

**The Introduction of Hepatitis B Vaccine in Rural
Vietnam**

**A thesis submitted in total fulfilment of the
requirements for the degree of
Doctor of Philosophy**

by

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Abstract

Vietnam, a nation of almost 80 million people with a high rate of chronic infection with the hepatitis B virus (HBV), is currently expanding its introduction of hepatitis B vaccine (HepB vaccine) for infants across the nation. This is occurring within an immunisation program widely commended for its high coverage and achievements in disease control.

During 1997, HepB vaccine was introduced for a small proportion of infants in urban areas, using a locally manufactured product which had not previously been objectively evaluated in the field. In addition, the problem of HBV infection itself had not been adequately quantitated, making subsequent evaluation of the program difficult.

To make HepB vaccine available more widely and at birth, as is needed to prevent the perinatal infection responsible for a large proportion of chronic HBV infection, its storage outside the cold chain has been suggested. This would enable its use for infants born in remote areas lacking access and refrigeration, but scientific verification of the vaccine's immunogenicity and protective efficacy (PE) when used in this way is lacking.

In addition, it is not certain that birth dosing, nor indeed the three required doses of the vaccine itself will be acceptable to Vietnamese mothers, who are unused to infants receiving any vaccines before the age of two months and not unreasonably concerned about injection safety.

In this thesis I examine the situation with respect to the conduct of the Expanded Program on Immunisation (EPI) in one rural province of central northern Vietnam, and community attitudes towards this program and the introduction of HepB vaccine. Grave concerns about the planning, safety, effectiveness and veracity of reporting of the Program are raised, and health worker and community education programs recommended prior to the introduction of birth dosing with HepB vaccine.

I report on a survey of the seroprevalence of HBV infection in this location, confirming very high rates of perinatal infection and a monotonous increase in exposure with age. I also compare the immunogenicity of the locally produced vaccine in two different formulations with that of two internationally licensed Korean vaccines, concluding that the dose currently used in the Vietnamese EPI should be increased.

I evaluate three different strategies for the introduction of HepB vaccine in varying geographic and demographic milieu, both scientifically in terms of their immunogenicity and PE, and for their operational feasibility and likely generalisability throughout Vietnam. I provide further evidence in support of the immunogenicity of HepB vaccine stored at ambient temperature, but only limited evidence relating to PE, probably because of the low dose of vaccine available.

I compare the responses of local communities to differing levels of dissemination of information relevant to the introduction of HepB vaccine, and of health workers to training to improve their conduct of the EPI. Improving the EPI, including introduction of HepB vaccine with a birth dose, seems both feasible and acceptable to all concerned.

Finally, I evaluate the activities conducted by examining changes in the prevalence of two objectively measurable indicators of the conduct of the EPI. Whilst rates of scars following bacille Calmette-Guerin vaccine increased substantially, rates of immunity to measles amongst older infants did not.

Declaration

This is to certify that:

- (i) With certain exceptions, this thesis comprises only my original work towards the PhD. The exceptions include:
 - the initial design of the project during which the research was conducted. This was undertaken by one of my supervisors, Dr Beverley-Ann Biggs at the University of Melbourne, and the project co-director, Dr James Maynard of the Program for Appropriate Technology in Health, Seattle, Washington, USA, before being refined by the three of us prior to and after project commencement.
 - field work, during the preparation and conduct of which I was assisted by local assistants and government health staff participating in activities I designed, and
 - the majority of statistical calculations. Whilst these were entirely designed and interpreted by me, the data entry and computation of all but the crudest statistics were mostly (90%) conducted by hired assistants and Dr Trung Nam Tran, a Vietnamese biostatistician working closely with me in Hanoi.
- (ii) due acknowledgement has been made in the text to all other material used, and
- (iii) the thesis is less than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

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Dr Biggs represented the other two project partners, the University of Melbourne and the International Health Unit at the Macfarlane Burnet Centre (MBC) for Medical Research, now The Burnet Institute. Apart from being a reliable supporter and an excellent source of information, Dr Biggs has also been my main thesis supervisor for which I am again very grateful. I also thank the support staff at these two institutions, particularly Ms Virginia de Crespigny at the University and Dr Mike Toole, Mr Kelvin Margetts and Mr Geoff Drenkhahn at MBC. Also at the University, I am grateful to Professor Terry Nolan, my other thesis supervisor, for his assistance by email and in person over the years.

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David Hipgrave, January, 2004

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List of Abbreviations

AD	Auto-disable (in reference to syringes)
Anti-HBc	Antibody to hepatitis B virus core antigen
Anti-HBs	Antibody to hepatitis B virus surface antigen
AusAID	Australian Agency for International Development
BCG	Bacille Calmette-Guerin (vaccine)
CBAW	Women of child-bearing age
CDC	Centers for Disease Control
CHS	Commune health station
CHW	Commune health worker
DNA	Deoxyribonucleic acid
DNS	Disposable needle and syringe
DTP	Diphtheria-Tetanus-Pertussis vaccine
DTP1	The first dose of Diphtheria-Tetanus-Pertussis vaccine
DTP3	The third dose of Diphtheria-Tetanus-Pertussis vaccine
EPI	Expanded Program on Immunisation
EPIW	Expanded Program on Immunisation worker
GAVI	Global Alliance for Vaccines and Immunisation
GMT	Geometric mean titre
HBeAg	Hepatitis B virus "e" antigen
HBeAg+	Seropositive for Hepatitis B virus "e" antigen
HBIG	Hepatitis B immunoglobulin
HBsAg	Hepatitis B virus surface antigen
HBsAg+	Seropositive for Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HepB vaccine	Hepatitis B vaccine
HW	Health worker
IgG	Immunoglobulin G
JE	Japanese Encephalitis
KAP	Knowledge, attitudes and practices
MoH	Ministry of Health
NA	Not available
NIHE	National Institute of Hygiene and Epidemiology
NT	Neonatal tetanus
OPV	Oral polio vaccine
PE	Protective efficacy
SIAMC	Strengthening Immunisation and Malaria Control
TT	Tetanus toxoid
UNICEF	United Nations Children's Fund
VFA	Vietnam Farmers Association
VHW	Village health worker
VIDRL	Victorian Infectious Diseases Reference Laboratory
VVM	Vaccine vial monitor
VWU	Vietnam Women's Union
WHO	World Health Organisation

NATIONAL INSTITUTE
OF
HEALTH AND EPIDEMIOLOGY

Hanoi, August 30, 2002

To Whom It May Concern:

This is to certify that all the activities of the AusAID-funded project "Strengthening Immunization and Malaria Control", conducted in Thanh Hoa Province during the period 1997-2002, were fully considered and approved by the Ethical Standard Committee of this Institute, and by the Heads of the Health Service of Thanh Hoa Province.

Yours faithfully,



Prof. Hoang Thuy Long, MD, PhD
Director of NIHE, Vietnam

Chapter 1: Introduction, situation analysis and literature review

Introductory note

The control of the hepatitis B virus (HBV) in Vietnam and similar nations is a public health intervention of the highest priority, with chronic HBV infection responsible for the early death of up to 5% of all Vietnamese people (Maynard JE, Kane MA et al., 1989), (Mahoney FJ & Kane M, 1999). Fortunately, in terms of the availability of vaccine and the existence of an adequate primary health care infrastructure, Vietnam is well placed to control HBV infection, particularly compared to its western neighbours Cambodia and Laos. However, there are important factors - economic, socio-cultural, geographical and technical - which impinge on this effort and have not yet been examined in an objective or critical manner.

Vietnam introduced free vaccination against HBV for infants in 1997. For financial and logistic reasons, the program targeted predominantly urban infants, reaching only ~20% of the infant population (Appendix 1) until early in 2002, and did not include the birth dose so important in preventing perinatal transmission of the virus. Until recently, a locally produced, plasma-derived vaccine in a low-dose formulation was the only vaccine available to the public sector, with production limited by poor supplies of the raw material used in its manufacture. Development of a locally produced recombinant-DNA vaccine has been in planning for several years, using technology transfer and funding from Korea, but production en masse is not expected before 2006. In the interim, with the author's assistance, Vietnam applied successfully to the Global Alliance for Vaccines and Immunisation (GAVI) for support (by way of vaccine) for expansion of immunisation against HBV, highlighting the immediate need to address potential problems therein.

This thesis examines the key scientific and qualitative issues pertaining to immunising infants in Vietnam, and by extension similar nations, against HBV. It comprises a mixture of qualitative research into the public health environment of the country, particularly as regards the Expanded Program on Immunisation (EPI), and quantitative evaluation of the extent of HBV infection, selected relevant aspects of vaccines against

HBV in general, the comparative performance of the indigenous hepatitis B vaccine (HepB vaccine) and two imported varieties in controlled conditions, and the performance of the local vaccine in the field. It also examines the operational feasibility and impact of a variety of implementation strategies tested over the years 1998 - 2000.

The research described herein contributes particularly to the scientific and operational knowledge regarding the use of HepB vaccine after storage at ambient temperature outside the cold chain. It aimed to provide further information for agencies such as the World Health Organisation (WHO), to enable them to fill the gap in official policy regarding the use of HepB vaccines in this way. Such a strategy will greatly contribute to accelerating the control of HBV infection, through enabling birth dosing for infants born at home or in health facilities lacking refrigeration. Indeed, Vietnam is now moving forward with a birth-dose strategy predicated on the thermostability of HepB vaccine.

The research was conducted as part of a broader project, "Strengthening Immunisation and Malaria Control" (SIAMC), targeting not only HBV, but also malaria, intestinal parasites and, to a small degree, tuberculosis. Funded by the Australian Agency for International Development (AusAID), the project was a collaboration between the International Health Unit of the Macfarlane Burnet Centre for Medical Research (now the Burnet Institute), the University of Melbourne Department of Medicine at the Royal Melbourne Hospital and the Program for Appropriate Technology in Health, based in Seattle Washington, United States of America.

Basic facts about Vietnam

Geography & climate

Vietnam is a tropical country in Southeast Asia covering an area of 330,991 km², stretching 1,650 km from north to south. The widest area from east to west is 600 km and the narrowest only 50 km. Vietnam borders China to the north, Laos and Cambodia to the west and faces the South China Sea on the east. Approximately 80% of Vietnam's land area comprises mountains, high plateaus or jungle; only 20% is flat, and a good deal of

this is delta land prone to flooding. The climate ranges from the hot monsoonal south to the seasonally cooler northern regions, which still receive most of their rain in summer.

Demography

The official population in 1999 was estimated at over 76 million, with a growth rate of 1.5% (Appendix 1). The population density is ~240/ km². In 1989, almost 40% of all Vietnamese were aged less than 15 years. A vigorous family planning campaign aims to decrease this to 31% by 2005. The majority of Vietnamese belong to the Kinh ethnic group, but there are 54 ethnic minorities ranging in number from the hundreds to the hundreds of thousands. Most communities of these groups live in the mountains.

Political and health administration

A descent through the administrative hierarchy of Vietnam passes through 61 provinces, around 623 districts, 10,450 communes and an unknown number (at least 100,000) of hamlets and villages. There are also four notional boundaries that separate the nation into northern, central, central highland and southern administrative regions. These are also important for the distribution of health commodities such as vaccines and administration of the EPI. Each province, district and commune in Vietnam has a local Peoples' Committee, which is represented on all the local administrative committees, including those relevant to health, education and agriculture. Peoples' Committee leaders serve as communicators and mobilisers of support for (or resistance to) any new initiatives impacting on their constituency. At all levels, there are also representatives of the Vietnam Communist Party who must also be informed and approve of new activities. Other local leaders include those representing the Vietnam Women's Union (VWU), Vietnam Farmers Association (VFA) and Youth Unions, each of whom meet members and distribute information to them on a regular basis (Chapter 2).

Structure of the health sector in Vietnam

The Ministry of Health (MoH) is responsible for the administration of the state-run health sector and regulation of the burgeoning official private sector. It works through a hierarchy of providers from central to grassroots level, but at each level is subject to the authority of the Government and People's Committees (Appendices 2 and 3). This

hierarchy is outlined in more detail in Appendix 3. The lowest cadre of salaried health staff work at commune level. They are usually local people who have been sent away for training and then return to work in their home area. They range from doctors with 6 years training (some of them initially as an assistant doctor, then upgrading, official salary US\$20 – 30/month) through assistant doctors (3 years/\$20) to trained nurses and assistant nurses (whose salary varies) (Multidonor Health Sector Review Committee, 2001). There are also pharmacy assistants and support staff at some commune health stations (CHSs).

The EPI in Vietnam

History

The EPI in Vietnam dates back to a pilot program in 1982, and expanded to a national program in 1985. In 1993, the first National Immunisation Days (NIDs) were launched, and these continued to support the routine program in maintaining high levels of coverage and disease control until the year 2000, when polio-free status was declared.

Table 1 shows the increments in official coverage of EPI antigens over the 10 years to 1996, and Table 2 the reduction in morbidity and mortality due to vaccine-preventable diseases. The most recent official coverage statistics posted on the UNICEF website (UNICEF, 2002) suggest this high coverage has been maintained, although a severe shortage of diphtheria-tetanus-pertussis (DTP) vaccine in 2002 will affect this.

Table 1: Immunization coverage of children under 1 year of age, 1986–96

<i>Vaccine type</i>	<i>1986</i>	<i>1990</i>	<i>1996</i>
Tuberculosis (BCG)	54.5	89.9	95.4
Polio	44.7	86.5	94.5
DTP	42.6	86.7	94.4
Measles	38.8	86.6	96.0
Fully vaccinated		87.0	95.1

Source: (Ministry of Health Vietnam, 1996)

Table 2: Morbidity and mortality rate per 100,000 inhabitants of vaccine-preventable diseases

<i>Disease type</i>	<i>Cases per 100,000 population</i>			<i>Deaths per 100,000 population</i>		
	<i>1985</i>	<i>1990</i>	<i>1996</i>	<i>1985</i>	<i>1990</i>	<i>1996</i>
Diphtheria	3.7	0.77	0.19	0.40	0.09	0.02
Pertussis	68.6	6.18	18.03	0.08	0.04	0.01
Polio	2.6	0.59	0.61	0.15	0.02	0.02
Tetanus	5.0	0.48	0.53	0.40	0.31	0.27
Measles	12.8	13.15	6.86	0.45	0.04	0.01

Source: (Ministry of Health Vietnam, 1996)

Funding

Around 75% of Vietnam's EPI is funded by the national government and the rest by bilateral and multilateral donors. Government support for the program currently runs at US\$6 – 8 million/year. This excludes special campaigns and NIDs or sub-national immunisation days (SNIDs). UNICEF is a major donor, and sources its contributions from internal funds as well as private and bilateral donors who direct their support for the EPI through UNICEF to preferred aspects of the program, such as vaccines (Japan) and other related materials (Australia). In addition, in keeping with the disparity in wealth between regions of the country, some provincial or district authorities also contribute to the local EPI by way of paying incentives to local staff, supporting local training initiatives or purchasing optional vaccines or equipment. In this way the conduct and standard of the program may vary considerably in different parts of the country. Local authorities also have considerable freedom to influence scheduling and practical or policy issues pertaining to the EPI, so that, for example, the former national policy on syringe type (disposable versus reusable) according to whether a district is labelled mountainous or delta/coastal could be over-ridden by these levels. Local policy on cost recovery for optional equipment (and program implementation or even on the EPI schedule) also varies from one commune to the next (Chapters 2 and 7).

Vaccine for Vietnam's EPI is sourced from a mixture of suppliers, but a strong preference and aim for local production prevails. For the last few years, all bacille Calmette-Guerin

(BCG) and oral polio vaccine (OPV), and (except in 2002) ~60% of the DTP and tetanus toxoid (TT) vaccine is produced in country and sold by the manufacturers to the MoH. Until earlier this year, all the HepB vaccine used in the EPI was produced in country, but this antigen had only been added to the EPI in locations housing ~20% of the annual birth cohort (Appendix 1). However, the four manufacturing plants (in Nha Trang (DTP, BCG and TT), Da Lat and Hanoi (PolioVac for OPV and the National Institute of Hygiene and Epidemiology (NIHE) for HepB vaccine) are not recognised by WHO as having reached an adequate standard of good manufacturing practice, and decisions on vaccine procurement for the National EPI are made by a small group of individuals who until recently also directed local vaccine production. Further, until recently the same individuals were also responsible for vaccine quality control. At the instigation of WHO, this situation was acknowledged in 1999 with the creation of a separate National Regulatory Authority overseeing vaccine production, but the preference for local product whose quality outside the laboratory has not been independently verified remains strong (Chapter 5). Notwithstanding these issues, Vietnam has reported a dramatic drop in the incidence of neonatal tetanus (NT) and measles and was declared polio free by WHO in October 2000 (WHO WPRO, 2000).

The balance of vaccine, including all measles vaccine for the EPI is funded by UNICEF and the Japanese International Cooperation Agency. An application for grant aid to support technology transfer enabling local production of measles vaccine has been made to the government of Japan, and a site identified in Hanoi for this facility. In addition, a soft loan of US\$28million from the government of Korea has been successfully negotiated. When drawn down, these funds will be used to support technology transfer and development of a second new facility in Hanoi for the production of a recombinant HepB vaccine, new cholera, typhoid and rabies vaccines (to replace existing local products currently produced at NIHE) and the increased production of the indigenous mouse-brain vaccine against Japanese Encephalitis (JE).

There are four manufacturers of needles and syringes in country, and the EPI procures 100% of its requirements from these domestic sources. Sterilisers, needles and syringes are theoretically in adequate supply, but there are problems with the supply of fuel in

non-electrified areas, comprising 40% of all communes (but 75% in mountainous communes). This fact contributed to the national policy that until recently favoured use of disposable equipment throughout inland and mountainous areas, where electricity is often unavailable, and sterilised reusable equipment elsewhere. Perspectives on the possible abuse of EPI equipment and Vietnam's injection safety program are discussed below and in Chapter 2. Fortunately, during 2003 Vietnam will phase in the use of locally produced auto-disable (AD) syringes for the EPI, obviating issues pertaining to sterilisation at least for this Program.

The supply of cold chain equipment is supported by UNICEF and other donors as well as from the local EPI budget. Funds are earmarked to replace 10% of the nation's cold chain equipment each year, but may not always be drawn down for this purpose. The Luxembourg Development Agency will shortly donate almost 4,000 small refrigerators which can use gas or electric power, for use at CHSs.

In real terms the government's contribution to the EPI has remained static over the last 5 years, frustrating those aiming to improve the program. It has also resulted in a dearth of support for regular training and community mobilisation activities, which are given low priority and reserved for districts created anew when new political boundaries are drawn, usually to facilitate administration of large areas. Most province- and district-level refresher training must be funded and organised locally, and is likely to be of lower technical and pedagogic quality than when national, more qualified and experienced trainers are involved. Because of its very high, published EPI coverage, Vietnam is ineligible for financial support from the immunisation services sub-account of GAVI. This source might have supported a comprehensive training and refurbishment program for the EPI, which is needed for the expanded introduction of HepB vaccine, particularly given that a birth-dose policy is being introduced for most provinces.

Program organisation and constraints

Vietnam has a well-established EPI, with published rates of full coverage exceeding 90% for most of the last decade. However, for most communities immunisation is at best available only on a designated day every one or more months, unless vaccines are kept

and sold privately by health workers, which is rare outside cities. In mountainous areas, the EPI may only reach a community every 3 – 4 months or even less often (Chapters 2 and 7), and there is a small proportion of so-called EPI-white villages, which the routine program does not reach. These villages rely on campaigns for their coverage.

With the exception of certain privately funded maternity units in the large urban centres, until recently Vietnamese infants were unable to receive any vaccine until aged at least several weeks (for urban infants or those living in easily accessible areas) or months (for rural infants, especially those living in mountainous areas). As no vaccines were stored in public hospitals or maternity units, the EPI until now did not allow for vaccination of newborns, even those delivered in health facilities with electric power and access to refrigeration. In addition, over 75% of the population live in rural areas (around 30% in areas which may be described as mountainous or remote) where, for a large proportion, there are regular interruptions to or no power supply, access is difficult and rates of home-birth are high (20 – 100%). These constraints have created major challenges for ensuring the timeliness of vaccination for Vietnamese infants.

