Proceedings of the 30ᵗʰ Annual Meeting of Kyushu Regional Society of Tropical Medicine
Held in Nagasaki on February 9 and 10, 2007.

The Khanh Hoa Health Project: Characterization of Study Population and Field Site Development for Clinical Epidemiological Research on Emerging and Re-Emerging Infectious Diseases

Hideki Yanai , Vu Dinh Thiem , Toru Matsubayashi , Vu Thi Thu Huong , Motoi Suzuki
Le Phuong Mai , Nguen Hien Anh , Le Huu Tho , Trung Tan Minh , Lay Myint Yoshida
Paul Kilgore , Dang Duc Anh and Koya Ariyoshi

INTRODUCTION

In developing countries such as Vietnam, there are numerous health challenges facing local residents. In Vietnam, a large percentage of the population suffers from infectious diseases including dengue, diarrheal disease and respiratory tract infections. Globally, these diseases also account for a large burden of disease, and this has led to recognition of the need for renewed efforts to improve treatment and promote the prevention of these diseases. Worldwide, acute respiratory tract infections (ARI) are a major cause of morbidity and mortality, especially in children. WHO estimates that about 20% of all deaths in children under 5 years are caused by acute lower respiratory infections and that 90% of these deaths are due to pneumonia [1-4]. As part of the Program of Founding Research Centers for Emerging and Reemerging Infectious Diseases supported by the Japanese government, the Research Center for Clinical Epidemiology of Emerging and Reemerging Infectious Diseases was established by Nagasaki University (NU) in collaboration with the National Institute of Hygiene and Epidemiology (NIHE) as its Vietnamese counterpart [5].

This NIHE-NU project includes the Khanh Hoa Health Project, which was launched as a collaboration of the NIHE, Khanh Hoa Health Service (KHHS), NU and International Vaccine Institute (IVI) in January 2006. In the course of discussions among the collaborating organizations, consideration was given to locations for future clinical, field and laboratory research. The study site of Nha Trang and Ninh Hoa districts in Khanh Hoa Province was selected due to local staff experience in field research, a well organized system for data management, close relationships among the NIHE staff, KHHS staff and hospital staff as well as experienced physicians and clinical microbiology laboratory staff. This paper introduces the plans and expected outcomes of the Khanh Hoa Health Project.

OBJECTIVES

(1) To enumerate the study area population in 33 communes of Nha Trang and Ninh Hoa districts and to update the existing population census database.
(2) To conduct a survey of health-care utilization that will indicate the proportion of children in the field site population who visit health-care providers for treatment of dengue fever, ARI and diarrhea.
(3) To establish a disease surveillance system for ARI, diarrhea, and dengue fever to obtain estimates of the burden for these diseases.
(4) To establish linkage of census and disease surveillance databases using the existing national health insurance identification card number for future prospective studies.

The following components were developed as key research activities that will help to identify the optimal approaches to disease treatment and prevention in Vietnam using the Clinical Epidemiology Conceptual Framework [6].

POPULATION CENSUS:

The study area is comprised of 33 communes in Nha Trang and Ninh Hoa districts of Khanh Hoa Province,

National Institute of Hygiene and Epidemiology (NIHE), Hanoi, Vietnam
Nagasaki University (NU), Nagasaki, Japan
Khanh Hoa Health Service (KHHS), Nha Trang, Vietnam
International Vaccine Institute (IVI), Seoul, Korea
Corresponding author
Email address: Koya Ariyoshi   kari@nagasaki-u.ac.jp

which is a coastal region in Central Vietnam with prosperous tourism and fishing industries. Khanh Hoa Province was selected because of the extensive experience among local staff in conducting household census for enumeration of residents in collaboration with NIHE and IVI. The census fieldwork was conducted from June 8 to July 25, 2006 in Nha Trang and Ninh Hoa districts separately. A total of 318 interviewers were recruited from among hamlet leaders or group leaders. Also, 102 supervisors and 20 managers were recruited from among community health staff. Altogether, six training courses were organized for interviewers, supervisors and managers two days prior to the start of fieldwork. Each district was divided into three regions, each of which had a training course. The initial tasks of this project included collection of census data from each household in the 33 study area communes. In the process of conducting the study area census, the field staff also collected the GPS (Global Positioning System) coordinates for individual households. We are now investigating the population risk factors using the demographic, household and other data collected during the census.

