sleep been disturbed due to wheezing?

    1. None 2. Less than one night per week
    3. One or more nights per week

27. In the last 12 months, has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breaths?

    1. Yes 2. No

---

28. Has your child ever had asthma?

    1. Yes 2. No

29. In the last 12 months, has your child's chest sounded wheezy during or after exercise?

    1. Yes 2. No

30. In the last 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or a chest infection?

    1. Yes 2. No

These questions pertain mainly to your child's chest.

DRY COUGH

31. Has your child ever had cough at night apart from a cough associated with a cold or a chest infection?

    1. Yes 2. No

    IF YOU ANSWERED "NO" PLEASE SKIP TO QUESTION 28

---

32. Has your child had cough at night apart from a cough associated with a cold or a chest infection in the last 12 months?

    1. Yes 2. No

    IF YOU ANSWERED "NO" PLEASE SKIP TO QUESTION 28

---

33. How many attacks of cough at night apart from a cough associated with a cold or a chest infection has your child had in the last 12 months?

    1. None 2. 1 to 3 3. 4 to 12 4. More than 12

34. In the last 12 months, how often, on average, has your child's sleep been disturbed due to dry cough at night apart from a cough associated with a cold or a chest infection?

    1. None 2. Less than one night per week
    3. One or more nights per week

35. In the last 12 months, has dry cough ever been severe enough to limit your child's speech to only one or two words at a time between breaths?

    1. Yes 2. No

---

36. In the last 12 months, has your child experienced dry cough at night apart from a cough associated with a cold or a chest infection during or after exercise?

    1. Yes 2. No

All questions are about problems which occur when your child DO NOT have a cold or the flu.

RHINITIS

37. Has your child ever had a problem with sneezing, or a runny, or a blocked nose when he/she DID NOT have a cold or the flu?

    1. Yes 2. No

    IF YOU ANSWERED " NO" PLEASE SKIP TO QUESTION 36

---

38. In the past 12 months, has your child had a problem with sneezing, or a runny, or a blocked nose when he/she DID NOT have a cold or the flu?

    1. Yes 2. No

    IF YOU ANSWERED " NO" PLEASE SKIP TO QUESTION 36

---

39. In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?

    1. Yes 2. No

40. In which of the past 12 months, did this nose problem occur? (Tick any which apply)

    1. January 2. February 3. March 4. April 5. May
    6. June 7. July 8. August 9. September
    10. October 11. November 12. December

41. In the past 12 months, how much did this nose problem interfere with your child's daily activities?

    1. Not at all 2. A little 3. A moderate amount 4. A lot

---

42. Has your child ever had allergic rhinitis?

    1. Yes 2. No

These questions pertain mainly to your child's skin.

ECZEMA SCABIES

43. Has your child ever had itchy rash which was coming and going for at least 6 months?

    1. Yes 2. No

    IF YOU ANSWERED "NO" PLEASE SKIP TO QUESTION 43

---

44. Has your child had this itchy rash at any time in the last 12 months?

    1. Yes 2. No

    IF YOU ANSWERED "NO" PLEASE SKIP TO QUESTION 43

---

45. Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?

    1. Yes 2. No

46. At what age did this itchy rash first occur?

    1. Under 1 year 2. Age 1 – 2 3. Age 3 – 4 4. Age 5 or more

47. Has this rash cleared completely at any time during the last 12 months?

    1. Yes 2. No

48. In the last 12 months, how often, on average, has your child been kept awake at night by this itchy rash?

    1. Never in the last 12 months 2. Less than one night per week
    3. One or more nights per week

---

49. Has your child ever had eczema?

    1. Yes 2. No

DIET

A. 0 to 3 months of age

50. What was the main food of your child when he/she was younger than 3 months of age?

50.
1. Breast milk
2. Cow's milk
3. Powder milk
4. Bananas
5. Rice
6. Others

(Specify_____)

51. What did you use for additional food during this period?

51.
1. Breast milk
2. Cow's milk
3. Powder milk
4. Bananas
5. Rice
6. Others

(Specify_____)

B. Weaning food

52. At what age was your child first given semisolid weaning food?

52. |__|__| months

53. What was your child's first weaning food?

53.
1. Rice
2. Fruit
3. Suji
4. Vegetables
5. Others

(Specify_____)