Vaccine procured locally or by UNICEF is transported by air to one of four regional storage points, where it remains for up to several months. Vaccine is distributed from these regional stores to communes in a systematic fashion. In general on a certain day each province's Preventive Medical Centre sends a vehicle to collect enough vaccine for one month from the relevant regional store. Some provinces in the Central Region collect vaccine every three months. The required amount is calculated using the estimated target population with a wastage rate of 2.8 for BCG and 1.6 for the other antigens (Appendix 1). There is theoretically no shortage of vaccine, but in many mountainous areas immunisation is conducted as an outreach activity and the provision of some vaccines in only two or three vials of 20-doses per commune causes problems if there are many EPI outreach points to visit, each with only a small number of infants (Chapter 2). Vaccine vial monitors (VVMs) and a multi-dose policy are not currently in use in Vietnam (except for the VVMs on recently supplied vials of HepB vaccine), but may be introduced in 2003 (Appendix 1).

From the provincial stores, vaccines are then distributed or dispensed to district hospitals, each of which, at least notionally, have adequate, appropriate and functioning refrigeration to enable overnight storage. Commune health workers (CHWs) then collect vaccine from district level, usually on the day prior to the monthly immunisation day. Their allocation assumes the above wastage rates. Fixed cold chain facilities end at district level; CHSs rarely have refrigeration and rely on cold boxes with ice packs or wet ice purchased locally to maintain the cold chain on EPI day(s). In theory the date of the monthly EPI day does not vary from month to month, but the inconsistent availability of transport and local prioritisation can create some variability. This places responsibility for community mobilisation on village-level informants who are informed just prior to or on the day of the EPI team visit (Chapter 2).

EPI vaccines are provided free of charge, but some local authorities approve a small fee if local costs in providing an improved service (such as a home visit or the option of a new disposable needle and syringe instead of a sterilised reusable one) are incurred. Some communes offer a fixed price service to pregnant women, including TT for them and all EPI antigens for their new infant, each with a new, disposable needle and syringe. Optional vaccination against JE, rabies, typhoid and cholera, using locally produced or imported vaccines, is also available in certain areas, usually for a fee.

The nationally approved EPI schedule in Vietnam is depicted in Table 3. Option 1 depicts the official schedule used until early 2002, although some versions stated that the first dose of HepB vaccine should be given at birth, with doses 2 and 3 at 4 and 8 weeks, necessitating an extra visit at 4 weeks. This schedule must have been used very rarely in practice in Vietnam. Option two is the schedule included in the application to GAVI, and is now official in those provinces using GAVI-funded vaccine.

Table 3: Current vaccination schedule with traditional and new vaccines

Age	Visit	Traditional antigens		New vaccines	
				Option 1	Option 2
Birth	1	BCG			HepB 1
8 weeks	2	OPV1	DTP1	HepB 1	HepB 2
12 weeks	3	OPV2	DTP2	HepB 2	
16 weeks	4	OPV3	DTP3	HepB 3	HepB 3
9-11 months	5		Measles		

In practical terms, few infants receive BCG at birth, most receiving it at their first EPI contact along with the first dose of DTP (DTP1). Measles vaccine is only offered to the unimmunised between the ages of 9 and 11 months. Theoretically if an infant is missed during this age range, they will receive measles vaccine on a NID or SNID (described below), but many doses may be late. There are plans for an OPV/DTP booster in the 2nd year of life and Vietnam recently commenced a program of second-dose measles vaccination targeting 9 month – 10-year old children in a series of sub-national campaigns being conducted in different regions over 2002 and 2003.

Many women and children were formerly vaccinated on NIDs or SNIDs, or a smaller scale local equivalent if a disease outbreak or higher-than-expected number of cases occurs. NIDs have a separate budget from the EPI, often supported by WHO or UNICEF, and have been important in boosting coverage rates, particularly in remote areas. NIDs or SNIDs were formerly conducted twice yearly, separated by about one month and covering the entire country (although the actual dates varied by region). They are less common since the declaration of Vietnam's polio-free status.

The cold chain

The system of maintaining cold storage for EPI vaccines in Vietnam is not well developed (Appendix 1). In particular, it stops before the point from which most vaccines are administered, relying on cold boxes and vaccine carriers, which must be supplied with ice packs or privately-procured wet ice. Cost constraints and limited availability of a consistent electricity supply have restricted the capacity of the EPI to improve this

situation, which is particularly critical in mountainous and remote areas where the EPI team may need to travel long distances and work over several days each month in order to maintain coverage (Chapter 2).

Injection safety

This is an acknowledged area of concern for the MoH and the National EPI, and a plan of action to improve injection safety has been drafted and approved. The findings of a survey described in Chapter 2 suggest that this is a critical area in need of improvement in Vietnam. Fortunately, recent developments relating to the use of AD syringes will obviate most of the problems identified.

Record keeping

As part of its health information system, each CHS across Vietnam keeps uniform maternity registers, records of vaccine received and EPI registers listing infants by village and vaccines administered by date, but the entries are difficult to verify and vary widely in their credibility. Disparities between data submitted by different levels also points to a general lack of capacity in the Vietnamese health information system.

The recording and monitoring of EPI activity and coverage is a major area of concern (Chapter 2). The National EPI Review of 1998 (Appendix 4) alluded to the disparity between reported coverage figures (upon which the high national coverage statistics are based) and those identified by the review team, which also expressed concern that the denominator of newborns may be understated. This may relate to the above-mentioned family planning policy in Vietnam, which strongly discourages more than 2 children per couple. In addition, the holding of a parent-held EPI record by mothers varies widely.

Background information on Thanh Hoa Province

The sites for the research described in this thesis were two districts in Thanh Hoa province located ~150 km south of Hanoi, the national capital of Vietnam. These districts mirror the variety of scenarios found in rural Vietnam, with the exception of very remote highlands, which are not represented.

General information

Thanh Hoa comprises 1 city and 26 districts, with a total population of ~3,400,000 and a population density of 305/km². Seven ethnic groups reside within its borders, and in certain areas most people are from minority groups using Vietnamese as a second language. The terrain ranges from densely populated, flat, coastal plain, through less crowded semi-mountainous hinterland to remote, sparsely populated and mountainous districts bordering Laos. Nineteen districts in Thanh Hoa are classified by the Vietnamese MoH as mountainous, which bears on certain aspects of public health policy such as its policy on disposable or reusable needles and syringes. The weather is hot and wet from June - August, warm-hot and sometimes wet in April, May, September and October, and otherwise cool and mainly dry. Rains completely isolate certain areas during the summer.

Health services in Thanh Hoa

There are CHSs in all 626 communes in Thanh Hoa, each with 3 – 5 trained staff, depending on the local population (if >6,000, staff number 5). One of these is responsible for all EPI activities, including collection of vaccines, sterilisation of re-usable equipment if any, organisation of and participation in outreach activities, promotion of vaccination and preparation for NIDs or campaigns. In Thanh Hoa, in 1999, the 2,728 CHWs included 95 doctors and 250 nurses. The main health problems in the province are malnutrition, diarrhoeal and other alimentary diseases and acute respiratory illnesses. Malaria has diminished in importance since 1991 when there were 28 outbreaks and 351 deaths attributed to this illness. However, a high risk of malaria outbreaks prevails in the province's mountainous districts.

Approximately 75% of Thanh Hoa villages have trained village health workers (VHWs) (70% are female). These cadres are trained for 6 – 9 months although the quality of this training and syllabus varies considerably. Some VHWs are retired CHWs or received training in the armed forces. Villages in coastal and remote mountainous areas are more likely to have a trained VHW, the former because of access and the latter because of prioritisation. VHWs may be salaried (~US\$5/month – more common in the mountains) or be paid in kind by their community with rice. A pledge of community support is

required before the provincial health education facility will train a VHW from a particular village, but a poor harvest can limit the support offered to VHWs paid in kind. Also at village level, some retired CHWs run licensed private pharmacies, and traditional medicine using leaves and roots is practised in most areas.

Information on sites for SIAMC and research

Project work began in 1997 in two districts, Quang Xuong (population approximately 270,000; population density 1,172/km²) and Ngoc Lac (population approximately 130,000; population density 273/km²), and expanded into a third district, Nhu Xuan in 1999. Activities in Nhu Xuan are not evaluated in this thesis. Maps are attached as Appendix 5.

Quang Xuong is a flat, coastal district of 41 communes, straddling the national highway and surrounding Thanh Hoa city, the provincial capital. The ethnicity of 99% of its population is Kinh, the majority ethnic group in Vietnam. The main income generating activities in this district are rice and vegetable farming, fishing and servicing the beachside tourist industry. Ngoc Lac is a semi-mountainous district of 20 communes and three towns, lightly forested in parts and centred ~60km inland from (west of) Thanh Hoa city. The population distribution differs from that in delta or coastal areas, as villages may be several kilometres distant from each other and from health services, and most roads are dirt tracks in poor condition. Over 80% of the people in Ngoc Lac are of Muong ethnicity, with smaller numbers of Kinh, Thai and Dao. Commercial and subsistence farming (of rice, sugarcane, cassava, maize and vegetables) are their main activities. Both districts have telephone access, but only in Quang Xuong does this extend beyond the district centre to commune level. All communes in Quang Xuong have reliable electric power, but this has only recently been connected to, and remains intermittent in most Ngoc Lac communes and even in the district centre.

There are trained VHWs in most villages in Quang Xuong and Ngoc Lac. Their main roles are in health education, assisting with outreach activities or campaigns (including EPI and malaria control), midwifery, promoting family planning, reporting outbreaks of disease and recording of births and deaths. Some VHWs run a private dispensary and

dispense drugs – with antimalarials and anti-tuberculous drugs provided nominally free of charge, and others sold to support a revolving fund or for profit. Although official MoH policy precludes them giving injectable medication, many VHWs assist with administering vaccines on EPI day.

Prevention of Hepatitis B infection by immunisation

The protection of infants from infection with HBV by immunisation is one of the most important public health advances of modern times. Although the mechanism of this is unclear, HBV is unequivocally associated with primary hepatocellular carcinoma (Beasley RP, Hwang LY et al., 1981a), (Beasley RP & Hwang LY, 1984a), (Lok AS, 2000), amongst the commonest cancers in the world. It is estimated to be responsible for 52.3 – 59.4% (Montalto G, Cervello M et al., 2002), (Pisani P, Parkin DM et al., 1997) of almost 550,000 (Parkin DM, Bray F et al., 2001) deaths due to primary hepatocellular carcinoma annually, over 80% of them in developing countries where the proportion caused by HBV is higher than elsewhere (Parkin DM, Pisani P et al., 1999). In individuals less than 50 years of age, more than 75% of this cancer may be attributed to HBV (Hall AJ & Wild CP, 2003). Worldwide, over 2 billion individuals have serologic evidence of current or past HBV infection, and over 400 million people are estimated to be chronically infected (Vryheid RE, Kane MA et al., 2000), (Lee WM, 1997), (Lai CL, Ratziu V et al., 2003) up to 25% of whom will die prematurely from its effects (Beasley RP & Hwang LY, 1984a), (Margolis HS, Coleman PJ et al., 1995). Over 1,000,000 people with chronic HBV infection are estimated to die every year (Lai CL, Ratziu V et al, 2003). Most of the HBV exposures resulting in chronic infection occur in infancy and early childhood (Beasley RP, Hwang LY et al., 1981b), (Beasley RP, Hwang LY et al., 1982), (Beasley RP, Hwang LY et al., 1983b), (McMahon BJ, Alward WL et al., 1985), (Roumeliotou-Karayannis A, Tassopoulos N et al., 1985), (Edmunds WJ, Medley GF et al., 1993), (Hyams KC, 1995), at which time immune tolerance to the virus is high (Lok AS, 1992).

HBV infection has been divided into three epidemiological categories, as shown in Table 4. The pattern of virus transmission and the age at which infection is initially encountered

(and hence the risk of progressing to chronic carriage) varies according to the community prevalence of HBV and also the type of infection amongst carriers. This pattern is well characterised and has been comprehensively reviewed elsewhere (Maynard JE, Kane MA et al, 1989), (Mahoney FJ & Kane M, 1999). Of particular relevance to Vietnam and similar nations of high HBV prevalence is the prevalence amongst carriers of the hepatitis B "e" antigen (HBeAg), a marker of viral turnover and also of HBV DNA circulating in the carrier (Beasley RP, Hwang LY et al, 1981b), (Lok AS, 1992), (Lok AS, 2000), (Stevens CE, Beasley RP et al., 1975), (Beasley RP, Trepo C et al., 1977), (Xu ZY, Liu CB et al., 1985), (Lee SD, Lo KJ et al., 1986), (Burk RD, Hwang LY et al., 1994), (Chu CM & Liaw YF, 1997). In Pacific, east and southeast Asian countries, where chronic HBV infection averages 10 – 20%, and 30 – 50% of hepatitis B surface antigen positive (HBsAg+) women are also HBeAg+, it is estimated that 3 – 5% of all infants may develop chronic infection at birth, and that 20 - 50% of all chronic infections may result from perinatal transmission (Maynard JE, Kane MA et al, 1989), (Mahoney FJ & Kane M, 1999), (Gust ID, 1996), (Margolis HS, Alter MJ et al., 1991), (Yao GB, 1996). By contrast, in most African countries in which it has been studied, although chronic infection may again average 10 – 20%, the rate of HBeAg positivity amongst infected women of child-bearing age (CBAW) is <20% (Pellizzer G, Ble C et al., 1994), (Marinier E, Barrois V et al., 1985), (Prozesky OW, Szmuness W et al., 1983), (Vardas E, Mathai M et al., 1999). Perinatal transmission in Africa is less common (1 – 2%) and only responsible for 10 – 20% of all chronic infections (Maynard JE, Kane MA et al, 1989), (Prozesky OW, Szmuness W et al, 1983), (Botha JF, Ritchie MJ et al., 1984), (Prince AM, White T et al., 1981). In these and similar countries, the majority of transmission occurs horizontally in early childhood, and HBeAg is lost before the age of childbearing, earlier than in Asian carriers. As perinatal infection can be prevented by immunisation in the first few days of life, this kind of epidemiological information is important for countries deciding on their HBV infection prevention strategy, particularly whether infants would benefit greatly from a birth dose of HepB vaccine.

Table 4: Global patterns of HBV infection

Characteristic	Low	Medium	High
Current infection*	0.2 – 0.5%	2 – 7%	8 – 20%
Evidence of infection at some time**	4 – 6%	20 – 55%	60 – 90%
Childhood infection	Infrequent	Infrequent	Frequent
Neonatal infection	Infrequent	Infrequent	Frequent

*positive for HBV surface antigen (HBsAg) **positive for HBsAg or antibody to HBV core antigen. Adapted from (Maynard JE, Kane MA et al, 1989)

Safe, effective vaccines against HBV have been available for almost 20 years and there has been a wealth of research on various vaccination strategies (Mahoney FJ & Kane M, 1999), (Andre FE & Zuckerman AJ, 1994), (Coursaget P & Kane M, 1993), (Yeoh EK & Young B, 1993). Many of these have concluded that in Asia, best results are obtained with a mixed vaccination strategy involving the screening of pregnant women to determine their HBV infection status and passive/active immunisation of infants delivered by infected women, or active immunisation alone for infants delivered by uninfected women, both commencing on the day of birth (Andre FE & Zuckerman AJ, 1994), (Wong VC, Ip HM et al., 1984), (Beasley RP, Hwang LY et al., 1983a), (Theppisai U, Thanuntaseth C et al., 1987), (Ip HM, Lelie PN et al., 1989). Such a strategy has been used in several countries of high or medium HBV prevalence with great success (Tsen YJ, Chang MH et al., 1991), (Huang K & Lin S, 2000), (Goh KT, 1997), but is not practicable in the poorer countries of the southeast and east Asian region, most notably China (Yao GB, 1996) and the nations of the southern Mekong region, where antenatal screening is usually not possible and anti-HBV specific immunoglobulin (HBIG) usually not available. Fortunately, active immunisation alone, if administered soon after birth, is almost as effective in preventing perinatal transmission (Maynard JE, Kane MA et al, 1989), (Poovorawan Y, Sanpavat S et al., 1992), (Chunsuttiwat S, Biggs BA et al., 1997), (Ruff TA, Gertig DM et al., 1995), (Wilson JN & Nokes DJ, 1999), (Liu Y, Liu X-Z et al., 1996) but presents its own logistic challenges in nations with high rates of home birth, like those in the Pacific, China, Indonesia, Vietnam, Laos, Cambodia, Myanmar and even India.

Fortunately, certain characteristics of HepB vaccine itself can reduce the difficulties associated with its introduction in the circumstances applying in these and similar nations. In particular, its safety and low reactogenicity at any age, its high rate of protective efficacy (PE) and immunogenicity and its heat stability (reviewed in detail in Chapter 4) make possible the storage of HepB vaccine outside the cold chain and its effective administration to newborns at the point of delivery, even in remote areas with limited access. Although not yet formally recommended by WHO, these characteristics are now being made use of in the EPI in Indonesia (Sutanto A, Suarnawa IM et al., 1999), (H Harmeinh, former Indonesia National EPI Manager, personal communication), and were included in Vietnam's successful application to GAVI (Appendix 1). China will also introduce a similar strategy in certain areas. They are also critical to other nations with high rates of home birth and poor geographic access.

Issues pertaining to HBV immunisation in Vietnam

Vietnam has been producing a plasma-derived HepB vaccine at NIHE since the mid-1990s, using technology transferred from the Kitasato Institute in Japan and with the supervision of the United States Centers for Disease Control (CDC). Internal evaluations of this vaccine (described in more detail in Chapter 5) determined its safety and immunogenicity, enabling the National EPI to commence use of this product for its program of infant HBV immunisation, commencing in 1997. The vaccine is formulated in 2-dose vials of 2.5µg/0.5ml/dose for infants and children <5 years and single-dose vials of 20µg/ml for others. The cost of a paediatric dose is around US\$0.50.

The government of Vietnam is committed to vaccinating its population against HBV, but can currently purchase only 50% of the 2 million doses produced annually by NIHE for use in the EPI. This is only enough to vaccinate ~20% of the birth cohort of over 1.6 million infants, and has been used mainly for those residing in provincial capitals. Vietnam's annual requirement for HepB vaccine is >5 million doses (Appendix 1). Only newborns are eligible to receive HepB vaccine free of charge through the EPI - there is no catch up program for older infants or children. The remaining NIHE vaccine

and some imported varieties of HepB vaccine are available for private purchase on the open market.

NIHE's capacity to increase its HepB vaccine production is limited by difficulties in procuring the raw material (human plasma) needed, and the capacity of the government to increase coverage is limited by the lack of funds to purchase vaccine. Until recently there was no immediate prospect for an expansion of the infant HepB vaccine program, but the situation improved dramatically with Vietnam's eligibility to apply to GAVI for a bridging supply of HepB vaccine pending development of their own recombinant-DNA product. An application to GAVI was successful in July 2001. The approved application requested sufficient imported vaccine to enable phased expansion of HBV vaccination to all Vietnamese newborns over a period of 2 years, but includes continued reliance on the indigenous vaccine for 20 - 25% of the country's needs during the entire 5-year period of GAVI support. At the end of this period, it is anticipated that Vietnam will be self-sufficient in local production of a recombinant-DNA HepB vaccine. The application also outlines the introduction of a birth-dose strategy for newborns in most provinces, using single doses of HepB vaccine pre-filled in Uniject devices stored outside the cold chain at CHSs, close to the point of delivery, for up to one month each. This radical change in policy follows the demonstration of the operational feasibility and also the serologic success of this approach demonstrated by this project and the research described herein.

In anticipation of this change of strategy, there has been a need for Vietnam to examine several questions germane to its program of HepB vaccine introduction. These include:

- the extent of HBV infection in country. No population-based prevalence rates of HBV infection in Vietnam have been published in the international literature, and with one possible exception, local surveys have been neither population-based nor age-stratified;
- the acceptability of the new vaccine to the local population, involving as it does three extra injections, a recommendation for birth dosing and protection against a largely covert infection whose important manifestations occur decades after the primary exposure occurs;

- independent evaluation of the immunogenicity of the locally produced vaccine, whose use will continue for up to one-quarter of the infant population for another 5 years, the only such evaluation having been conducted by the manufacturers and
- the feasibility, immunogenicity and PE of HepB vaccination beginning with a birth dose for infants delivered both in hospitals and at home in Vietnam.

The following chapters examine each of the above issues in detail. Fortuitously, answering these questions has entailed an examination of many aspects of the EPI, concluding that expansion of HBV vaccination may be viewed not only as a fillip to public health in Vietnam, but also as a lever to engender overall improvements in immunisation services.