As for GIS (Geographic Information System), we are comparing the classical method of mapping households using GPS receivers with aerial photographs (QuicBird is 25 km -satellite images). Pilot studies will be initiated during this period in the area of entomological research.

The census survey covered 74,228 pre-registered households from a previous census and also detected about 10,000 new households. Thus, the total number of active households with residents was approximately 76,000. The total census population registered in this area since 1996 (first census) is about 450,000. The "active" population in mid-2006 was about 360,000. The percentage of children $\leq$ 5 years old and $\leq$ 15 years old was 9% and 29%, respectively. Data collected during the household census identified the children age ($\leq$ 15) hospitalized over the preceding one-year period for dengue, ARI, meningitis and diarrhea.

We plan to examine demographic and household characteristics as a way to determine risk factors for disease among identified cases. For example, we will investigate the hypothesis of high prevalence of an association between the household smoking and the risk of disease burden, e.g., ARI. The survey also identified a very high prevalence of household animals, e.g., swine, buffalo, dogs, cows, cats, chickens/other poultry, ducks/geese. We will investigate associations between these household animals and the disease burden, e.g., pigs with diarrhea. Furthermore the boiling of drinking water can be a strong preventive measure effective even for open wells as the source of drinking water. When boiled, the many sources of unsafe water can be used without a high risk of diarrhea. These associations will be studied very carefully. GIS mapping of household animals and other risk factors should be done along with other investigations to control potential confounding.

HEALTH CARE UTILIZATION STUDY

At the time of the population census, we simultaneously collected the information to examine the health care utilization patterns of the study population with respect to children with diarrhea, ARI and Dengue fever. The study area has two major district hospitals, four polyclinics, a community health center in each commune, and numerous private practitioners, traditional healers, and pharmacies. These characteristics do not seem to differ from those of other health systems in Vietnam. The study instruments for the health care utilization survey were originally developed to look into health care seeking patterns among children's caregivers. This study was conducted on households with a child ($\leq$ age 15) who had clinical symptoms suggestive of ARI as well as diarrhea in the preceding two weeks. For example, information on the history and nature of coughing and fever as well as health care seeking patterns was collected in detail.

The preliminary results presented [7] at a conference and prepared for a manuscript are summarized below. We identified several characteristics of health care utilization patterns for childhood ARI. First, pharmacies were found to be the leading health care modality chosen by caregivers, who acquired antibiotics frequently without conferring with a pediatrician. Considering that the most common etiology of ARI is viral and needs no antibiotics, this has significant public health implications. For example, this practice may enhance the risk of drug resistance and produce unnecessary side effects in children. Also, the economic cost may be substantial. Partnerships between medical/public health practitioners and pharmacies with the aim of avoiding unjustifiable antibiotic use are warranted. Second, the decision by caregivers to take children to a hospital was based, not upon referrals from community health centers as we expected, but simply upon the clinical symptoms of the children. It is noteworthy that the presence of tachypnea was the strongest predictor of utilizing hospitals. Given that respiratory rate is a valuable clinical indication of lower respiratory tract infections, these caregivers seem to have been rather accurate in detecting a severe disease. More detailed qualitative studies, however, are needed to examine the perceptions of caregivers in terms of their children's disease, the reasons for taking children to hospitals rather than other facilities, etc. Further comparative analysis of the census data and health care utilization data will be carried out when such data become available. Also, correlation with

health care utilization patterns for other diseases (e.g. diarrheal diseases) will be helpful in further clarifying the health care seeking behaviors. Detailed knowledge of health care seeking patterns in the study population is expected to help us to estimate and monitor the actual trend of respiratory infections in the study area based upon the passive surveillance data in the next phase.

PASSIVE DISEASE SURVEILLANCE

Prior to the surveillance, one Japanese clinician was dispatched to study [8] the characteristics of childhood ARIs and the clinical management in hospital. We analyzed the hospital inpatient database, which provides age, sex, birth date, residential address, date of admission and discharge, and ICD-10 coding of diagnosis at discharge. An experienced chest physician participated in the morning clinical rounds and daily consultations at Khanh Hoa General Hospital (KHGH) from the end of July 2006. KHGH is the provincial referral hospital located in the center of Nha Trang city. This hospital has 700 beds and provides comprehensive medical services. The department of pediatrics has 90 beds including neonatal ICU (NICU), pediatric ICU (PICU), recovery room, neonatal room, respiratory disease room, unknown fever room, diarrhea room and malaria room.