54. What was the main food for your child at the first birthday?
(Choose any answer which apply.)

54.
1. Breast milk
2. Rice
3. Suji
4. Powder milk
5. cow's milk
6. Fruit
7. Others

(Specify_____)

BEDDING

55. What kind of bedding does your child use?

55. 1. Cotton cloth
2. Synthetic quilt
3. Blankets
4. Other ( )

56. What kind of pillow does the child use?

56. 1. Cotton
2. Synthetics
3. Feather
4. Others ( )
5. Does not use a pillow

FAMILY HISTORY

We would like to obtain information about the natural parents of the child.
(Even if he or she passed away.)

A. Female parent

57. Has the child's natural mother ever said to have:

A.	Asthma?	1. Yes	2. No
B.	Allergic rhinitis?	1. Yes	2. No
C.	Eczema?	1. Yes	2. No

58. Did the child's mother smoke?

	Yes	No
During the child's first year of life	( )	( )
During her pregnancy of this child	( )	( )

B. Male parent

59. Has the child's natural father ever had:

A.	Asthma	1. Yes	2. No
B.	Allergic rhinitis	1. Yes	2. No
C.	Eczema	1. Yes	2. No

HOME ENVIRONMENT

A. Household Affaires

68. How many rooms (not counting bathrooms) are there in your house? Number of rooms — 68. ⌊__⌋

69. How many people sleep in the same room as the child?

69. What is your economic status? — 69.
1. Surplus
2. Balance
3. Deficit
4. Do not know

Amount of income, please. _____ Tk/month

71. How many children under 5 sleep in the same room as the child?

70. Does anybody in the household, at present, smoke? — 70. 1. Yes. 2. No

B. Household Smoking & Others

71. How many in total are smoked per day in the child's home? — 71.

1. Cigarettes ( )
2. Cigars ( )
3. Biri ( )
4. Pipe ( )
5. Hukka ( )
6. Tobacco ( )
7. Other ( )

72. Where do you usually cook? — 72.
1. In the separated kitchen in the house
2. In the kitchen outside of the house
3. In the kitchen area in the house
4. Outside
5. Others
(Specify _____)

Next we would like to obtain some information about the present guardians of the child.

C. Female parent or guardian

60. Please indicate whether the female guardian is:

60. 1. Natural mother
2. Stepmother
3. Other

61. What is the highest grade of education she completed?

61. Total years |__|__| years

62. What is her present job?

62. 1. Housewife
2. Others_____

63. How many years has the child been with her?

63. |__| years

D. Male parent or guardian

64. Please indicate whether the male guardian is:

64. 1. Natural father
2. Stepfather
3. Other

65. What is the highest grade of education he completed?

65. Total years |__|__| years

66. What is his present job?

66. 1. Service
2. Fisherman
3. Rickshaw or van puller / boatman
4. Business
5. Laborer
6. Student
7. Other _____

67. How many years has the child been with him?

67. |__| years

73. Where does the child stay when meals are cooked?

73. What fuel is used most for cooking in your house?

73. 1. Wood
2. Coal
3. Gas
4. Electricity
5. Kerosene
6. Dry leaves

74. How many windows are there in your house?

75. Do you have a fan at your home?

74. What is the main source of your drinking water?

74. 1. Piped into residence
2. Piped outside residence
3. Tube well
4. Surface water
5. Others
(Specify _____)

75. What is your sanitation facility?

75. 1. Open latrine
2. Pit latrine
3. Water sealed / slab latrine
4. Septic tank, modern
5. No facility / bush
6. Others
(Specify _____)

76. Do you have electricity at your house?

76. 1. Yes 2. No

77. What is the roof of your house made of?

77. 1. Thatched
2. Tin
3. Cement / concrete
4. Others
(Specify _____)

78. What is the wall of your house made of?

78. 1. Jute / bamboo / mud
2. Wood
3. Brick/concrete
4. Tin
5. Others
(Specify _____)

79. What is the floor of your house made of?

79. 1. Earth
2. Wood
3. Cement / concrete
4. Carpet
5. Others
(Specify _____)

Thank you very much for your cooperation.