An assessment of immunisation practices in the two project districts during 1998**Introduction**

SIAMC was funded by AusAID to conduct field and scientific evaluations of the HepB vaccine being produced at NIHE in Hanoi, and to assist with the development of a strategy to most effectively introduce this vaccine into the local EPI. To this end, SIAMC worked initially in the 2 project districts (Quang Xuong and Ngoc Lac) in Thanh Hoa, gathering baseline information, designing new publicity materials, orienting health promoters and conducting training programs for VHWs, CHWs and community leaders.

During this preliminary period, the author noted problems with the conduct and reporting of the EPI in Thanh Hoa and felt that a formal survey of CHWs' EPI-related knowledge and practices should be undertaken, in advance of further activities related to introduction of HepB vaccine. The survey, reported in this chapter, was timed to closely follow a large household survey undertaken in February 1998, in which over 900 female heads of households in 15 communes of these 2 districts were questioned about their knowledge, attitudes and practices (KAP) regarding liver disease, HBV and the EPI (Chapter 2B). It thus enabled the project to compare CHWs' perception of their performance with that of mothers in their locality.

The aim of this survey of CHWs was to assist SIAMC to avoid the anticipated failure of existing EPI services to cope with the extra requirements of a program of immunisation against HBV as planned for Vietnam, namely a birth dose and three additional injections of HepB vaccine (Maynard JE, Kane MA et al, 1989), (Mahoney FJ & Kane M, 1999), (Department of Vaccines and Biologicals, 2001). Between 20 and 50% of cases of chronic HBV infection in Southeast Asia result from perinatal exposure to the virus (Beasley RP, Hwang LY et al, 1981b), (Maynard JE, Kane MA et al, 1989), (Mahoney FJ

& Kane M, 1999), (Yao JL, 1996), (Margolis HS, Alter MJ et al, 1991) (Chapters 1 and 3), necessitating a birth dose for optimum protection.

The survey also aimed to provide the project with much-needed objective, general information on Vietnam's immunisation program, which, largely on the basis of high published coverage rates (Multidonor Health Sector Review Committee, 2001), (UNICEF, 2002) is hailed internationally as a great success (Inskip HM, Hall AJ et al., 1991), (UNICEF, 2001a) in the absence of objective or published information on its conduct at grassroots level; and to identify areas of the EPI in which strengthening might be required.

Method

Timing, location and strategy

The survey was undertaken at 12 CHSs in the 2 project districts (6 in Quang Xuong and 6 in Ngoc Lac) over 6 days in late March and mid-April, 1998. A further assessment of certain equipment items was undertaken in October 1998. The choice of communes in Quang Xuong was based on geographic spread around the district. Those in Ngoc Lac were also geographically dispersed, but were selected for their perceived malaria endemicity, as suited another component of SIAMC.

The knowledge and practices of CHWs in these communes were assessed using a structured questionnaire followed by a focussed interview.

Topics surveyed

The questionnaire and topics for the interview were developed by the author, based on surveys of EPI activities conducted in Vietnam and elsewhere by WHO and UNICEF, and by others in Thailand. They included the following:

- general demographic information about the commune
- EPI activities at each CHS (staffing, training, organisation, frequency, achievements and performance in 1997)

- cold chain and sterility issues (equipment availability and appropriate usage, knowledge and practices)
- interactions between the district hospital, CHWs and VHWs in the conduct of the EPI (particularly regarding supervision and informing the local population about forthcoming EPI services)
- EPI education and
- data collection and report writing (including use of under 5 or immunisation cards).

All members of the interviewing team were familiar with the topics and had had experience as interviewers before.

Questionnaire

To save time, CHWs were given the opportunity to present their EPI capacity and activities by answering a list of simple questions mainly regarding objective EPI-related parameters (local population demography, CHS-staffing, EPI organisation and achievements, availability of equipment to ensure sterile technique and maintenance of the cold chain, and EPI promotion and reporting materials). These questionnaires (see Appendix 6) were distributed to each CHS several days prior to the visit of the interviewing team. Responses were entered by a CHW and later compared to the CHS EPI register, monthly EPI summary report (both of which are standard records at all the CHSs surveyed) and equipment store, by the interviewers.

Focussed interview

Given the presence of provincial and district health officials and their co-workers in the survey team, the author felt that a round table "focus-group" discussion involving all staff at a CHS might not put interviewees at ease. To overcome this limitation, one member of the project's staff, together with a representative of the Thanh Hoa Preventive Medical Centre, interviewed one of the CHWs (usually the one designated as the EPI worker (EPIW) for that CHS), while the author, and/or the representative from NIHE, together with one other interviewed the head of the CHS. This strategy enabled inconsistencies between their accounts to be noted, and comparison of CHWs' responses with those of householders during the previous householder survey.

In Quang Xuong, this interviewing strategy could be undertaken in each of the 6 project communes. In Ngoc Lac, it was possible in 4. In the 5th, the interviewees were the CHS head and 3 local VHWs who took the place of the EPIW who was absent (along with the EPI register for this CHS). In the 6th (near to and geographically similar to another), no questionnaire was completed, only one interviewer was able to attend, and the interviewee was a CHW.

Data analysis and report writing

Qualitative data were recorded by hand at the interviewing site, translated where necessary and analysed by the author using keyword selection and comparison of information from different respondents. Quantitative data were entered onto a computer using Epi Info version 6.03 (CDC, Atlanta). Where gross inconsistencies in quantitative data were noted after data entry (for example, unlikely discrepancies in numbers of infants and under 5s), CHS-heads were given an opportunity to revise by post those questionnaire responses which seemed most unlikely by completing a proforma data revision form, although in most cases this resulted in little change.

Results (See Figure for this Chapter in Appendix 8)

General comment on the data

Despite the use of the strategies described above to ensure responses were verified and reasonably accurate, the difficulties encountered by this survey exemplify the problems of acquiring good quality information about the activities of grassroots health workers (HWs) in Vietnam. There were clearly problems with the literacy and numeracy of many respondents, some of whom were initially trained many years (even decades) ago as military HWs. Although in most cases several days were available to complete the questionnaire, many were not complete at the time of the interview and many questions were clearly not understood by the interviewees, despite being translated into plainly worded Vietnamese by project staff experienced with the previous household questionnaire. Several CHSs were unable to provide basic statistics, such as third doses

of DTP (DTP3) or measles vaccine given in 1997, let alone more complex EPI statistics, such as the percent of mothers of infants receiving DTP1 who had themselves received 2 or more doses of TT (so-called infants "protected at birth"). In most cases, data of an appropriate quality to yield these statistics was simply not available, and some CHWs were even unclear on the standard immunisation schedule. These and other difficulties reported below led SIAMC to question the validity of routine EPI data, and the results of the 1998 national survey (Appendix 4) (for which the general locations and methods were known and preparations at field sites in Thanh Hoa commenced weeks in advance).

Interviewing was also at times difficult, with interviewees often employing strategies of long-winded circumlocution or avoiding the question by simply leaving the room, or simply acknowledging their ignorance. Usually no explanation was offered for inconsistencies between questionnaire responses and data entered in the EPI register or monthly reports.

There were also frequent inconsistencies between the responses of the CHS-heads and the EPIWs interviewed separately, again suggesting that information supplied to higher authorities, either in the monthly reports or in other surveys, is not necessarily accurate. Areas in which there is most doubt about the veracity of data are highlighted below.

Demography and mortality statistics

Data was sought from each CHS regarding certain statistics relevant to the EPI: total population served; number of villages, households and ethnic groups present; infants (aged <1 year), children aged <5 years, CBAW - reclassified in Vietnam as those aged 15 - 35 years but still subject to variable interpretation of 15 - 45 or 15 - 49), births in 1997 and place of delivery, perinatal mortality (born after 24 weeks gestation but died aged 28 days or less), infant mortality (death between 29 days and 12 months) and under 5 mortality. Eleven communes responded. As already mentioned, where there were obvious errors in data consistency, such as the numbers of births in 1997 compared to the number of under fives in a commune, this was pointed out to the head of the CHS who was then given an opportunity to revise the data by post. The data are presented below.

Table 1: Demographic data from 11 commune health stations (CHSs) responding to a questionnaire on the Expanded Program on Immunisation (EPI), early 1998

Name of Commune	Quang Xuong district						Ngoc Lac district				
	Quang Tho	Q. Vinh	Q. Phong	Q. Ninh	Q. Trung	Q. Dong	My Tan	Ngoc Son	Nguy-et An	Thuy Son	Cao Ngoc
Population	6889	8232	6565	5889	5489	4457	4987	3827	8230	7305	4243
# Villages	14	15	13	8	4	12	11	10	19	15	16
# Households	1457	1636	1450	1229	1195	1044	868	751	1500	1354	790
# Active VHWs	9	12	11	5	5	11	7	0	14	13	3
# Inactive VHWs	15	2	0	4	8	0	4	11	5	NA	10
# Ethnic groups	1	1	1	1	1	1	3	2	2	2	2
# Infants < 1y	81	92	85	90	108	64	84	161	180	129	76
# Children < 5y	681	856	550	486	635	463	426	562	1065	880	824
# CBAW	1015 ^a	1840 ^a	1127	789	1289 ^a	1088 ^b	842	526	1147	962	NA
Women giving birth in 1997	103	110	87	91	105	62	86	63	180	129	134
Livebirths - 1997	103	106	87	90	105	62	84	63	180	129	128
Births at CHS	71	46	21	52	36	45	0	14	15	33	14
Births at other health facility	2	2	54	34	0	6	2	2	8	9	0
Births at home (% livebirths)	29 (28)	58 (55)	12 (14)	4 (4)	69 (66)	10 (16)	82 (98)	47 (75)	157 (87)	87 (67)	120 (94)
Perinatal deaths in 1997	1	3	0	1	1	2	2	2	4	0	2
Infant deaths in 1997	0	0	NA	0	0	0	1	NA	0	0	4
Deaths of 1 - 5 year olds in 1997	1	0	1	0	0	1	NA	2	2	0	5

Notes: a: Aged 15 - 49 years. NA = not available VHW = Village health worker
b: Aged 15 - 45 years CBAW = Child-bearing age women # = number of Q. = Quang

Although there remain some inconsistencies, some trends appeared in the parameters measured. The average number of residents per household in Quang Xuong was 4.7, and in Ngoc Lac, 5.4. Village size tended to be larger in Quang Xuong, averaging 569 persons in comparison to 403 in Ngoc Lac. The 1997 crude birth rate in Quang Xuong was 15/1000 and 21/1000 in Ngoc Lac (or 19 if Cao Ngoc's unrealistically large number of live births for that year is ignored), compared to the 1999 national average of 19.9 and Thanh Hoa average of 20 (Vu Minh Huong, United Nations Fund for Population Activities Reproductive Health team member, personal communication). The total number of under fives is disproportionately large in comparison to the number of infants aged < 1 year in both districts, regardless of the impact of Vietnam's pervasive family planning program. Attention is drawn to the high rate of home birth in Ngoc Lac communes.

The mortality statistics give an overall infant mortality rate of ~20/1000/year (national average in 1999, 36.7) but because of the obvious inaccuracy in the numbers of children aged under 5, an under 5 mortality rate cannot be calculated on the data given. Data not presented give the causes for these deaths: drowning, burns, and "food poisoning" for deaths under 5; prematurity, cleft palate, and growth retardation for perinatal deaths; and a solitary case of pneumonia in one infant. Apart from the low numbers of deaths reported, this list is noteworthy for the virtual absence of the respiratory and diarrhoeal diseases responsible for most child mortality in the developing world.

Staffing of CHSs and the EPI

Data on staffing at the CHSs surveyed are presented in Table 2. There is reasonable consistency in the number of HWs at each, with several having doctors who have completed a 6-year medical training or 3 years of upgrading after training as an Assistant doctor. The mean number of daily health service contacts in Thanh Hoa in 1997 was 1.84 per HW, compared to the average of 2.33 for the northern Central Region and 2.93 for the whole country (Multidonor Health Sector Review Committee, 2001). Despite this, in the communes surveyed EPIWs reported often working alone or assisted only by VHWs at outreach vaccination points on EPI day.

Most EPIWs had some training in 1997, although there was an unexpected inconsistency in this, with certain CHSs not benefiting from what was presumably a training exercise organised at district level. All CHSs have at least one CHW with some training in EPI.

Table 2: Staffing of CHSs and their training in EPI

Name of commune	Quang Xuong district						Ngoc Lac district				
	Q. Tho	Q. Vinh	Q. Phong	Q. Ninh	Q. Trung	Q. Dong	My Tan	Ngoc Son	Ngu-yet An	Thuy Son	Cao Ngoc
# Doctors	1	0	0	0	0	1	1	0	0	1	0
# A-Drs*/Nurses	3	4	4	3	4	2	2	4	3	3	3
# CHWs* involved in EPI	3	3	3	1	1	2		1	1	1	2
# CHWs trained in EPI	3	5	4	2	4	3	1	2	3	4	1
# trained in 1997	1	2	2	2	4	2	0	2	3	0	0

*A-Drs = Assistant Doctors; CHWs = commune health workers

EPI strategy

In general, the EPI in Thanh Hoa is conducted in the same way as elsewhere in Vietnam, with vaccines collected by the province from a central point (in Hanoi) on one day each month, then collected by the districts from the provincial store, usually on the next day (Chapter 1). The cold chain is well maintained to this point, assuming a consistent power supply at district level (in fact not a safe assumption, particularly in mountainous districts such as Ngoc Lac). CHWs collect vaccines from the district hospital on the day before their monthly EPI activity commences.

Beyond district level, however, there was a remarkable degree of variability between the strategies employed in the conduct of the EPI. Often communes virtually adjacent to each other conducted their EPI very differently – perhaps one requiring all infants in the commune to be brought to a fixed point such as the CHS and another sending an outreach EPIW to several points around the commune over one or more days.

The 1997 EPI strategy of the 6 communes surveyed in each of the 2 districts is summarised below.

(i) Quang Xuong:

The district health service collected vaccines from the province on the same day, and all 6 communes surveyed conducted the EPI on 1 or 2 days (the 15th/16th), of each month. Two offered immunisation at the CHS only, whilst the other 4 visited a number of points (range 2 – 4) around the commune. All CHS heads reported going to each point each month, although there was inconsistency in one commune in which the EPIW reported going to only one point per month (hence reaching each point only every 4 months). The strategy for administering BCG varied. Some waited until the first EPI contact (meaning that infants received it at the age of 2 months, as mothers in Vietnam will generally not take newborns out of the house before the age of one month [Barbara Bale, medical anthropologist, Hanoi, Vietnam, personal communication]), but 3 gave it separately either the night before or on EPI day at the homes of newborns whose births had been reported to the CHS. This involved carrying an opened ampoule of BCG around the commune in a vaccine carrier, as only one 20-dose ampoule is available to each CHS per month.

(ii) Ngoc Lac:

The situation in this district was very different. At the time of the survey, the day on which the district health service collected vaccines from the province varied each month, making it impossible for CHWs to inform mothers exactly when their next visit would be. In only one commune was every village reached each month, with most taking at least 3 months to cover the whole commune. EPI activities were conducted over 2 or 3 days in all but one commune, but none mentioned access to ice other than the ice packs collected from the district along with the vaccines, so vaccines were almost certainly only cold on the first day. VVMs were not in use. In the worst commune, VHWs interviewed said that no EPI activities had been conducted there all year, and that when they had been previously, they continued for 5 days in succession (by inference, using warm vaccines). This could not be confirmed, as the head of this CHS gave a different account and the EPIW was absent (with the key to the locker containing the register!).

These two paragraphs reflect well the findings on this matter of the other survey SIAMC conducted amongst householders in the same communes (Chapter 2B). When asked if the EPI operates in their locality, 99% in Quang Xuong and 96.4% in Ngoc Lac answered in the affirmative, but the frequency of its availability in a location convenient for the interviewee varied widely between the two districts (Figure 1, Appendix 8).

It is apparent from the Figure that the EPI is accessible to the population of Quang Xuong far more frequently than in Ngoc Lac. Although the absence of cold chain facilities meant that neither district could offer vaccines on a daily basis, the infrequency of EPI contact in Ngoc Lac, its difficult geography, relatively low population density and high rate of home birth suggested that a program of neonatal vaccination against HBV would be very difficult there.

Communication between the CHSs and VHWs/mothers

The intent of this part of the survey was to identify how villagers are informed of forthcoming EPI activities; how CHWs conducting EPI by outreach know how many infants to expect at each EPI point (to enable planning of vaccine distribution amongst points); how CHWs know which vaccine each infant is due to receive; and how mothers know about their infant's EPI schedule and status. Reporting of immunisations given was also reviewed, as covered below in the section on *Recording and Reporting*.

Once again, the situation in each of the 2 districts is summarised below:

(i) Quang Xuong:

In most communes surveyed in this district there is a meeting between the CHS and village-level cadres (VHWs or family planning workers) on the day prior to EPI day (4/6 communes) or later each month (2/6 communes). At this meeting new births are reported and a list of infants needing vaccination may be given to the EPIW. VHWs mobilise mothers prior to EPI day using the village loudspeaker system or home visits. Occasionally the commune "postman" is enlisted to notify either the VHW or village

headman of upcoming EPI activities. A reliance on village cadres characterised all but one commune, in which the CHS reported sending invitations (again via the VHW) to mothers to attend EPI day. This appeared to be the only CHS in which the EPIW was involved in ensuring that all infants are immunised, but apart from BCG, follow up of infants who failed to attend was not mentioned there. However, when interviewed during the household survey, most mothers believed such follow up would occur should their infant miss a dose.

(ii) Ngoc Lac:

A major difference in this district in 1997 was the inconsistency of the EPI day each month. This precluded EPIWs giving mothers an appointment for their infant's next EPI contact, and was due to the district's inability to collect vaccines on the same date each month due to lack of transport priority at that time. (With the subsequent acquisition of a second vehicle the district is now more able to guarantee a consistent date of vaccine collection). In addition, in no commune surveyed could the CHS head or EPIW show the team a plan for which villages they would visit over forthcoming months, suggesting no plan to ensure coverage.

The haphazard nature of EPI services in Ngoc Lac would have precluded any forward planning of their infant's vaccination by mothers, particularly those planning to move to another district or province.

With regard to monthly planning, only one commune surveyed in this district mentioned a regular meeting with village cadres prior to EPI day. Most conducted such a meeting later in the month. All CHSs notified VHWs or village headmen of forthcoming EPI activity on the day prior. This short notice and the infrequency of visits must have placed many Ngoc Lac infants at high risk of missing doses of vaccine until long after they are due, as was indeed noted.

Recording and Reporting

This was the most complex and inconsistent aspect of EPI strategy uncovered by the survey. It is also the most disturbing, given that several EPIWs admitted to estimating, guessing or simply fabricating the data in their reports. There were also frequent inconsistencies between the accounts of the 2 interviewees at the same commune, and between these accounts and the EPI registers and monthly reports.

In both districts, implausible uniformity characterised the entries in the EPI registers of many communes. Data for several months was often entered in the same handwriting using the same pen, with no corrections. In one case a register supplied in November 1997 contained entries beginning in April 1997. Not one commune surveyed used the EPI register as its record on EPI day. In several communes, the registers contained many gaps in the records of individual infants, including many cases where vaccination started with the second or third dose of DTP because the infant was "too old" to receive the first dose. (In another CHS not part of this survey, the number of infants reported to have received BCG in 1997 was double the number of births for that year.)

Immunisation cards were not being used as intended in any of the communes surveyed. Some were stored at the CHS; others kept by the village headman. Most were not in use. It is likely that very few mothers in these communes possess an accurate record of immunisations received by their infant. Indeed, in the householder survey, only 32.3% of respondents had heard of these cards, and only 13.3% reported keeping them at home.

The conclusion reached by the interviewers was that at the time of surveying, there was no system for accurately assessing any infant's true immunisation status, and therefore vaccine coverage, in the areas surveyed. Interestingly, Thanh Hoa was one of the provinces surveyed in the 1998 EPI review (Appendix 4), in which cluster surveys of EPI coverage used EPI cards and infants' EPI history to calculate coverage. Chapter 7B reveals little change in the use of EPI cards in 2000, suggesting that either the 1998 survey data was collected in very different locations or was prepared in advance. District summaries follow:

(i) Quang Xuong:

As mentioned, none of the communes surveyed use, at the EPI delivery point, the EPI register kept by the CHS. All described the use of loose-leaf draft records of EPI-day activities, later transcribed into the register at the CHS. (Use of this strategy was even reported in the communes immunising only at the CHS.) But no interviewee was able to show any such draft record, and one admitted simply making up the data entered in the register. Another showed a list of names of children not found in the CHS EPI register. When this was queried, she said these were older children who were recurrently vaccinated because their mothers kept bringing them to EPI sessions with no records.