Nucleic acid amplification tests (NAATs) are a useful way to clarify the aetiology of ARIs. As a critical step in determining the burden of bacterial and viral pathogens causing ARI in Vietnam, we sought to establish laboratory capacity for NAATs in a national reference laboratory [9]. Standard bacterial strains were used as controls for the establishment of multiplex PCR assays to detect typical and atypical pathogens of pneumonia. Detection of *N. meningitidis* was also included in the assay to be used in pneumonia with meningitis cases, as meningococcal meningitis is a documented cause of meningitis in Vietnam. Specific primers were designed for target genes of four common respiratory bacterial pathogens: ply gene of *S. pneumoniae*, bex A of *H. influenzae*, cop B gene of *M. catarrhalis* and ctr A gene of *N. meningitidis*. A second assay included gene targets for three atypical pathogens: Pst-1 fragment of *C. pneumoniae,* MIP gene of *L. pneumophila* and P1 gene of *M. pneumoniae*. After establishment of the multiplex assays, 20 cerebrospinal fluid (CSF) and 30 serum samples from hospitalized pneumonia cases have been so far tested by conventional bacterial culture of CSF and blood as well as multiplex PCR for typical pneumonia pathogens. Two multiplex PCR assays (one for detection of typical pneumonia and another for atypical pneumonia pathogens) were successfully established.

FUTURE ACTIVITIES INCLUDING THE PREPARATION OF A BIRTH COHORT STUDY

We are preparing a birth cohort, which can be applied to many aspects of health research in the future for infectious disease risk factors, vertical transmission issues, vaccination impact and other potentials.

We systematize the operation of the study by the concept of clinical epidemiology [6], i.e., estimating the burden of disease, looking at the health seeking behaviors of people to understand the gap between passive surveillance and these burden of diseases, and continuing the passive disease surveillance to monitor and evaluate the impact of the possible implementation of intervention. We hope to work with many potential collaborators in order to continue this clinical epidemiological research activity in the field.

REFERENCES:

http://www.who.int/en/

Williams BG, et al, Estimates of world-wide distribution of child deaths from acute respiratory infections. Lancet Infect Dis, 2002. 2 (1): 25-32

Jones, G., et al., *How Many Child Deaths Can We Prevent This Year?* The Lancet, vol.362, 2003, pp.65-71

Bryce, J., et al., *Can the World Afford to Save the Lives of 6 Million Children Each Year?* The Lancet, vol.365, 2005, pp.2193-2200.

Center of Research Network for Infectious Disease (CRNID): available from URL: http://www.crnid.riken.jp/eng/base/index.html

Tugwell P, de Savigny D, Hawker G, Robinson V. Applying clinical epidemiological methods to health equity: the equity effectiveness loop. BMJ. 2006 Feb 11; 332 (7537): 358-61.

Anh DD, Matsubayashi T, Thiem VD, Yanai H, Mai LP, Anh NH, Tho LH, Minh TT, Kilgore PE, Ariyoshi K The health care utilization patterns of children with acute respiratory infection (ARI) in Khanh Hoa Province, Vietnam. *Asian Research Forum on Emerging and Reemerging Infections -2007, Nagasaki, Japan, January 15-16, 2007.*

Suzuki M, Cat NDL, Yanai H, Matsubayashi T, Thiem VD, Ai NTT, Tho LH, Tien NM, Anh DD, Ariyoshi K Clinical management of acute respiratory infections (ARIs) in Khanh Hoa General Hospital and implication of ARI surveillance. *International Symposium on Emerging and Reemerging Infectious Diseases, Hanoi, Vietnam, December 4 -6, 2006*

Yoshida LM, Huong VTT, Anh NH, Anh DD, Paul E. Kilgore PE, Suzuki M, Yanai H, Ariyoshi K Establishment of Nucleic Acid Amplification Tests for Etiological Diagnosis of Typical and Atypical Pathogens in Acute Respiratory Infections *International Symposium on Emerging and Reemerging Infectious Diseases, Hanoi, Vietnam, December 4 -6, 2006*