In general, EPIWs relied on the VHW to provide a list of infants needing vaccination on site. This is a list of names; it does not specify which dose is required. Only one EPIW said she provided herself with such a list of immunisations needed, presumably based on the register at the CHS. In no other commune was it clear how the EPIW knew which vaccine(s) an infant required on EPI day. Questions on this point yielded several different responses, including deciding the dose on the baby's age, the mother's or VHW's memory, or the number of EPI visits to that site in recent times. Often the reported strategy changed if the question was repeated or a point of detail was queried.

(ii) Ngoc Lac:

The scenario in this district was no better than in Quang Xuong and some worrying admissions were made. The same use of draft records of vaccines given was made in all communes, and the same lack of planning of which infants were due which vaccines was noted. One EPIW admitted to guessing which vaccine to use (DTP or measles) based on the infant's size, and later using memory to fill the register at the CHS. Another estimated the number of doses administered by examining the volume of vaccine remaining in the ampoule or vial at the end of the day. In only one commune was it claimed that some VHWs assist with the decision on which vaccine to give a particular infant, basing this decision on records kept in the village.

Administration of vaccines - equipment/sterile technique/cold chain/transport

This survey revealed substandard practices in areas crucial to the safe and effective delivery of vaccines to infants. Major concerns were:

- the almost universal admission of re-use of unsterilised needles and syringes – sometimes for up to 5 infants;
- re-use of single-use equipment;
- poor knowledge of sterilisation procedures;
- lack of adequate sterilisation equipment, and
- poor maintenance of the cold chain as mentioned above (see *EPI strategy*).

Another unexpected but worrying finding was the regular decanting of vaccine from one vial into several old, empty vials to enable parallel visiting of several EPI points at the same time. This was required because allowance for vaccine wastage was low, such that too few vials of vaccine were made available to enable CHSs to visit several outreach points each month. In particular, BCG is provided in 20-dose ampoules, which cannot be resealed, in general at the rate of only one per commune per month. This precludes use of BCG at more than one point unless it is transported in an open vial or decanted, as described above.

Regarding EPI equipment, in principle in Vietnam at the time of this survey, priority was given to districts in mountain areas, such as Ngoc Lac. These were receiving supplies of new, disposable, single-use needles and syringes (DNS) for the EPI, whilst coastal/delta areas were in general only supplied with reusable equipment, sterilised with pressure sterilisers. This strategy acknowledged the lack of electricity or funding for fuel available to CHSs for boiling water in mountain areas. However, based on CHW statements regarding re-use of DNS and inadequate sterilisation practices, the interviewers gained the impression that neither adequate supplies of DNS nor sterilisation equipment were available for the EPI at any of the CHSs surveyed.

SIAMC investigated this further in October 1998, with a separate survey of the number of DNS distributed by the provincial and district health services to each CHS, and their

records of receiving these during 1997/98 (Table 3). There was no inconsistency between the records of what was distributed and received.

Table 3: Needles and syringes delivered to Quang Xuong and Ngoc Lac during 1997/98

Date of delivery	Disposable needles and syringes (in ml)			Reusable syringes (ml)		Reusable needles (by gauge)			
	1	0,1	5	2	0,5	24	22	27	18
Ngoc Lac									
12/11/96	42400	4400	1860	0	0	0	0	0	0
1997	0	0	0	0	0	0	0	0	0
Total for 1997	42400	4400	1860	0	0	0	0	0	0
18/3/98	10800	1450	750	0	0	0	0	0	0
12/8/98	10800	1450	750	0	0	0	0	0	0
29/9/98	9500	1600	75	0	0	0	0	0	0
Total for 1998	31100	4500	1575	0	0	0	0	0	0
Quang Xuong									
12/11/96	0	0	52	32	0	1230	1148	0	205
1997	0	0	0	0	0	0	0	0	0
Total for 1997	0	0	52	32	0	1230	1148	0	205
31/3/98	1230	0	0	0	820	820	1300	0	0
12/6/98	0	211	98	0	2533	7599	0	633	295
25/9/98	1300	0	0	0	0	5700	0	0	0
Total for 1998	2530	211	98	0	3353	14119	1300	633	295

In Ngoc Lac, the district health service reported approximately 2,400 births in 1997. At the time of this survey (i.e. before introduction of HepB vaccine) each infant required one, 0.1ml DNS (for BCG) and four, 1ml DNS (for DTP and measles) to complete their EPI schedule. In addition, the administration of two doses of TT to pregnant women would have consumed another ~5,000, 1ml DNS, totalling approximately 15,000 needed for the year. Clearly, even allowing for campaigns or other supplementary immunisation activities (albeit not mentioned) there were adequate numbers of these distributed for newborns and pregnant women in Ngoc Lac in both 1997 and 1998. Therefore, at least in Ngoc Lac, the conclusion about inadequate supplies of DNS was incorrect.

By contrast, in Quang Xuong, where in 1997 there were approximately 6,500 births, the supplies of reusable needles and syringes were probably inadequate. This depends on

how many times they are re-used, of which no records are kept. Many CHSs in Quang Xuong said they buy new DNS in bulk from local suppliers and sell them to mothers (including on immunisation day) for a small profit, otherwise using a "sterilised" (disposable or reusable) needle and syringe free of charge.

Given the admitted re-use of equipment, it would be expected that sterilisation equipment would be in good condition, but in fact it was either missing or in poor condition in many CHSs. In Quang Xuong most CHSs possessed a steriliser, but all were old and knowledge of its use varied widely. In Ngoc Lac, most lacked a pressure steriliser and used a cooking pot to boil syringes and needles, despite apparently receiving adequate supplies of DNSs (Table 3). Only one CHS reported having a spare gasket or valve. Some CHSs also possessed a stove, but electricity was not available in most Ngoc Lac CHSs, and fuel for gas cookers was not provided. Accordingly, it was claimed that wood collected or bought privately by CHWs was being used as fuel for boiling in communes with no power. Forceps were rarely available for handling needles during sterilisation.

Knowledge of sterilisation procedures varied widely, but it was clear that even the heads of some CHSs were unclear on details of this. Questions on sterilisation techniques required considerable prompting to elicit responses. Errors included leaving needles and syringes together during boiling, boiling for an inadequate duration, and at two CHSs the EPIW stated that they simply flushed needles and syringes with hot water or poured hot water over them in a pot.

Regarding the cold chain, Vietnamese vaccine manufacturers, who produce ~60% of the DTP and all of the oral polio and BCG vaccines used in the EPI here, do not place VVMs on vaccine vials, citing cost as the main reason. Cold boxes were inadequate in number to manage more than one EPI point at a time in any of the CHSs surveyed. Some claimed that they borrowed extra boxes to enable them to attend two or more points in parallel rather than single points in series, but not one mentioned using locally available private refrigeration to extend the life of vaccines collected from the district hospital, despite often conducting EPI activities over more than one day. Of greater concern was the

discovery that the freezer at Quang Xuong district had been out of order for over a year, and could not produce ice blocks. The cold chain there thus relied on broken blocks of wet ice distributed with vaccines the day prior to EPI day, a known risk for freezing of vaccine which diminishes the potency of TT-containing and HepB vaccines.

No CHS surveyed possessed a safe receptacle for the disposal of used needles, nor a document outlining safe disposal techniques. Most buried them, or used them to inject chickens (perhaps with antibiotics). Others gave the old syringes to children to play with. Every CHS listed more needles and syringes and cold boxes as equipment needed for improvement of their EPI program. Others included pressure sterilisers, ice blocks, forceps and more vaccines. Interviewers were left with the impression that all these requests were very reasonable, although there was clearly a problem with how the DNS already provided in Ngoc Lac are being used.

Finally, although expected to cover infants born throughout their commune, not one CHS had been provided with any form of transport to use for outreach EPI services. A few CHWs own motorcycles, but most used their own bicycles. No monetary allowance for bicycle maintenance was reported.

The conclusion reached was that at the time of this survey and despite Vietnam's high published EPI coverage statistics which have changed little since 1998 (UNICEF, 2002), a combination of ignorance (relating to EPI practice), plus geographic, economic and technical factors were precluding the conduct of effective and safe EPI services in these two districts (and by inference, elsewhere in Thanh Hoa and the rest of Vietnam).

EPI achievements: 1997

All CHSs surveyed were given the opportunity to list the number of doses of each EPI vaccine administered in 1997, plus several other vital EPI statistics. As already mentioned, many clearly did not understand the concept of "number of doses of DTP3 given", "children fully vaccinated" and "percent of mothers of infants receiving DTP1 who had received 2 or more doses of TT", although a column for entering this

information for each infant vaccinated exists in the EPI register used by all CHSs. Similarly, some clearly did not understand that the number of doses of BCG or measles vaccine given should not usually exceed the number of births in any one year by more than a few percent – except during campaigns. The crude data provided by respondents are presented in Table 4. One problem with the survey instrument was that it requested TT data on women aged 15 - 45, but the definition of a CBAW in Vietnam is now 15 - 35 years. Nonetheless, some responses referred to women aged 15 - 49.

Table 4: 1997 EPI achievements of communes surveyed

Name of commune	Quang Xuong district						Ngoc Lac district				
	Q. Tho	Q. Vinh	Q. Phong	Q. Ninh	Q. Trung	Q. Dong	My Tan	Ngoc Son	Nguy-et An	Thuy Son	Cao Ngoc
#Infants < 1 year	81	92	85	90	108	64	84	161	180	129	76
#Doses BCG given	102	106	85	84	208	63	76	161	80	213 ⁱ	32
#Doses DTP3	281	132 ^b	116	206 ^a	506 ^a	63	72	58	178	169	41
#Doses OPV3	281 ^a	132 ^b	116	206 ^a	2050 ^b	63	82	64	180	169	43
#Doses measles	115	132 ^b	106	78	186 ^c	64	61	90	80	239	28
#Infants fully	115	132	104	78	186 ^d	64	61	58	60	211	25
#TT2+ in women delivering in 1997	109	40	73	89	107	63	46	42	160	108	14
#TT2+ in CBAW	40	75 ^f		78 ^h	NA ^e	100 ^g	327	189	282	111	111
% infants protected at birth ^j	67.3							68.25		74	

Notes: DTP = diphtheria-tetanus-pertussis vaccine; BCG = bacille Calmet-Guerin vaccine; OPV = oral polio vaccine

- Indicates total number of doses of these vaccines given in 1997, not just dose 3. (No explanation for high number in Q. Trung.)
- Includes doses of OPV given on national immunisation day.
- Said to include children from other localities.
- Said to include children not complete from 1996.
- This group not subject to routine vaccination with TT in this commune.
- This group not subject to routine vaccination with TT in this commune. Doses given on NID.
- Includes babies born in 1996. Separate 1997 figures "not available".
- Includes only "unmarried women" aged 15 – 49.
- Includes babies born in 1995 and 1996.
- TT2+ in mothers of infants receiving DTP1

Despite the inconsistent recording methods, these figures look good, especially those on measles coverage in Quang Xuong (but see Chapter 8 regarding the efficacy of this). They also concur with the high EPI attendance rates (over 94%) averred by interviewees in the household survey and with Vietnam's published EPI coverage (UNICEF, 2002).

However, the concerns remain about the already mentioned reliability of these data, not least being the uncertain denominators (number of infants born in each commune).

Project staff were concerned that it is possible for a woman to be pregnant and deliver without knowledge of local health promoters, especially in mountainous areas where the population density is much lower. Although it would be uncommon, this possibility makes it particularly difficult to conduct surveillance for a killer of neonates, such as neonatal tetanus (see section on *EPI-preventable illnesses* below). The figures also clearly fail to reach a standard of uniformity adequate to generate district coverage data.

EPI-preventable illnesses seen in 1997

In Vietnam, diphtheria is now uncommon, and polio has not been reported since 1997. Mass vaccination against polio (along with catch-up measles immunisation and vitamin A distribution) was formerly conducted regularly – and with considerable success – on NIDs, usually twice each year. Vietnam is now officially polio-free and these are now being replaced by disease-specific (e.g. measles) campaigns. CHSs were asked to report on the number of cases of EPI-preventable diseases seen in 1997, with the exception of tuberculosis. No cases of poliomyelitis, NT, tetanus or diphtheria were reported in any commune (Table 5).

In contrast to these responses, when interviewees in the household survey were asked if they were aware of any cases of NT amongst newborns or CBAW in the 2 years preceding the survey, 8.4% in Quang Xuong, and a worrying 14.8% in Ngoc Lac said they were. Some of the remainder were unsure, leaving open the possibility of higher figures. Although maternal recognition of NT may be unreliable, these reports are at odds with the absence of cases of NT reported to the national tetanus control program from any of the communes surveyed during the same two-year period.

Table 5: EPI-preventable diseases seen during 1997 in communes surveyed

Name of commune	Quang Xuong district						Ngoc Lac district				
	Quang Tho	Q. Vinh	Q. Phong	Q. Ninh	Q. Trung	Q. Dong	My Tan	Ngoc Son	Nguy-et An	Thuy Son	Cao Ngoc
Pertussis	0	0	0	0	0	0	5	0	0	0	2
Measles	5	0	0	0	0	18	14	12	0	9	7-8

Antenatal care / tetanus vaccination of women

The survey sought information on antenatal services at each CHS, and their program for vaccination of CBAW against tetanus. This was sought during the interview sessions. No formal program to target all CBAW was found. Most communes vaccinated pregnant women (PW) or CBAW opportunistically on EPI day or at antenatal clinics on the same or next day. All relied on VHWs to publicise TT vaccine and remind women of their need for immunisation. The results are summarised by district below:

(i) Quang Xuong:

The infrastructure for a good antenatal TT vaccination program was present in this district. Each CHS conducted an antenatal clinic on the 16th of each month. In general women were encouraged to attend twice during pregnancy. The stated numbers attending ranged from 4 – 30/month, with an average of 20. One issue mentioned by several CHWs was the non-attendance of women expecting their 3rd or subsequent child, because of the stigma now associated with large families in Vietnam. Hence estimates of the range of PW receiving 2 doses of TT during pregnancy ranged from 40 – 100%. One CHS reported charging 20,000 dong for antenatal care and immunisation of PW and their newborns, including a DNS for each vaccine given. No program to target all CBAW for TT was mentioned. No system of recording the numbers of doses already given to individual women was found, apart from registers kept at the CHS. In particular, lifetime TT cards, used in some other localities in Vietnam were not in use here.

(ii) Ngoc Lac:

In this district, women were again targeted for TT on EPI day. Some communes mentioned including all CBAW, others only PW. Heavy reliance on VHWs was again

noted – with them being primarily responsible for informing women of their need for vaccination. One CHW commented that TT2 was often given too late in pregnancy (usually a week before confinement) for it to be effective. Two communes reported that they hold an antenatal clinic but it is often unattended, and that PW only come for antenatal care when they perceive there is a problem with their pregnancy.

Information, Education and Communication (IEC)

The household survey (Chapter 2B) affirmed a good awareness and general understanding of the EPI, and that HWs are an important source of this knowledge. Although specific questions about CHW education activities were not asked, objective evidence regarding sources of knowledge about the EPI was available. Across both districts, an average of 81.8% of householders surveyed mentioned HWs, and 67.1% mentioned the VWU. Other sources included the mass media (particularly the loudspeaker system in Quang Xuong) and printed materials.

Publicity of EPI activities in Quang Xuong is facilitated by a loudspeaker system, which was present in all communes surveyed. In 1998, this was not present in Ngoc Lac, much of which lacked electricity at the time of this survey. Many, but not all CHSs kept a supply of posters and booklets relevant to EPI, particularly in Quang Xuong. The role of village level communicators and promoters, usually members of mass organisations such as the VWU, was clear to the survey team.

Discussion and Recommendations

Vietnam has all the elements necessary for a high-standard EPI, including a far-reaching health-system with established management and information systems (Multidonor Health Sector Review Committee, 2001); well-organised mass organisations; a remarkably high capacity to publicise activities using mass media; a high standard of central, technical capacity involved in vaccine manufacture and EPI-related research; a supportive population and an active (but previously, rather closed) EPI leadership. As a result, a solid record of achievement has been established, both in regard to coverage for the six,

standard EPI antigens (Multidonor Health Sector Review Committee, 2001), (UNICEF, 2002) and as exemplified by two recent milestones, both in late 2000: Vietnam's inclusion in a group of nations of the WHO Western Pacific Region declared polio free (WHO WPRO, 2000) and the completion of the first campaigns of second-dose measles vaccination for all aged 9 months – 10 years. However, this survey clearly suggests that at grassroots level there are problems with the program which require urgent attention if the successes of the past are to be sustained or embellished.

This survey identified major problems with the quality of EPI services at commune level in two districts of rural Vietnam, resulting in two main conclusions. First, the poor planning and recording of immunisation activities makes it highly likely that existing coverage statistics are exaggerated, at least for infants aged less than 12 months. Second, the technical aspects of the program relating to its safety and effectiveness are well below standard, such that vaccine recipients may be receiving impotent vaccines and unsterile injections. Informal discussions with project and MoH staff have suggested that the problems identified are common to many locations in Vietnam, suggesting that current improvements to the EPI (introduction of new vaccines, birth-dosing for HepB vaccine and a national second-dose campaign for measles) must be accompanied by renewed attention to the quality of its most basic programmatic elements. Fortunately, the problems identified are not at all insurmountable - some could be solved with funding alone, and others with training and new equipment. There was nothing in the survey findings to suggest a drop in standards; in fact it appeared that many HW practices were misconceived from the outset.

The most alarming findings raised the possibility that the EPI itself may in fact have been doing harm, via unsterile injection practices. This is due not only to the ignorance of HWs (itself a product of poor basic training and supervision), but also to their poor working conditions, resulting in misplaced priorities regarding the use of (or theft of) equipment and scheduling of activities. The re-use or abuse of DNS is a good example of this. During training conducted after this survey, some CHWs told the author that they had never received practical training in use of a pressure steriliser, did not know of the

risk involved in re-use of injection equipment, and relayed their perception that use of any needle and syringe only once is wasteful. Although difficult to prove, it seems likely that some of the "missing" DNSs in Ngoc Lac have been sold by HWs in their private practice. The government of Vietnam needs to improve the level of support for grassroots HWs, who work under conditions of extreme hardship and lack a living wage, regular on-site supervision, opportunities for retraining and professional development, and infrastructure support. Such increased support and supervision should reduce CHWs' sense of isolation and minimise independent practices and decision-making, improving the uniformity of key practices such as EPI planning and use of an under 5 or immunisation card.

Sponsoring of the EPI by UNICEF and WHO commenced in Vietnam in 1981. Early training was conducted at central level and a commitment to periodic retraining for provincial staff is still held. However, the limited budget available for this has meant that refresher classes for existing provincial staff are very infrequent. The splitting of districts and provinces has also meant that funding for most such training is directed at new staff (Dang Duc Trach, formerly National EPI Manager, personal communication). Thus retraining within provinces relies on local funding and use of existing staff as trainers. Staff turnover has resulted in some provinces and districts having no people with this skill, so that even senior staff may have received their only EPI training many years ago. The National EPI also holds a commitment to retraining grassroots-level EPIWs, but funding for this is the responsibility of the provinces. This survey found that some EPIWs were trained in 1997, but it seems likely that the standard was low. Priority appears not to have been given to the cold chain and the need for timeliness and sterility in vaccine delivery. Planning to ensure high coverage levels to maintain herd immunity was also clearly not covered, nor was accurate reporting of activities. It seems likely that supervisors from district level rarely actually look critically in the CHS EPI registers.

Apart from the equipment needs identified, it is evident certain technical inputs are needed to improve the EPI in these districts and probably elsewhere in Vietnam. In particular, a greater allowance for wastage and production of larger quantities of vaccine

in vials of reduced dosage-number is essential. This would facilitate a move towards daily availability of vaccine as opposed to the current monthly program, particularly in province and district hospitals and intercommunal polyclinics, where refrigeration is usually available but daily immunisation is currently not. In the longer term, supply of refrigeration at CHSs and the application of the multi-dose vial policy now advocated by WHO (WHO Department of Vaccines and Biologicals, 2000) will greatly improve timely EPI coverage in Vietnam, but close monitoring of vaccine storage and viability would be required, at a minimum including the application of VVMs to all liquid vaccine formulations.

Regular assessment and replacement of cold chain and sterilisation equipment, where necessary, is also essential, and should not be solely the responsibility of the province or the district. The National EPI provides for replacement of 10% of cold chain equipment each year. The need for a degree of flexibility in this is shown by the poor condition of the freezer in Quang Xuong at the time of this survey, and the general lack of sufficient vaccine carriers to enable parallel outreach activities in Ngoc Lac. The Luxembourg refrigeration donation (Chapter 1) may obviate some of these issues, but vial size and vaccine wastage rates will need to be overcome before daily availability of vaccines is established.

Improved monitoring and reporting is likely to highlight all these needs more clearly, if the surveyed districts are anything to go by. Periodic, well-publicised and pre-answered surveys of EPI performance do not provide the kind of qualitative information this survey has provided. For example and as mentioned above, Thanh Hoa was one of the sites surveyed by WHO in its assessment of the EPI in Vietnam in 1998 (Appendix 4) and was given a good rating on its activity. In another province, local statistics overstated full immunisation coverage by more than 40% (Appendix 4). Although politically tough and technically more difficult, less structured, qualitative surveys like this one, coupled with serological assessment of EPI coverage should be considered at least on a small scale in the near future. For example, random serological analysis of measles immunity and a

survey of BCG scarring amongst infants or toddlers, as reported in Chapter 8, might be considered.

At a time when the prospects for vaccination to control even more diseases have never been greater, Vietnam needs to ensure its EPI is well placed to include these new antigens as they become available. In its original form as a report for the leaders of the national and Thanh Hoa EPIs, this Chapter was intended to prompt a much needed restoration of focus away from national coverage statistics and implementation of campaigns, and back to the conduct of the EPI at grassroots level in Vietnam, to stimulate renewed priority and commitment at all levels.

The national managers of Vietnam's EPI need to secure funding for ongoing monitoring and retraining of both the senior and junior cadres involved in the program. This will require the establishment of a large, dedicated, experienced and mobile training team, or at least the availability of such people at regional level, who can also act as monitors of provincial programs. The introduction of HepB vaccine provides a lever which EPI leaders should use to mobilize this support, requiring as it will a considerable amount of new training at all levels of the health service, and associated community mobilisation, particularly in support of the proposed birth dose. Unfortunately, until now funding to support these is not available, but there are some promising opportunities for this.

SIAMC introduced some immediate solutions to some of the problems outlined herein. Equipment was procured through UNICEF to replenish, in line with then National EPI policy, the supplies of reusable equipment and sterilisers in Quang Xuong, and cold-boxes of appropriate sizes in all 3 districts where the project was active. A program of IEC has been undertaken from district to village level, involving HWs, People's Committee members, village leaders and the VWU, to raise the profile of timely and safe vaccination. More specifically, promoters from all project villages have been trained in the principles and scheduling of the EPI, and CHWs retrained in key technical aspects of EPI conduct (focussing on sterile injection practices, the cold chain and EPI planning), using a syllabus devised by SIAMC and based on WHO and local training materials. In

one-third of Quang Xuong and Ngoc Lac communes, SIAMC also introduced a pilot scheme (described in Chapter 6) to improve the linking of infant births to their entry into the EPI, using a reporting and feedback system commencing at village level. This was designed to enable any mother or local official to easily determine the exact immunisation status of infants at a given time. The outcomes of these inputs is reported in Chapter 7A.

Community perspectives on liver disease, hepatitis B infection and the Expanded Program on Immunisation in rural Vietnam

Introduction

The introduction of a new vaccine into the EPI of any nation is a major effort, requiring policy development, technical and material resources, publicity and training. In addition, but often not considered carefully enough, the cooperation of health staff and the communities benefiting from a new vaccine are important factors in the success or failure of its introduction (Maynard J, Steinglass R et al., 1990), (Wong WC & Tsang KK, 1994), (Ruff TA, Gertig DM et al, 1995), (Chunsuttiwat S, Biggs BA et al, 1997).

Vietnam is currently expanding its introduction of monovalent HepB vaccine beyond the predominantly urban areas to which it was formerly limited. The schedule planned now incorporates a birth dose, followed by two more doses to be administered by separate injections at two and four months. As a country of high HBV endemicity, and with the high rates of perinatal infection characterising this global region (Sung JL, 1990), broad community acceptance of three extra infant vaccinations and particularly a neonatal dose will be required for this initiative to be successful (Wittet S, 2001). This is especially the case in rural Vietnam, where, as mentioned in Chapter 1, rates of home birth are high (Multidonor Health Sector Review Committee, 2001), vaccines are not available on a daily basis and where, although still accessible, newborns are usually confined to their home for several weeks after being born (Barbara Bale, medical anthropologist, Hanoi, Vietnam, personal communication).

This chapter reports on a baseline survey of community KAP with respect to HBV, liver disease and the EPI in the two districts already described (Chapter 1), and discusses the findings with respect to the prerequisites for and likely success of the planned expansion of vaccination against HBV. The survey aimed to assess several parameters impacting on

the introduction of HepB vaccine, including the perceived prevalence of liver disease; the level and sources of knowledge regarding liver disease, HBV and the EPI; local access to, and perceptions and opinions of the EPI, and the acceptability of birth dosing. The survey also sought to identify demographic, socio-economic and surrogate knowledge variables impacting on existing knowledge levels.

Method

Survey participants, location and timing

This was a survey of the female heads of randomly selected households in same six communes of both Quang Xuong and Ngoc Lac as were assessed in the HW survey (Chapter 2A), plus a further 3 communes in Ngoc Lac (for reasons relating to the design of the project's malaria component). Interviews took approximately 45 minutes each and were conducted in a confidential environment, either in the respondent's home or a quiet location in her village, over eight days in February and March of 1998. Interviewees received a small gift as a token of gratitude for their participation.

Project design and survey sample size

SIAMC aimed to improve KAP in a range of areas relevant to the EPI, but given that funds for community mobilisation are unlikely to be available to the Program, it also modelled what impact different levels of publicity might have on the introduction of HepB vaccine across Vietnam. This involved stratifying project inputs across different communes and comparing householders' responses on this survey to those obtained on a subsequent one reported in Chapter 7B.

There were three strata (ideal, routine and control) in each project district, defined by the strategy of vaccine introduction, and with community mobilisation activities undertaken in two (Chapter 6). The third acted as a control stratum for comparison with the other two. At baseline, each stratum comprised three communes in each district.

As the aim of this baseline survey was observational, there were no pre-hoc assumptions as to differences in KAP between project strata or districts, and calculation of the survey sample size did not assume any such differences. Rather, the sample size was calculated to enable demonstration during the project of an improvement of at least 50% in knowledge on six key variables relating to the causes and transmission of liver disease, facts about HBV and maternal access to a record of infant vaccinations at village level. It was planned to later assess for these differences in each stratum by comparing all the data gathered at baseline with that gathered in each of the strata during the follow up survey (Table 6, Chapter 7B). It was also planned to assess for these differences across the two surveys within the two project districts at follow up (Table 6A, Chapter 7B).

Accordingly, the sample sizes chosen at baseline and follow up needed to be adequate for these comparisons to be made. It was assumed that the proportions of correct responses at baseline would be low, generally around 25%. The sample size required to demonstrate a 50% increase in correct responses, from 25% to 37.5% within a district or stratum, with a power of 90%, was estimated at 300 (Lwanga SK & Lemeshow S, 1991). In fact, for the key variables with a low prevalence at baseline, the project aimed for a much higher rate of knowledge acquisition than 50%, but based on these criteria the sample required a total of approximately 600 households, 300 in Quang Xuong and 300 in Ngoc Lac. Of course, this sample size also enabled analysis for differences of at least 50% between the two districts at baseline. These 600 comprised households in each of two project strata in both districts. In addition, for reasons related to other areas of project focus also surveyed at this time, another 300 households in Ngoc Lac, in the control stratum, were surveyed.

Sampling method

The communes making up each stratum were selected non-randomly for their geographic spread, and also (in Ngoc Lac) for their perceived capacity to undertake birth-dosing later in the project. This was a necessary compromise for the scientific evaluation of the birth-dosing strategy (Chapter 6).

For the ideal and routine strata, the sampling scheme adopted was based on the standard EPI two-stage cluster survey methodology, in which groups of houses (villages) formed the cluster unit. In each district, the relative population of the two strata in the sampling frame weighted the number of households selected in each stratum. Sampling intervals were calculated in each district, based on the total and required number of houses, and used to select the clusters. Individual households were then selected randomly from within each of these. A similar method was used to select the 300 extra households in the three Ngoc Lac control communes. The total number of houses sampled by district and stratum is tabulated below, verifying achievement of the required sample size in each district.

Distribution of interviewees in ideal, routine and control communes, by district

Stratum	Quang Xuong	Ngoc Lac	Total (%)
Ideal	193	183	376 (40.4)
Routine	115	125	240 (25.8)
Control	0	315	315 (33.8)
Total	308 (33%)	623 (67%)	931 (100)

It was expected that this selection process, and the diversity of the locations surveyed, would enable this and the planned follow-up survey to forecast in other districts across Vietnam the impact (measured as *changes* in prevalence of the key variables) of similar inputs to those made by the project.

Survey team and instrument

Thirty, experienced, local interviewers and six supervisors were recruited from within Thanh Hoa city and the two districts surveyed. Over three days prior to the survey, all were trained on the survey topics and their interviewing skills upgraded. Their input was also used to refine the questionnaire, which was slightly revised after a fourth day spent field-testing the survey instrument and their skills. Within and between interviewer repeatability was not assessed during the survey, nor, due to financial and logistic constraints, was the data validated during any repeat survey at this time. However, the

results compared favourably with a similar survey in the third project district, and, in terms of data quality, with the malaria survey also conducted in Ngoc Lac.

The questionnaire was partly based on surveys conducted elsewhere in Vietnam and Thailand, but primarily on the project's goals and on background information already available. The final set of questions is attached as Appendix 7.

Data compilation and analysis

Data were entered using Epi Info version 6.03 (CDC, Atlanta) and subsequently analysed using STATA Release 6 (STATA Corporation, College Station, Texas), and EpiCalc 2000 (Version 1.02) (available at www.myatt.demon.co.uk/epicalc.htm). Check programs were used to facilitate data entry and reduce errors.

Chi-square testing was used to assess for differences in the frequency of certain variables across the two districts.

Knowledge on liver disease was assessed by adding the number of correct responses to five, equally weighted questions, resulting in a score of up to five for each mother. F testing was used to assess for crude differences between the districts in levels of such knowledge.

To assess the influence of certain demographic, socio-economic and surrogate knowledge variables on mothers' knowledge on liver disease, multivariate analysis was undertaken in STATA. Although intuitively a relationship might be considered to exist between, for example, higher education and knowledge that HBV can cause liver disease, for the purposes of this exploratory analysis, these variables were assumed to be independent from each other, and no interaction was tested for. Level of knowledge was classified as good or poor according to the number of correct responses, and a causal pathway relating to knowledge was assumed, with direct relationships between it and three levels of education (primary, secondary and high-school/university), access to three kinds of mass media and access to an active VHW; and indirect relationships between knowledge and

membership of the two major mass organisations, the holding of an EPI card, and having heard of HBV as a cause of liver disease, a total of 11 variables. After backward selection with a P-value of 0.25 (Rothman K & Greenland S, 1998) to select which values to include in the regression models, multiple logistic regression (MLR) was undertaken. For one of the models reported, reducing the P-value in the backward selection to 0.20 resulted in the dropping of one more variable, but a decision was made to use the more inclusive model in this case, given its inclusion of a variable intuitively perceived to be important. For the other models reported (with stricter definitions of "good" knowledge), there was no difference in which of the variables should be included in the final model after the two backward selection processes. Adequate goodness of fit of the models reported was confirmed in each case.

In addition to MLR, linear regression, in which the number of "knowledge" questions answered correctly (out of five) is treated as a continuous variable, was also undertaken, again after backward selection of the variables to include. P-values of 0.20 and 0.25 were again used in the backward selection, with no difference in which of the variables were included in the final model.

In choosing which variables to include in the final models with backward selection, the effect of the cluster design of the survey could not be allowed for. Accordingly the final models reported do not allow for any such effect. In addition, although sampling was based on grouping of communes by project strategy, there was no allowance for pre-existing differences across strata or districts. In other analyses of project data, design effects were calculated to be small (Chapter 3).

All P-values reported in this thesis are two-tailed. Confidence intervals (c.i.'s) in this chapter and throughout this thesis were calculated using EpiCalc and in Stata. All c.i.'s were calculated using the actual number of respondents for which data was available for the variable of interest.

Results (See Figures for this Chapter in Appendix 8)

1. Respondent characteristics

Demographic information

The age distribution of all interviewees is depicted in Table 1. In Quang Xuong, 100% were of Kinh ethnicity, the majority group in Vietnam. In Ngoc Lac, 85% were Muong, one of the larger ethnic minorities in this country, with small numbers of Kinh and other minorities clustered within certain communes.

Table 1: Age distribution of interviewees

Age range (years)	15-20	21-25	26-30	31-35	36-40	41-45
Percentage of interviewees	4.6	13.5	24.9	24.6	20.7	11.7

Language facility/education level

The claimed education level of interviewees in Quang Xuong was higher, with 87.8 (95% c.i.'s: 83.5-91.2)% reporting more than five years of formal education, compared to 48.9 (44.9-52.9)% in Ngoc Lac (Figure 2, Appendix 8). However, almost all those interviewed said that they can both speak and read Vietnamese (99 (96.6-99.7)% in Quang Xuong, 91.3 (88.7-93.3)% in Ngoc Lac).

Mass media access, membership of mass organisations and access to health services

Table 2 depicts marked differences between the districts in household access to mass media, particularly television (TV) and the loudspeakers often used for propaganda community announcements in Vietnam. By contrast, it shows that a similar majority of interviewees in both districts were members of the VWU, and some were members of the VFA. Also shown is the difficulty some in Ngoc Lac have in accessing a qualified government HW during the wet season.

Table 2: Access to mass media, and membership of the Vietnam Women's Union (VWU) and Vietnam Farmers Association (VFA), by district (percent)

District	Radio in house	TV in house	Loudspeaker in audible range	VWU membership	VFA membership	Walk to health-worker (HW) in wet season in <2 hrs
Quang Xuong	47.4 (41.6-53.3)	51.8 (46.0-57.6)	98.7 (96.4-99.6)	87.8 (83.5-91.2)	31.3 (26.2-36.9)	99.7 (97.9-100)*
Ngoc Lac	47.8 (43.8-51.8)	27.8 (24.3-31.5)	39.2 (35.3-43.2)	89.9 (87.2-92.1)	36.1 (32.4-40.0)	84.8 (81.7-87.5)

*95% confidence intervals in brackets

2. Liver disease and HBV

Differences between the districts

Five survey questions (numbers 3, 4, 6, 7, and 8 in Appendix 7) were designed to broadly assess interviewees' general knowledge of the impact of liver disease on their community and whether its causes are transmissible. The mean number of correct responses in Quang Xuong was 3.7 (3.5-3.8) and in Ngoc Lac 3.4 (3.3-3.5). Assuming equal importance for each question, residents of Quang Xuong knew more on this subject than those in Ngoc Lac ($F = 7.66, P < 0.01$).

Influence of certain independent variables on knowledge of liver disease

As described above, MLR was used to assess the level to which certain variables predicted interviewees' total score on five, equally weighted questions. Initially, knowledge was categorised as good (≥ 3 questions answered correctly) or poor (2 or less). Using backward selection and a cut-off P-value of 0.25 as described above, a group of eight variables were selected as possible predictors of knowledge about liver disease. Somewhat surprisingly, the backward selection process did not include access to any of the electronic mass media (TV, radio and loudspeakers) as predictors of interviewees' performance, so these variables were excluded from the regression model. Models were also tried in which "good" knowledge was categorised as ≥ 4 correct or 5 correct, with broadly similar results (Table 3). As would be expected, a smaller number of predictors

(five in each case) were included in these two models after the backward selection process.

In the model where "good" knowledge was defined as ≥ 3 correct, education seemed to predict good knowledge, as did membership of the VFA, recognition of HBV as a cause of liver disease and whether the interviewee kept a record of her children's immunisations at home, which was assumed to be a proxy for her level of interest in or access to knowledge about matters pertaining to health. Based on the odds of having a good level of knowledge, the influence of education (in comparison to having received no education) clearly increased from primary to secondary level, but a trend in the association of education with knowledge was not observed for the small numbers of mothers with education above this level. In the model where "good" was defined as ≥ 4 correct, only high school/university education was associated with better knowledge, along with VWU membership, recognition of HBV as a cause of liver disease and possession of an immunisation record. In the model where "good" was defined as 5 questions correct, curiously, primary school education was probably associated with poorer performance than having no education, perhaps by chance. VWU and VFA membership, recognition of HBV as a cause of liver disease and possession of an immunisation record were associated with better knowledge.

A similar outcome was also observed using linear regression. Again, the backward selection process resulted in the omission of variables relating to mass media access from the final model, and secondary education, VWU and VFA membership, recognition of HBV as a cause of liver disease, possession of an immunisation record, and living in a village with a trained VHW were all associated with better knowledge (Table 3).

Causes of liver disease and HBV infection

Although 51.9 (48.6-55.2)% of interviewees knew of someone having chronic illness due to or dying of liver disease, few could list any causes of this without prompting. Unhealthy food (relating to food hygiene) and alcohol were mentioned by 19.3 (17.1 - 22.3)% and 7.6 (6-9.6)% of interviewees respectively, but viruses by only 1.8 (1.1-2.9)%.

By contrast, when prompted by its name, 36.2 (30.8-41.9)% in Quang Xuong and 12.6 (10.2-15.5)% in Ngoc Lac had heard of liver disease caused by HBV, a highly significant difference ($\chi^2 = 70.8$; $P < 10^{-7}$), but still a low proportion of 20.4 (18.1-23.4)% overall.

Encouragingly, amongst those who knew when prompted that HBV is a cause of liver disease ($n = 190$), 60 (52.6-67)% knew without prompting at least one mode of its transmission, mentioning blood transfusion, sexual contact, sharing needles, razors and toothbrushes. However, only 49.7 (42.4-57)% of this group (~10% of all interviewees) also knew that HBV infection can be prevented with a vaccine. The frequency of this knowledge was again significantly higher in Quang Xuong ($\chi^2 = 17.61$; $P < 10^{-4}$).

Table 3: The odds of certain variables being associated with a good level of knowledge of liver disease, defined by score on five equally weighted questions

Definition of "good" knowledge in model	Primary education, compared to none	Secondary education, compared to none	High school, or university compared to none	VFA membership	VWU membership	Recognition of HBV as a cause of liver disease	Having record of child's immunisation	Living in a village with a trained VHW
3 questions correct								
OR	1.73	3.09	2.06	1.61	1.45	1.91	1.10	1.08
	0.11	< 0.01	0.07	< 0.01	0.12	< 0.01	0.02	0.24
% c.i.	0.88 - 3.40	1.58 - 6.06	0.93 - 4.55	1.13-2.27	0.91-2.31	1.21 - 3.01	1.01 - 1.19	0.95 - 1.22
1 question correct								
OR	1.32	2.44	1.39	N/A	2.08	1.72	1.11	1.13
	0.42	< 0.01	0.40		< 0.01	< 0.01	< 0.01	0.07
% c.i.	0.68 - 2.56	1.26 - 4.70	0.65 - 2.96		1.35-3.21	0.40 - 0.84	1.04 - 1.20	0.99 - 1.28
2 questions correct								
OR	0.52	0.76	0.72	1.48	1.78	1.50	1.08	N/A
	0.06	0.43	0.41	0.01	0.03	0.03	0.03	
% c.i.	0.26 - 1.03	0.39 - 1.48	0.33 - 1.57	1.10-2.00	1.05-3.04	1.05 - 2.13	1.01 - 1.15	
near expression								
OR	0.59	0.01	0.22	0.01	0.01	< 0.01	< 0.01	0.03

VFA = Vietnam Farmers' Association; VWU = Vietnam Women's Union; VHW = village health worker; HBV = hepatitis B virus; OR = odds ratio; c.i. = confidence intervals; N/A = After backward selection, not included in this model

Differences in knowledge on the six key variables across the two districts

Differences in the knowledge of respondents in the two districts on some of the six key variables were identified in this survey (Table 6A, Chapter 7B). The major difference was the relative unfamiliarity with HBV and HepB vaccine in Ngoc Lac.

3. Vaccination and the EPI

General knowledge on vaccination

Two questions addressed important issues pertaining to immunisation (questions 15 and 15A). Prevention of disease was recognised as the single most important use of vaccination from a list of proffered alternatives by 670 interviewees (72 (69-74.9)%), and 865 (93.4 (91.6-94.9)%) knew that even healthy infants need vaccination. Quang Xuong interviewees (81.6 (76.7-85.7)% for the first question and 97.4 (94.7-98.8)% for the second) again performed significantly better on these questions than those in Ngoc Lac (67.3 (63.4-71)% and 91.5 (88-93.5)%) ($\chi^2 = 20.8$; $P < 10^{-5}$ and $\chi^2 = 11.4$; $P < 10^{-3}$ respectively). Respondents were clearly aware of the EPI, with 99% of those from Quang Xuong and 96.5% from Ngoc Lac affirming its operation in their locality.

Sources of knowledge on the EPI

When asked who is responsible for informing mothers about the EPI, differences between the two districts again emerged. Whilst similar numbers of interviewees in both districts mentioned particularly HWs (village- or commune-based) (average 81.8 (79.1-84.2)% and the VWU (67.1 (64-70.1)%), family planning workers were mentioned more often in Quang Xuong (42.1 (36.5-47.9)%) than Ngoc Lac (22.3 (19.1-25.8)%) ($\chi^2 = 39.03$; $P < 10^{-5}$). The converse was true for village headmen (Quang Xuong, 3.6 (1.9-6.5)%; Ngoc Lac 38.5 (34.7-42.5)%) ($\chi^2 = 126.01$; $P < 10^{-5}$).

The mass media was clearly perceived as an important method of education about the EPI, despite their apparent lack of influence on knowledge about liver disease. Over 51

(47.7-54.3)% of interviewees mentioned radio or television in both districts; many also mentioned the local loudspeaker system (Quang Xuong 95.1 (91.9-97.1)%; Ngoc Lac 34.4 (30.7-38.3)%, figures which roughly equal their availability in each) and posters (average 26.4 (23.6-29.4)%). A few interviewees also mentioned newspapers (average 8.4 (6.7-10.4)%).

Many respondents had no access to children's EPI records, particularly in Ngoc Lac where only 16.7 (13.9-19.9)% were familiar with EPI cards, which are intended by the Vietnam MoH to provide families with a record of their children's vaccination status. In Quang Xuong 63.8 (58.1-69.2)% were familiar with these cards, but in both districts, less than half of those who knew of the card actually kept it themselves, others being kept by a VHW or the village headman. In Quang Xuong, 11 (7.8 - 15.2)% and in Ngoc Lac 17.8 (14.9-21.1)% reported the card lost.

EPI delivery in the two districts

The EPI activity schedule appeared to differ markedly between the two districts (Figure 1, Appendix 8). EPI contact for infants was clearly more frequent and regular in Quang Xuong at the time of this survey.

Mothers' delivery practices

Given the planned introduction of a birth dose of HepB vaccine, the survey examined infant delivery practices. These differed greatly between the two districts, with most interviewees in Quang Xuong reporting that the majority of women deliver in a health facility or with the assistance of a HW, but many in Ngoc Lac delivering at home with only local assistance (Table 4) (see also Table 1, Chapter 2A).

Table 4: Mother's reported delivery practices in the two districts surveyed

Usual place of confinement	Quang Xuong (%)	Ngoc Lac (%)
At home without help	0.7 (0-1.6)*	6.3 (4.4-8.2)
At home with help	6.9 (4-9.8)	55.7 (51.8-59.6)
At home with HW	9.2 (5.9-12.5)	30.5 (26.9-34.7)
At the commune health station	83.2 (79-87.4)	7.5 (5.5-9.6)

*95% confidence intervals

Attitudes to vaccination, including of newborns

The vast majority (94.2 (92.4-95.6)%) of interviewees reported that they take their babies for vaccination on EPI day. The most common reasons for not doing so were similar to those given for missed opportunities for immunisation in developed countries (infant too sick on the scheduled day, mother too busy, mother forgot).

Most (93.2 (89.6-95.7)% in Quang Xuong and 92.4 (90-94.3)% in Ngoc Lac) also considered that mothers would agree to their infants receiving a new vaccine on the first or second day after birth, as is desirable for the administration of a birth dose of HepB vaccine. Amongst the small number who said mothers might disagree, most gave the small size of the baby as the most likely reason.

Discussion

Many factors influence the success of an important, new public health program, such as the introduction of a new antigen to the EPI. These include the need for the program, as perceived by the target population, the degree to which it inconveniences or may harm the intended beneficiaries, the support of those implementing it and the ease with which it can be promoted. Although some might criticise the use of a questionnaire rather than more qualitative methodologies for assessing community KAP (Heggenhougen HK & Clements CJ, 1990), this survey has provided useful information on most of these factors in relation to the expansion of infant HBV vaccination in Vietnam beyond the predominantly urban areas it was reaching at the time of the survey. The findings suggest

that although the level of knowledge about HBV was low, there is an encouraging level of access to mass media and other sources of information, and a high regard for and understanding of the EPI. There seemed also to be likely agreement to vaccination of newborns when this is introduced.

As already reviewed, it has been estimated that in countries of high HBV endemicity in Asia, 20 - 50% of those HBV infections resulting in chronic virus carriage occur perinatally, from infected mother to immunologically immature infant, at or soon after the time of delivery (Okada K, Yamada T et al., 1975), (Stevens CE, Beasley RP et al, 1975), (Beasley RP, Hwang LY et al, 1981b), (Lee SD, Lo KJ et al, 1986), (Pramoolsinsap C, Pukrittayakamee S et al., 1986), (Chan SH, Tan KL et al., 1985), (Wong VC, Lee AK et al., 1980), (Xu ZY, Liu CB et al, 1985), (Maynard JE, Kane MA et al, 1989). Up to 95% of these infections may be preventable with active neonatal immunisation alone (Maynard JE, Kane MA et al, 1989), (Andre FE & Zuckerman AJ, 1994), (Poovorawan Y, Sanpavat S et al, 1992), (Liu Y, Liu X-Z et al, 1996), (Wilson JN & Nokes DJ, 1999) but much less if the first dose of vaccine is deferred beyond the first few days of life (Ruff TA, Gertig DM et al, 1995), (Lee SD, Lo KJ et al, 1986), (Andre FE & Zuckerman AJ, 1994), (Goudeau A, Lo KJ et al., 1983), as discussed further in Chapter 6. The success of Taiwan's HepB vaccination program (Chen HL, Chang MH et al., 1996), (Lee CL & Ko YC, 1997), (Chang MH, Chen CJ et al., 1997), (Hsu HM, Lu CF et al., 1999), (Huang K & Lin S, 2000) argues strongly in favour of neonatal vaccination, without which an intermediate prevalence of chronic HBV infection (carriage rates of 2 - 7%) and its sequelae are likely to persist amongst Vietnam's and similar nations' infants and children for several decades.

To overcome the problem of perinatal HBV infection, Vietnam is introducing a strategy that will clearly rely on a high level of community involvement and acceptance. In most of Vietnam, the EPI is conducted once each month as a fixed or outreach activity by staff working at commune or village level. As reliable refrigeration generally stops at district level, daily access to heat-sensitive vaccines at commune level is not feasible. In addition, as vaccines are not usually stored at provincial or district hospitals or commune-based

maternity units, daily immunisation of newborns (or older infants attending for any reason, and due for a vaccine) is not possible. Vietnam plans to overcome these obstacles to protecting newborns against HBV by storing single-dose vials or Uniject devices at all hospitals, maternity units and CHSs, outside the cold chain for up to one month where required, relying on the vaccine's known heat stability (Just M & Berger R, 1988), (Anonymous, 1991), (Van Damme P, Cramm M et al., 1992), (Otto BF, Suarnawa IM et al., 1999), and the presence of VVMs on the vials. Infants born in health facilities will be vaccinated before the mother is discharged. For home-births, village-based cadres will be responsible for notifying a qualified HW who will attend and vaccinate the newborn at home. A similar strategy was trialed and is being introduced in Indonesia (Sutanto A, Suarnawa IM et al, 1999), and is discussed further in Chapter 6.

Although many respondents were familiar with some aspects of liver disease, the baseline level of knowledge on its causes and how it can be prevented was low. In addition, only around one person in three in Quang Xuong, and one in eight in Ngoc Lac had heard of HBV. A good level of public understanding of HBV-induced disease would seem to be an important precursor to the successful introduction of infant HepB vaccination, as unlike other EPI antigens, the latency for HBV disease resulting from infection acquired in infancy is measured in decades. In addition, HepB vaccine prevents chronic hepatitis and liver cancer in older adults, but not most cases of acute hepatitis in the young. As it does not protect against the more common causes of acute hepatitis in countries like Vietnam (such as the hepatitis A virus), it is important that public expectations are not falsely elevated by the vaccine.

Accordingly, the introduction of monovalent HepB vaccine, involving as it does three more injections for infants including a dose for newborns, requires a comprehensive promotion strategy. Appropriate messages, and means of communication, targeting particular groups must accompany the program (Wittet S, 2001), (Expanded Program for Immunization RoA, 2000). This is especially the case in inland or more remote areas of Vietnam such as Ngoc Lac where, as this survey indicates, education and knowledge levels are lower, access to HWs more difficult (both geographically and through less

frequent contacts with programs such as the EPI) and some means of mass communication less accessible.

This survey provides information regarding potential means of communication of new messages on liver disease and HBV in rural Vietnam. First, it verified (as much as is possible with a questionnaire) Vietnam's very high published literacy rates (males 95%; females 88%) (UNICEF, 2002), suggesting that even in rural areas with high numbers of people in ethnic minority groups, most should easily understand simple, printed materials such as posters, banners, billboards and pamphlets promoting HepB vaccination, if they read them. Second, most respondents affirmed membership of the VWU or the VFA, and membership of the latter at least was associated with improved knowledge of liver disease. Mass organisations could easily be used to support a community education program relating to HBV. Third, and not surprisingly, education also predicted better knowledge. The "life skills" curriculum taught in Vietnamese primary schools could be a useful vehicle for promoting control of HBV transmission amongst children and their parents. Finally, the association of knowledge with proximity to an active village HW, and the role of village head men as EPI promoters in Ngoc Lac, suggests the importance of educating professional as well as lay communicators about HBV and its control.

This survey also yielded information about use of the mass media for education about HBV. For whatever reason no effect of proximity (defined as living in a village with a loudspeaker system, but discounting the possibility of poor acoustic fidelity of the system in some villages) to a loudspeaker was noted with respect to knowledge on liver disease. Similarly, neither radio nor TV ownership predicted such knowledge, but like loudspeakers, they were mentioned as sources of information about the EPI. The most likely reasons for this discrepancy are a lack of relevant materials for broadcasting, or strategies for doing so relevant to the target populations, which factors the National EPI will be easily able to alter. Informative and attractive TV advertisements promoting recent measles vaccination campaigns, immunisation against JE infection and the EPI have been shown regularly on Vietnam TV. Although it did differ between the districts, TV ownership was surprisingly high given Vietnam's low gross national product per

capita (\$370) (UNICEF, 2002), and is increasing (General Statistics Office, 2000) (Chapter 7). The lower level of TV ownership in Ngoc Lac probably typifies most (poorer) mountain areas of Vietnam, where signal quality may also be weak and electric power is inconsistent. However, in the increasing number of areas where these are not problems, TV would seem to be a good vehicle for disseminating new information.

Thus as well as promotion through printed materials, mass organisations, schools, and HWs, the National EPI should produce video materials promoting HepB vaccine. This multi-faceted approach would concur with UNICEF's recommendations on health promotion / community mobilisation in Vietnam (UNICEF, 2001b). Such promotion may benefit not only the introduction program, but also the rate of transmission between older children and adults who will not be offered free vaccination against HBV as part of the EPI. It may also be used to promote means of reduction of rates of transmission of other blood-borne infections, including the hepatitis C and human immunodeficiency viruses.

This survey identified low (Quang Xuong) to almost uniform (Ngoc Lac) rates of home birth, suggesting that in Vietnam, neonatal vaccination will require much-improved communication of infant delivery and HW access to newborns. Although this will be logistically difficult, it was very encouraging that despite the low proportion of mothers keeping an EPI card for their children, most had a high regard for and understanding of the principles of the EPI and neonatal vaccination seemed very likely to be acceptable. Whether it proves true in practice remains to be seen, but this acceptance also augurs well for a low degree of wastage of this relatively expensive vaccine, assuming its delivery is also supported by the HWs implementing it.

However, given the increased workload anticipated in delivering vaccine to babies born at home, this very support may in fact be the most dangerous to assume and was not assessed by this survey. Several studies (reviewed in (Gilson L, Walt G et al., 1989) have warned that poorly prepared public health initiatives involving a high degree of commitment from community HWs may fail at the outset or be unsustainable. This is particularly relevant to those areas of Vietnam in which population density is low and

access to newborns is anticipated to be poor, and in which it is estimated that at least 30% of the nation's population live. Indeed, almost 30% of live births in the period 1994-96 were attended by neither a doctor nor a nurse or midwife (Multidonor Health Sector Review Committee, 2001). In the absence of financial or other incentives (Chapter 6), it is difficult to believe that HWs will deliver birth doses of vaccine to individual infants born far from their workplace simply upon request. A high level of demand creation through social mobilisation strategies, and a high level of HW motivation, possibly through a system of community-derived reward and feedback (Robinson SA & Larsen DE, 1990) will be required. Good quality anthropological research on this is required in Vietnam (Heggenhougen HK & Clements CJ, 1990).

Chapter 3: Hepatitis B infection in rural Vietnam and the implications for a national program of infant immunisation

Introduction

Despite the availability of effective vaccines for almost two decades, infection with the HBV remains a major problem in many nations outside Australia, northern Europe and North America. However, renewed priority and lower prices have now enabled well over 130 nations to include the HepB vaccine in their immunisation programs (Hemanthi Dassayanake, Technical Officer, WHO, Geneva, personal communication), and prospects for further introduction are excellent (Wittet S, 2000).

In south and east Asia, a large proportion of HBV transmission is perinatal, from mother to infant during or soon after birth (Okada K, Yamada T et al, 1975), (Stevens CE, Beasley RP et al, 1975), (Wong VC, Lee AK et al, 1980), (Beasley RP, Hwang LY et al, 1981b), (Chan SH, Tan KL et al, 1985), (Xu ZY, Liu CB et al, 1985), (Pramoolsinsap C, Pukrittayakamee S et al, 1986), (Lee SD, Lo KJ et al, 1986), (Yao JL, 1996). Whilst some countries use a combined passive/active immunisation strategy to prevent perinatal infection, this confers only a marginal increase in PE over the use of an adequate dose of HepB vaccine alone within a few days of birth, which has a PE of 70 - 95% (Wong VC, Lee AK et al, 1980), (Maynard JE, Kane MA et al, 1989), (Andre FE & Zuckerman AJ, 1994), (Poovorawan Y, Sanpavat S et al, 1992), (Liu Y, Liu X-Z et al, 1996), (Wilson JN & Nokes DJ, 1999). In Taiwan, administration of HepB vaccine (with or without HBIG, depending on maternal infection status) to all newborns since 1986 has dramatically reduced rates of chronic infection, fulminant hepatitis amongst infants and the incidence of primary hepatocellular carcinoma amongst recipients (Hsu HY, Chang MH et al., 1986), (Chen HL, Chang MH et al, 1996), (Chang MH, Chen CJ et al, 1997), (Lee CL & Ko YC, 1997), (Hsu HM, Lu CF et al, 1999), (Huang K & Lin S, 2000), (Kao JH, Hsu HM et al., 2001). Taiwan's program demonstrates how careful documentation of baseline (Hsu HY, Chang MH et al, 1986) and follow-up (Huang K & Lin S, 2000), (Hsu HM, Lu

CF et al, 1999), (Chen HL, Chang MH et al, 1996), (Hsu HM, Chen DS et al., 1988) data can verify the efficacy and impact of HepB vaccine.

Vietnam is currently expanding its program of infant vaccination against HBV. Findings published in the Vietnamese medical literature suggest that HepB vaccine will impact similarly on local rates of primary hepatocellular carcinoma and chronic liver disease, but good quality, population-based data on HBV transmission patterns and carriage rates in Vietnam are currently unavailable. Indeed the prevalence of HBV infection amongst almost 100 million people living in the southern Mekong region, whilst assumed to be high, has not been well documented.

To assist decisions on the strategy for and future evaluation of Vietnam's nascent program of vaccination against HBV, SIAMC conducted a population-based, age-stratified serology survey of HBV markers amongst rural Vietnamese. The findings are reported and interpreted in this chapter.

Method

Survey location, timing and sample

The survey took place over seven days in August 1998 in villages in 18 communes in the two project districts (Chapter 1). Fifteen of the communes were the same as those surveyed in the KAP survey (Chapter 2B). Participants from four age-groups (infant, child, adolescent (teenage) and adult) were randomly selected using a multi-stage, stratified, random-sampling method, and bled by venesection. Age of the infant, child and teenage participants relied on mothers' and community records. In Vietnam, population control and family planning have been a priority for over a decade, and the health information system includes a birth register at commune level which, albeit probably incomplete given the discrepancies between the various population denominators used by various agencies in country, is perceived to be quite accurate for those individuals registered. In addition, as all members of the population are required to possess an

identity card which records a date of birth acknowledged by the local authority, the majority of younger Vietnamese' birthdates are known quite reliably.

On specific questioning, none of those surveyed had received HepB vaccine before sampling. Informed consent for participation was given by those selected after a community wide publicity campaign and the survey was given ethical approval by NIHE, and approval by leaders of the participating communities and by the Vietnam Ministry of Health. All of those tested were given a small gift in return for their participation.

Sampling strategy and sample size

As described earlier (Chapter 2B), the 18 communes sampled (nine in each district) were selected non-randomly for their geographic spread, and were divided into three strata (three groups of three communes) for follow-up analyses based on future HepB vaccine introduction strategy. From each of these strata (groups of six communes, three in each district), 30 clusters of households (villages, average population range 250 – 1,500) were chosen using a method in which the probability (of selection) was proportional to size (or number of households per village). Because the total population of each stratum was higher in Quang Xuong, more clusters were selected in this district than in Ngoc Lac. In total, 86 villages were selected (some larger ones included two clusters), 46 in Quang Xuong and 40 in Ngoc Lac, and lists of all eligible persons from each of the four age groups were requested from the village chief in each. From these lists, persons of appropriate age were chosen randomly, using a simple random sampling method. The different survey locations also enabled consideration of influences on the infection rates identified, such as knowledge about risks for HBV infection, ethnicity, education level, access to immunisation, penetration of mass media, and other demographic indicators. These variables were described in the KAP survey described in Chapter 2B.

The size of the sample and the distribution by age group was limited by cost, but was chosen to enable meaningful comparison of infection rates amongst infants before and after the introduction of HepB vaccine (soon after this survey), and a reasonably accurate estimate of the rate of HBV infection amongst adults. Although the final precision of the

data is expressed by the confidence intervals in the tables and figures in this Chapter, based on existing data from within Vietnam and the region, the assumed pre-hoc seroprevalence rates were 5% in infants, and 12% in children, adolescents and adults. It was intended to maintain a precision around these estimates of around 2.5% for infants and 4% for adults, allowing for a design effect of two in calculating the sample size and confidence of 95%. It was not possible, with the funds available, to reach this level of precision for the child and adolescent groups. These criteria suggested a sample of approximately 500 in the infant and 600 in the adult groups (Lwanga SK & Lemeshow S, 1991). The final sample comprised 536 infants aged 9 – 17 (mean 13.8) months; 228 children aged 4 – 5 (mean 5.1) years; 219 adolescents (or teenagers) aged 14 – 15 (mean 15.0) years and 596 adults aged 25 – 39 (mean 32.9) years, totalling 1,579 persons.

Serology testing

On the evening of collection, blood samples were centrifuged, separated using a single micropipette tip for each sample and the serum frozen for subsequent transport to and analysis at NIHE, which participates in the WHO quality assurance program. Haemolysis was observed for occasional samples, as might be expected given the difficulty often encountered in venesecting infants. All sera were assessed by enzyme linked immunosorbent assay (ELISA, Sanofi Diagnostics Pasteur, France) for HBsAg and total antibody to HBV core antigen (anti-HBc). HBsAg + samples were also tested for HBeAg, and HBsAg-negative samples for antibody to HBsAg (anti-HBs). Repeated thawing and freezing of specimens was avoided. Quality assurance (QA) testing (for HBsAg and anti-HBs only) of all HBsAg + and a random selection of 10% of the HBsAg-negative samples was undertaken at the Victorian Infectious Diseases Reference Laboratory (VIDRL) in Melbourne, Australia, using Murex GE ELISA kits (Murex Biotech Limited, UK). Sera were transported frozen to VIDRL, which is the regional WHO collaborating centre for virus reference and research. Project staff were not present during testing at VIDRL.

All sera were coded with a unique identifier. The lists linking names with codes were destroyed upon completion of sampling. NIHE staff were not blinded as to the age-group

and location from which each sample derived, but VIDRL staff were blind to all aspects of the code and the results at NIHE at the time of QA testing.

Data analysis

Data were analysed by computer using EpiInfo, version 6.03 (EpiInfo, CDC, Atlanta), and STATA (Release 6, STATA Corporation, College Station, Texas).

Chi-square tests were used to make crude evaluations for relationships between the four independent variables measured (age, sex, district and ethnicity) and the three outcomes of interest (prevalence of *current infection* or HBsAg, prevalence of HBeAg, and serological evidence of HBV *exposure*, defined as HBsAg + or anti-HBc + or anti-HBs +, given the absence of any history of vaccination against HBV amongst any individual tested). Clustering of HBsAg and exposure at village level was examined in STATA and found to be negligible. For ease of exposition, 95% c.i.'s based on simple random sampling are reported and are known to be accurate.

As in Chapter 2B, MLR was used to examine these relationships further. The models assumed a direct relationship between the above four independent variables and the three outcomes of interest. Independence was assumed for the four variables and interaction was not tested for. Goodness of fit for the three models was calculated in STATA and found to be adequate.

In this case, backward selection was not used as the number of possible variables was small, so allowance for the design effect of the stratified nature of the sample was possible. Treating age group as the stratum and village as the primary sampling unit, design effects were calculated for each model and found to be generally close to one. However, these values were incorporated into the calculations of the 95% c.i.'s for the odds ratios (ORs) presented.

The Mantel-Haenszel test for trend was used to assess associations between HBV infection, exposure and age, and the kappa coefficient to assess for concordance between

the two laboratories. A sensitivity analysis was conducted to assess the influence of discordant results between the two laboratories on the outcomes of interest.

Results (See Figures for this Chapter in Appendix 8)

Sample characteristics

Despite careful attempts to choose a representative sample, there were significantly more males than females ($\chi^2 = 155, P < 10^{-8}$), due to the relative predominance of males amongst the adults (Table 1). This was primarily due to substitution of many of the CBAW selected from the population lists with their husbands on the days the survey was undertaken, and occurred particularly in Ngoc Lac. Although it may also represent bias in the sex distribution of the adult population in these districts, there was no demographic or qualitative evidence to suggest this.

Table 1: Distribution of individuals sampled by age, sex and district

Age group	Number	Quang Xuong			Ngoc Lac		
		Males (%)	Females	Total	Males	Females	Total
Infants	536	127 (46.2)	148 (53.8)	275	148 (56.7)	113 (43.3)	261
Children	228	69 (53.1)	61 (46.9)	130	53 (54.1)	45 (45.9)	98
Teenagers	219	48 (39.3)	74 (60.7)	122	47 (48.5)	50 (51.5)	97
Adults	596	232 (69.9)	100 (30.1)	332	250 (94.7)	14 (5.3)	264
Total	1579	476	383	859	498	222	720

Current infection with HBV

Table 2 shows the rates of infection (HBsAg +) and exposure (HBsAg + or anti-HBc + or anti-HBs +) of individuals by age and sex. Table 3 shows the same parameters by age and district. Only one sample (a female infant) tested HBsAg + / anti-HBc-negative. The differences in infection and exposure by age, sex and district, are also depicted in Figures 3, 3A, 4 and 4A (Appendix 8).

Table 2: Rates of HBsAg seropositivity^a, or HBV exposure^b, by age and sex in percent (\pm 95% confidence intervals (c.i.'s))

Age group	Males			Females			Total		
	No.	HBsAg+	Exposure	No.	HBsAg+	Exposure	No.	HBsAg+	Exposure
Infant	275	12.4 \pm 3.9	21.5 \pm 4.9	261	12.6 \pm 4.0	17.6 \pm 4.6	536	12.5 \pm 2.8	19.6 \pm 3.4
Child	122	18.0 \pm 6.8	37.7 \pm 8.6	106	18.9 \pm 7.5	34.9 \pm 9.1	228	18.4 \pm 5.0	36.4 \pm 6.2
Adolescent	95	26.3 \pm 8.9	66.3 \pm 9.5	124	16.1 \pm 6.5	46.8 \pm 8.8	219	20.6 \pm 5.3	55.3 \pm 6.6
Adult	482	19.5 \pm 3.5	79.0 \pm 3.6	114	15.8 \pm 6.7	79.8 \pm 7.4	596	18.8 \pm 3.1	79.2 \pm 3.3
Totals	974	18.0 \pm 2.4	56.4 \pm 3.1	605	15.0 \pm 2.8	38.3 \pm 3.9	1579	16.8 \pm 1.8	49.5 \pm 2.5

a. Hepatitis B surface antigen positive

No. = number

b. Exposure = serological evidence of exposure to HBV: HBsAg + or anti-HBc + or anti-HBs +

The overall prevalence of current infection (HBsAg +) in the two districts, depicted by sex and age group, is presented in Figure 3. The mean rate amongst infants was 12.5%, children 18.4%, teenagers 20.6% and adults 18.8% (Table 2). Assuming a natural state of infection of zero and ignoring acute infections at the time of the survey, these results show that approximately 2/3 of the HBV infections resulting in chronic carriage occur by 18 months, and most of the rest by age 6 years.

MLR confirmed the influence of age (in comparison to infants, OR for current infection amongst children = 1.6 (P = 0.03), teenagers = 1.8 (P < 0.01) and adults = 1.6 (P = 0.01) (Table 4). Crude comparisons of rates of current infection between children and teenagers (χ^2 [1] = 0.32, P = 0.57) and teenagers and adults (χ^2 [1] = 0.32, P = 0.57) revealed no increment beyond childhood. A further (crude) analysis found that teenage males were 1.86 times more likely to be HBsAg + than teenage females (χ^2 [1] = 3.42, P = 0.06). Although the regression suggested no overall difference between the sexes or across the districts, non-Kinh ethnicity may have been associated with current infection (OR = 1.8, P = 0.13) (Table 4). This association seems to derive from the higher rates of infection evident amongst (predominantly Muong) infants and adolescents in Ngoc Lac (Table 3).

Table 3: Rates of HBsAg seropositivity, or HBV exposure by age, sex and district in percent ($\pm 95\%$ c.i.'s)

Age group	Sex	Quang Xuong			Ngoc Lac		
		No.	HBsAg+	Exposure	No.	HBsAg+	Exposure
Infant		275	8.7 \pm 3.3	16.0 \pm 4.3	261	16.5 \pm 4.5	23.4 \pm 5.1
	Male	127	9.4 \pm 5.1	19.7 \pm 7	148	14.9 \pm 5.7	23 \pm 6.9
	Female	148	8.1 \pm 4.4	12.1 \pm 5.3	113	18.6 \pm 7.2	23.9 \pm 8
Child		130	18.5 \pm 6.7	36.9 \pm 8.3	98	18.4 \pm 7.7	35.7 \pm 9.5
	Male	69	14.5 \pm 8.3	39.1 \pm 11.8	53	22.6 \pm 11.3	35.8 \pm 13.3
	Female	61	22.9 \pm 10.5	34.4 \pm 12.2	45	13.3 \pm 9.9	35.5 \pm 14.5
Adolescent		122	16.4 \pm 6.6	52.5 \pm 8.9	97	25.8 \pm 8.7	58.8 \pm 9.8
	Male	48	18.8 \pm 11.1	60.5 \pm 14.4	47	34 \pm 13.5	72.3 \pm 13.3
	Female	74	14.9 \pm 8.1	47.3 \pm 11.6	50	18 \pm 11.6	46 \pm 14.3
Adult		332	19.6 \pm 4.3	78.3 \pm 4.4	264	17.8 \pm 4.6	80.3 \pm 4.8
	Male	232	22 \pm 5.3	78 \pm 5.4	250	17.2 \pm 4.7	81.5 \pm 6.5
	Female	100	14 \pm 6.8	79 \pm 8.1	14	28.6 \pm 23.7	82.4 \pm 17.7
Totals		859	15.5 \pm 2.4	48.4 \pm 3.3	720	18.5 \pm 2.8	50.7 \pm 3.7

Exposure to HBV

In contrast to the plateau in rates of current HBV infection across the age groups (Table 2, Figure 3), the rate of exposure to HBV (Table 2, Figure 3A) shows a monotonous increase for both sexes, as reflected in the mean rates amongst infants, 19.6%; children, 36.4%; teenagers, 55.3%; and adults 79.2%.

Assessing the influence of same four variables, MLR suggested a possible difference in any evidence of exposure to HBV between the sexes, with a slightly higher risk in males (OR = 1.27, P = 0.06). Again, on crude analysis, this effect was much more apparent in male teenagers, who were 2.2 times more likely than females in this age group to have ever been infected ($\chi^2 [1] = 8.31, P < 0.01$). The effect of age was again apparent (in

comparison to infants, OR for exposure to HBV amongst children = 2.40 ($P < 0.01$), teenagers = 5.32 ($P < 0.01$) and adults = 15.08 ($P < 10^{-3}$). In addition, crude comparisons across contiguous age-groups also revealed that for each increment in age, the rate of exposure increased (between children and teenagers: $\chi^2 [1] = 16.0$, $P < 10^{-3}$) and teenagers and adults ($\chi^2 [1] = 46.3$, $P < 10^{-3}$). No effect of district or ethnicity was evident.

Trends and associations with infection and exposure

Mantel-Haenszel tests for trend for current infection with and exposure to HBV demonstrated both to be associated with age ($\chi^2 [3] = 11.38$, $P = 0.01$; and $\chi^2 [3] = 396$, $P < 10^{-5}$ respectively). These results, and figures 3 and 3A suggest that this trend is more apparent for exposure, as would also be expected from the odds ratios and crude analyses reported above.

Differences in HBV infection and exposure in the two districts are depicted in Table 3 and in Figures 4 and 4A. On crude analysis, the rate of infection and exposure amongst Ngoc Lac infants was significantly higher than in Quang Xuong (χ^2 for infection [1] = 7.35, $P < 0.01$; χ^2 for exposure [1] = 5.12, $P = 0.02$), but this had disappeared by childhood and was not evident in the adult group. Ngoc Lac teens tended to be more often infected, but not exposed than their Quang Xuong counterparts ($\chi^2 [1]$ for infection = 2.91, $P = 0.09$; $\chi^2 [1]$ for exposure = 0.87, $P = 0.35$). Within this age group there were more infections and exposures amongst male Ngoc Lac teenagers than females ($\chi^2 [1]$ for infection = 3.26, $P = 0.07$; $\chi^2 [1]$ for exposure = 6.94, $P < 0.01$). These differences amongst teenagers were not evident in Quang Xuong ($\chi^2 [1]$ for infection = 0.32, $P = 0.57$; $\chi^2 [1]$ for exposure = 2.01, $P = 0.16$), although the trend resulting in the overall higher rate of exposure amongst male than female teenagers across both districts ($\chi^2 [1] = 8.31$, $P < 0.01$), as reported above) is evident in Table 3.

As mentioned, MLR did not elucidate other major influences on HBV infection or exposure amongst the limited number of independent variables assessed. The ORs for

district and ethnicity for both infection and exposure were low and indeed divergent in the case of infection. This may be because of the very strong association between district and ethnicity (colinearity). Only for infection was there a suggestion that non-Kinh ethnicity might be important (OR = 1.8, P = 0.13). As there were only 3 non-Kinh individuals sampled in Quang Xuong, this may reflect the higher rate of HBsAg amongst non-Kinh (19.1%) than Kinh (11.7%) in Ngoc Lac ($\chi^2 [1] = 2.01, P = 0.17$). However, in a separate regression model comparing non-Kinh to the small numbers of Kinh in Ngoc Lac district alone, the P was also 0.17.

Table 4: Effects of age, sex, ethnicity and district on HBsAg, HBV exposure and HBeAg status*.

Independent variables	HBsAg		Exposure		HBeAg ^b	
	OR (95% c.i. ^a)	P	OR (95% c.i.)	P	OR (95% c.i.)	P
Age						
Infants	1.0	--	1.0	--	1.0	--
Children	1.6 (1.1 - 2.5)	0.03	2.4 (1.7 - 3.5)	< 10 ⁻³	1.3 (0.4 - 4.0)	0.65
Teenagers	1.8 (1.2 - 2.9)	<0.01	5.3 (3.8 - 7.4)	< 10 ⁻³	0.4 (0.2 - 0.9)	0.06
Adults	1.6 (1.1 - 2.2)	0.01	15.1 (10.8 - 21.1)	< 10 ⁻³	0.1 (0.0 - 0.2)	< 10 ⁻³
Gender						
Female	1.0	--	1.0	--	1.0	--
Male	1.1 (0.8 - 1.6)	0.37	1.3 (1 - 1.7)	0.06	0.6 (0.3 - 1.1)	0.10
Ethnicity						
Kinh	1.0	--	1.0	--	1.0	--
Non - Kinh	1.8 (0.8 - 4.1)	0.13	1.0 (0.5 - 1.8)	0.94	3.6 (0.7 - 18.1)	0.13
District						
Quang Xuong	1.0	--	1.0	--	1.0	--
Ngoc Lac	0.7 (0.3 - 1.6)	0.38	1.2 (0.7 - 2.2)	0.48	0.4 (0.1 - 1.7)	0.24

*Odds ratios measured by multiple logistic regression, controlling for cluster-effect in design.
a. confidence intervals b. Hepatitis b "e" antigen

Hepatitis B "e" antigen status

Figure 5 depicts HBeAg status amongst sera testing HBsAg + in both districts, by age group and sex. As age increased beyond childhood, a decreasing proportion tested HBeAg + (infants 85.1 ± 8.5%, children 88.1 ± 9.8%, teenagers 71.1 ± 13.2%, adults 30.4 ± 8.5%). This was confirmed with the MLR analysis (Table 4). The ORs comparing each older age group's HBeAg status with the infants' decreased from 1.3 (children) to 0.40 (teenagers) and 0.09 (adults) with P values of 0.65, 0.06 and <0.01 respectively

(Table 4). Crude comparison of the rates amongst children and teenagers suggested this downward trend ($\chi^2 [1] = 3.82, P = 0.05$) and confirmed it between teenagers and adults ($\chi^2 [1] = 21.9, P = < 10^{-3}$). Males tended to have lower HBeAg rates than females, (OR = 0.6, P = 0.10), but in univariate analyses the difference between the sexes only approached significance amongst teenagers ($\chi^2 [1] = 3.38, P = 0.07$).

Discordance between the laboratories

There was insufficient serum for all samples sent to VIDRL to be tested for both HBsAg and anti-HBs. For HBsAg, there were 34/268 discordant results (Kappa coefficient = 0.73, $p < 10^{-6}$), and for anti-HBs, 14/104 (Kappa coefficient = 0.71, $p < 10^{-6}$). The discordant results are summarized in Table 5.

Table 5: Summary of discordant results on testing for HBsAg and anti-HBs at the two laboratories

		NIHE HBsAg result					NIHE anti-HBs result		
		Positive	Negative	Total			Positive	Negative	Total
<i>VIDRL* HBsAg result</i>	Positive	152	20	172	<i>VIDRL anti-HBs result</i>	Positive	36	3	39
	Negative	14	82	96		Negative	11	54	65
Total		166	102	268	Total		47	57	104

* Victorian Infectious Diseases Reference Laboratory

For the samples testing HBsAg + at NIHE, there were 14 discordant results at VIDRL (one infant, one child, one teenager and 11 adults (five of them from Ngoc Lac, all Muong; nine of them males; all HBeAg-negative)). All had tested anti-HBc + at NIHE (testing for anti-HBc was not conducted at VIDRL). Reclassification of their status as HBsAg-negative impinged little on the three younger age groups because of the low numbers for each group, but reduced the rates of HBsAg amongst adults to $17.1 \pm 3.0\%$ overall ($18 \pm 3.4\%$ in males and $13.2 \pm 6.2\%$ in females).

For the samples testing HBsAg-negative at NIHE, there were 20 discordant results at VIDRL (seven infants, two of them male; one male child; three teenagers (all females) and nine adults (all males); seven from Ngoc Lac, all except one Muong; seven anti-HBs +). Seven such discordant samples were anti-HBs + and also anti-HBc + at NIHE. In addition, six of these seven were both HBsAg + and anti-HBs + at VIDRL, suggesting incipient seroconversion to HBsAg-negative status, possibly with low levels of HBsAg. Reclassification in the younger three age groups would have had little impact on the HBsAg results, and would obviously negate the previous reclassification of HBsAg + discordant samples amongst nine other adult males mentioned in the previous paragraph.

There were two equivocal results on testing for HBsAg at VIDRL, both of them on samples testing HBsAg-negative / anti-HBc + at NIHE. One of them was anti-HBs + at both laboratories, again suggesting incipient seroconversion to HBsAg-negative; the other was anti-HBs-negative at VIDRL.

A sensitivity analysis was performed to assess the influence of the discordant HBsAg results on the findings. Ignoring equivocal results and applying the results at VIDRL as the gold standard yielded sensitivity of testing for HBsAg at NIHE of 91.6%, and a specificity of 80.4%.

Amongst the 14 samples discordant for anti-HBs, 11 were amongst those testing anti-HBs + at NIHE, and the other three tested anti-HBs-negative there. There were no equivocal results in this case. Again applying the results at VIDRL as the gold standard, the sensitivity of testing for anti-HBs at NIHE was 76.6%, and specificity 94.7%.

Other results of interest

At NIHE, the number of samples testing anti-HBs + but negative for anti-HBc in the absence of a history of HBV vaccination was only 15 (6 infants, 2 children, 1 teenager and 6 adults). There were 113 HBsAg-negative persons who tested anti-HBc + but anti-HBs-negative. Only 16 of the latter group were infants. The average age of this group of 16 was not less than that of the infant group overall.

Discussion

To my knowledge, this was the first population-based, age-stratified serological survey of HBV infection to be conducted in Vietnam. Very little data on this subject, either from this country or from neighbouring Laos and Cambodia have been published in the medical literature, and until recently there has been little tradition of seeking to publish the results of locally conducted surveys or research outside Vietnam, particularly amongst scientists in the north of the country. The results of several large surveys have been published locally, but full, translated versions of these are not available, resulting in a reliance on local HBV experts for the following information.

In 1995, an age-stratified survey of 1,801 people in one district of the southern province of An Giang found 11% to be HBsAg +, ranging without a trend across the age groups from 6.8 – 17.5% (Chau Huu Hau, Ministry of Defense Army Medical Corps, 1995, PhD thesis). Another survey of 6,911 Post Office employees reported 13.6% HBsAg + (Anonymous, abstract available), and another of 1,780 residents of Hanoi found 14.4% HBsAg + (Anonymous, abstract available). Two published surveys of healthy populations in Ho Chi Minh City and Hanoi found 9 – 14% to be HBsAg + (Tran VB, Buu M et al., 1993), (Nakata S, Song P et al., 1994). Another population-based survey in 1999, albeit in only one commune of central Binh Dinh province, found an overall presumptive carrier rate of 9.9% (11.5% in males and 8.4% in females, and 13.8% amongst males over 20 years of age) (Alexander Milne, The Hepatitis Foundation, Whakatane, New Zealand, personal communication). The data in this chapter suggest that HBV infection prevails at higher levels than in these previous surveys, but is supported by a small published survey of children in rural southern Vietnam, which reported 19.5% HBsAg + (Katelaris PH, Robertson G et al., 1995).

The findings also indicate a larger problem than suggested by reports of HBV infection amongst expatriates from this region. Amongst 14,347 Indochinese in Canada, 11.6% were HBsAg + (Chaudhary RK, Nicholls ES et al., 1981), and in the United States, 14%

of 709 (Catanzaro A & Moser RJ, 1982). In the latter study, there was no difference between Lao, Cambodian, Vietnamese and Hmong groups. Similar HBsAg rates come from Japan (14% of 904 Vietnamese) (Katsumata T, Kohno S et al., 1993), and Britain (15-16% of 632 Indochinese) (Chadwick RG, Hall AJ et al., 1982). Compared with the current findings, these slightly lower rates suggest that HBV infection may have increased since these people left, questioning injection safety in the context of the wider availability of injectable medication in this region over recent decades (Reeler AV, 2000). Alternately, they may reflect the lower transmission of HBV subsequent to the arrival of those tested in the countries in which these surveys took place, or the poor socio-economic status of those tested here, a known risk factor for HBV infection. Although socio-economic status was not specifically measured in this survey, it is considered that the participants were representative of poor, rural Vietnamese, and that the trend towards higher rates of infection amongst the ethnic minority community in the even poorer Ngoc Lac district may also reflect this increased risk.

The relative predominance of males amongst the adults in the survey sample was noted particularly in the inland district, Ngoc Lac, and occurred because on the day of the survey village chiefs sent the male partners of women selected for sampling. The implications of this sampling bias are minor. Despite the gender inequity in the adult sample, the plausible trend of infection and exposure rates, the quality of the data and the good rate of concordance between the laboratories (discussed further below) enables confidence in the results. Although maternally-derived anti-HBc may have been present in some of the youngest infants' serum (Beasley RP, Hwang LY et al, 1981b), (Chen HL, Chang MH et al, 1996), (Stevens CE, Taylor PE et al., 1987), (Pongpipat D, Suvatte V et al., 1988), (Poovorawan Y, Sanpavat S et al., 1989), (Moullia-Pelat JP, Spiegel A et al., 1994), the average age of the 16 infants with anti-HBc but lacking anti-HBs was not lower than that of the infant group overall. The inclusion of these samples in the overall analysis, and the possibility that some of the HBV infections identified were transient does not impinge on the conclusions, particularly amongst the adult group in whom acute infection is less likely because of previous exposure.

Differing patterns of outcome after, and risks for HBV exposure have been well characterised in many previous serological surveys. It is established that chronic carriage of HBV is far more likely to result from exposure to the virus in the perinatal period (90%) than in childhood (~20%) or adulthood (0 - 7%) (Beasley RP, Hwang LY et al, 1981b), (Beasley RP, Hwang LY et al, 1982), (Beasley RP, Hwang LY et al, 1983b), (McMahon BJ, Alward WL et al, 1985), (Roumeliotou-Karayannis A, Tassopoulos N et al, 1985), (Edmunds WJ, Medley GF et al, 1993), (Hyams KC, 1995). It is also well recognised that for many reasons, different ethnic or socio-economic groups within one nation may have differing risks for exposure and infection (Derso A, Boxall EH et al., 1978), (Milne A, Allwood GK et al., 1985), (Ghendon Y, 1987), (Alter MJ, Hadler SC et al., 1990), (Wan X, Currie B et al., 1993), (Gust ID, 1996), (Goh KT, 1997). However, attempts to control HBV by targeting particular groups in communities have generally been acknowledged to fail (Alter MJ, Hadler SC et al, 1990), (Jonas MM, Schiff ER et al., 1987), (Franks AL, Berg CJ et al., 1989), and a policy of universal infant immunisation has been supported by relevant authorities for 10 years (Centers for Disease Control, 1991), (American Academy of Pediatrics Committee on Infectious Diseases, 1992), (World Health Organisation, 1992).

This survey has identified some interesting differences in HBV infection and exposure across age and sex, and suggestions of differences between the two districts and possibly across ethnic groups. The differences across the age groups are not surprising, and the differences between males and females seem mainly to occur amongst adolescents. Teenage males, (particularly those in Ngoc Lac) were more often exposed and infected than their female counterparts. These differences were absent from the child group and less evident amongst the adults, and are not consistent with any established trend in the literature on HBV epidemiology. They are most likely due to a cohort effect peculiar to males of this age in this location, perhaps relating to a disease outbreak, rough play or shaving with unsterile equipment. A repeat survey would be needed to pay serious credence to these findings.

Differences in infection and exposure rates between infants and children in the two districts are also interesting. They indicate much higher exposure and infection rates amongst infants in Ngoc Lac than Quang Xuong, but no difference amongst children, suggesting that children in the latter district have higher interim rates of exposure and hence infection between 18 months and 4 years of age. For the infants, the higher rate of infection in Ngoc Lac may be explained by differences in maternal infection (for which data in Ngoc Lac are scant in this survey) or injection safety between the 2 districts (perhaps within the EPI itself – Chapter 2A). For young children, the relatively higher interim rate of exposure in Quang Xuong might be explained by the higher population density (over 4 times that of Ngoc Lac) or rates of kindergarten attendance (with concomitant risks of HBV exposure) there.

A suggestion of a higher risk of current HBV infection amongst non-Kinh ethnic groups was also identified. Although ethnicity is certainly associated with HBV infection risk, particularly where it is associated with socio-economic status (Derso A, Boxall EH et al, 1978), (Milne A, Allwood GK et al, 1985), (Ghendon Y, 1987), (Wan X, Currie B et al, 1993), (Gust ID, 1996), (Goh KT, 1997), given the relatively uniform, high regional endemicity of HBV in south east Asia and the Western Pacific, (Goh KT, 1997; Gust ID, 1996), (Sung JL, 1990), (Mahoney FJ & Kane M, 1999), if real this higher risk in non-Kinh is more likely due to environmental or socio-economic influences than inherited risk factors. With respect to other differences between the districts, the preceding household survey (Chapter 2B) identified differences in education level, knowledge about liver disease and HBV, access to a VHW, mass media and immunisation, and in the delivery practices of mothers during confinement. In all cases these differences favoured Quang Xuong, suggesting that the possibility of a higher risk of infection in Ngoc Lac is indeed likely to be a real phenomenon.

In addition to these plausible considerations, it is also possible that the incremental rates of infection and exposure identified are a product of some other age cohort effect impinging on HBV infection at a particular time. As mentioned already, the most likely of these is injection safety in the context of increasing availability and popularity of

injectable medication and new vaccines in Vietnam (but possibly also due to a shortage of supplies or poor sterilization technique for a period of time). Crowding, as the population has increased, or increasing rates of child-care in poor circumstances, even in rural areas, are other possibilities.

The sensitivity and specificity of testing at an experienced laboratory such as NIHE's merits brief discussion. In general, serological tests for HBV markers are highly sensitive and specific, but for borderline samples there may be discordance between results from different manufacturers' tests. This is considered to be the main reason for the differences observed by the serologist who did the testing at VIDRL (Alan Breschkin, Senior Scientist, VIDRL, personal communication). In the case of HBsAg, one reason for this may be that different companies' ELISA test kits use different substrates of differing sensitivity. This may have explained the seemingly higher sensitivity for HBsAg at VIDRL (which used a test of known high sensitivity), especially amongst samples with low levels of antigen present. Serology testing also depends on the skill of the laboratory staff and strict adherence to the conduct of steps such as changing of pipette tips, use of correct volumes of sera and reagents, and numbers of washes undertaken during automatic ELISA testing. There was no reason for suspecting the quality of testing at NIHE, itself housing the reference laboratories for serology testing in northern Vietnam, in this survey, although it is likely that they cut corners (such as in the use of controls for each batch of samples) to save time and money, as is common in all areas of life in Vietnam. In addition, the usual procedure in a commercial laboratory with an equivocal result is to retest with a different variety of test kit or a neutralisation assay. This could not be undertaken at either NIHE or VIDRL during this survey, for reasons of cost and limited quantities of serum.

The data presented enable a robust estimation of the contribution to long-term HBV infection made by perinatal, early childhood and subsequent infection in rural Vietnam. Although the number of adult females was small, their rate of HBeAg positivity (27.8%) approximates the figure of 28.8% amongst 2,193 HBsAg + females aged 20 - 39 years in Taiwan (Chu CM, Sheen IS et al., 1993), and similar rates identified elsewhere in this

global region (Gust ID, 1996). Assuming the absence of cohort effects as discussed above, based on this figure, a rate of 15.8% HBsAg + for adult females, as found in this sample, and mid-range rates of 80% for perinatal transmission of HBV from HBeAg + mothers to their infants (Beasley RP, Hwang LY et al, 1981b), (Okada K, Kamiyama I et al., 1976), (Beasley RP, Trepo C et al, 1977), (Stevens CE, Neurath RA et al., 1979), (Beasley RP, Hwang LY et al, 1983a), (Pongpipat D, Suvatte V et al., 1985), (Lo KJ, Tsai YT et al., 1985), and 10% from HBsAg + / HBeAg-negative mothers (Mahoney FJ & Kane M, 1999), (Smego RA, Jr. & Halsey NA, 1987) it is calculated that each Vietnamese infant has a 4.7% risk of perinatal HBV infection, with its associated high risk (90%) of chronicity. A further 7.8% acquire infection during the first 18 months of life, and 5.9% by age 6. After this, infections seem generally not to result in chronic carriage, as expected (Roumeliotou-Karayannis A, Tassopoulos N et al, 1985), (Edmunds WJ, Medley GF et al, 1993), (Hyams KC, 1995). These data suggest that around 25% of chronic HBV infection in Vietnam is acquired at birth, and concur with estimates that in highly endemic Asian nations, 20 – 50% of all chronic HBV infection results from largely preventable perinatal infection (Maynard JE, Kane MA et al, 1989), (Mahoney FJ & Kane M, 1999), (Margolis HS, Alter MJ et al, 1991), (Yao GB, 1996), (Yao JL, 1996).

These findings argue strongly for national neonatal immunisation against HBV in all countries in this region, as already implemented in Thailand (Chunsuttiwat S, Biggs BA et al, 1997), and parts of China (Xu ZY, Zhao S et al., 1998), (Zhu X, Zhang X et al., 2000), (Yao GB, 1996), (Dr Craig Shapiro, CDC, Beijing, personal communication). Vietnam is currently embarking on such a program, and new programs to introduce HepB vaccine are commencing in Laos and Cambodia, but do not include a neonatal dose at this stage. Existing data involving use of HepB vaccine alone (without HBIG) is scant, but suggests that a dose of HepB vaccine must be given within a week of birth to confer protection against perinatal exposure (Andre FE & Zuckerman AJ, 1994), (Goudeau A, Lo KJ et al, 1983), (Ruff TA, Gertig DM et al, 1995), (Department of Vaccines and Biologicals, 2001). Vietnam will introduce a birth dose where this is feasible. These results provide a yardstick against which to measure the reduction in HBV infection that

should result from this, and to compare neonatal vaccination with regimens commencing later in life.

As of late 2002, HepB vaccine is available in Vietnam free of charge for infants in many provincial capitals and now many rural areas, but usually starts at the first vaccination contact beyond 1 week of age. The new plan includes a birth dose using single-dose vials or pre-filled Uniject injection devices and takes advantage of HepB vaccine's heat stability (Van Damme P, Cramm M et al, 1992), (Just M & Berger R, 1988), (Galazka A, Milstien J et al., 1998), (Otto BF, Suarnawa IM et al, 1999). This will enable vaccination of infants born at home by allowing for storage of these doses outside the cold chain for short periods of time, as has been successfully trialled in Indonesia (Sutanto A, Suarnawa IM et al, 1999).

Estimates suggest that 15 - 25% of chronic HBV carriers will die of primary hepatocellular carcinoma or complications of HBV-induced chronic liver disease, depending on their age at the time of infection (Mahoney FJ & Kane M, 1999), (Beasley RP & Hwang LY, 1984b; Beasley RP, 1988), (Hsieh CC, Tzonou A et al., 1992), (Margolis HS, Coleman PJ et al, 1995). This survey has identified a rate of chronic infection in Thanh Hoa of around 18.5%. If this applies to all of Vietnam's 76 million people, then over 3.5 million may be at risk of premature death due to HBV infection. This agrees with estimates that in highly endemic countries with a seroprevalence of 10 - 15%, HBV is responsible for at least 3% of mortality (Maynard JE, Kane MA et al, 1989). Before dying, usually in late middle age, many will suffer chronic ill health with obvious economic ramifications. Assuming a success rate similar to that achieved by programs of immunisation against HBV in Alaska, the Pacific, Taiwan, China, Thailand, Indonesia, Saudi Arabia and The Gambia (Huang K & Lin S, 2000), (Hsu HM, Lu CF et al, 1999), (Yao GB, 1996), (Chunsuttiwat S, Biggs BA et al, 1997), (Ruff TA, Gertig DM et al, 1995), (Harpaz R, McMahon BJ et al., 2000), (Mahoney FJ, Woodruff BA et al., 1993), (Wilson N, Ruff TA et al., 2000), (Liao SS, Li RC et al., 1999), (Al-Faleh FZ, Al-Jeffri M et al., 1999), (Viviani S, Jack A et al., 1999), Vietnam can anticipate a reduction

in chronic HBV infection to between 0.5 and 3% once universal infant immunisation is established.

Indeed, the benefits of the program may accrue more rapidly than anticipated. Although much better funded, and involving the use of HBIG which is rarely available in Vietnam, the Taiwanese experience suggests that tangible benefits may be seen within 8 years of commencing national neonatal vaccination with HepB vaccine (Chang MH, Chen CJ et al, 1997), (Lee CL & Ko YC, 1997). In addition to benefiting those immunised, studies of HBV prevention programs have also identified a reduced rate of HBV infection amongst older or unimmunised children, presumably because of reduced rates of horizontal infection (Hsu HM, Chen DS et al, 1988), (Mahoney FJ, Woodruff BA et al, 1993), (Tsen YJ, Chang MH et al, 1991). This is even more likely if older children and uninfected adults can also be targeted for vaccination (Hsu HM, Chen DS et al, 1988), (Harpaz R, McMahon BJ et al, 2000). Although it will only be available free of charge for infants, a public education campaign recommending vaccination against HBV and the wider availability of HepB vaccine in Vietnam may yield a similar effect.

Chapter 4: The heat stability of hepatitis B vaccine and its use outside the cold chain in programs of immunisation

Introduction

The earliest, crude but effective formulation of HepB vaccine was developed and tested by Krugman and colleagues on mentally ill persons in controversial circumstances in the late 1960s (Muraskin W, 1995). Its production involved simply boiling the serum of a known virus carrier (Krugman S, Giles JP et al., 1971). Although the first commercial formulations of plasma-derived HepB vaccine, produced at the Merck laboratories, made use of a largely chemical purification process (Hilleman MR, 1993), an alternative process developed by Prince and colleagues used a flash-heat purification method, which was not only far cheaper but also increased the potency of the vaccine, and hence the yield of doses from a litre of the relatively precious raw material, infectious human plasma (Muraskin W, 1995). The use of heat in the purification process and the extraordinary conformational stability of the 22 nanometre HBsAg particles (Alfred Prince, New York Blood Center, HepB vaccine pioneer, personal communication), which relies on the presence of highly stable disulphide bridges between cysteine residues in the HBsAg protein (Joe Torresi, University of Melbourne, hepatitis virus expert, personal communication), suggested to researchers the possibility that vaccines containing HBsAg might in fact be heat stable, enabling their use in areas beyond the reach of the refrigeration normally required for the vaccines used in the EPI.

This chapter summarises the available research data on the immunogenicity of HepB vaccine exposed to heat, and discusses how this immunogenicity might relate to the PE of HepB vaccines given to newborn infants exposed in the perinatal period. It also presents data on the heat stability of the locally produced vaccine. Two of the project's strategies for use of this vaccine involved its storage at ambient temperature in CHSs for periods of up to one month. Although the manufacturer's data supported the heat stability of their vaccine, prior to this research it had not been used in this way.

Method

Published research on the immunogenicity of heat-treated or heat-exposed HepB vaccine was sought using the Medline database accessed online through PubMed at the following website: <http://www.ncbi.nlm.nih.gov/PubMed/>. In addition, an Embase search and a second Medline search (using the service offered by the New England Journal of Medicine at http://content.nejm.org/search_medline.dtl) were conducted. The keywords used were “hepatitis B”, “HBsAg”, “hepatitis B vaccine”, “heat stability”, “heat”, “heat tolerance”, “thermostability” and “heat exposure” in various combinations, with an entry point of 1980. For summaries of unpublished literature, I also relied on published reviews of vaccine thermostability (Galazka A, Milstien J et al, 1998) and HepB vaccines in clinical practice (Ellis RW, 1993), overviews of the introduction of immunisation against HBV (Department of Vaccines and Biologicals, 2001), and on information gained through email contact with experts in the field including Drs Steve Hadler, Craig Shapiro, James Maynard and Mark Kane (all currently or formerly at the US CDC), Dr David West at the Merck Laboratories in Virginia, USA, where the first commercial HepB vaccine was developed, and Dr Alfred Prince (New York Blood Center), who along with Dr Seung-il Shin in Korea, developed the rival Cheil vaccine using his flash-heat purification method.

Results of literature search and discussion

Plasma-derived vaccine

To my knowledge, no controlled assessment of the immunogenicity of heat-treated, plasma-derived HepB vaccine has been published, although there is apparently a wealth of unpublished data from animal studies at the laboratories where the Merck vaccine was developed (Dr David West, formerly of Merck, personal communication). However, field research conducted in Bali, Indonesia, and involving the use of such a vaccine outside the cold chain has been reported (Otto BF, Suarnawa IM et al, 1999).

This study evaluated the immunogenicity of three doses of a 5µg Korean plasma-derived HepB vaccine amongst three groups of infants. In the first group (n = 66), all doses of vaccine were stored in the cold chain in 10-dose vials, and administered using a disposable needle and syringe at birth, 9 weeks and 18 weeks according to standard procedures in Indonesia. In the second group (n = 98), the first dose of vaccine had been stored within the cold chain but in a pre-filled, single-dose injection device (Uniject). In the third group (n = 103), the Uniject formulation was again used for the birth dose, but was stored at ambient temperature for periods of up to one month, as described elsewhere (Sutanto A, Suarnawa IM et al, 1999). For groups two and three, the second and third doses were stored and administered in the same way and at the same time as for group one. For the vaccine stored outside the cold chain, the study controlled for exposure to excessive temperatures using a VVM, which changes colour upon exposure to 49°C or higher. In fact, no vaccine had to be discarded on these grounds.

The research compared the geometric mean titre (GMT) of anti-HBs amongst the three groups of infants 4 - 6 weeks after the final vaccine dose, and hypothesized that no difference would be found. An adequate follow-up blood sample was collected on 233 of the 267 infants initially enrolled, with no difference in the rate of follow up between the groups. 97% of those followed up had detectable anti-HBs (>1 mIU/ml) and 91.4% had a level defined as protective (>= 10 mIU/ml). No significant difference between the three groups was found, but there was a non-significant trend for infants in the third group (dose one stored outside the cold chain) to fail to reach a protective level of antibody in comparison to the others (88.2% v. 93.6%, P = 0.15). The GMT was calculated on 217 samples for which adequate serum remained, and again no difference between the groups was identified. As the samples were taken when infants were aged < 6months, it is important to note that amongst all three groups, rates of maternal anti-HBs (which might still be detectable six months after birth following passive transfer to infants when in utero) were all similar (range 16.3 – 18.6%). However, the comparative titres of anti-HBs between the mothers of the three groups of infants were not reported, nor were any differences in the prevalence or GMT of anti-HBs amongst infants of mothers seronegative for anti-HBs.

This study provides some information about the use of HepB vaccine in an area of moderate HBV endemicity (chronic infection prevalence 2 – 8%) (Maynard JE, Kane MA et al, 1989). Although it did not provide any information on the average, maximum or minimum temperatures to which the vaccine in group three was exposed, nor the average duration of storage outside the cold chain (which one must assume was around 15 days, based on a normal distribution between one and 31 days) it suggests that the first dose of HepB vaccine can be safely stored at ambient temperature in a tropical environment for up to one month without a course of vaccine losing its potential to induce protective levels of antibody.

In 1991, another small field study of HepB vaccine used outside the cold chain in Long-An County, China, was reported (Anonymous, 1991). Although reported as “preliminary findings” only, the research concluded that HepB vaccine stored outside the cold chain for up to three months can remain effective. This study was conducted in an area in which >80% of births occur at home, attended by village midwives or village doctors. In one group of infants, the first dose of vaccine had been stored for up to three months at ambient temperature and was administered at birth by the attending midwife. In the other, the first dose of vaccine had been stored in a refrigerator and was administered within 72 hours of delivery by the village doctor. Doses two and three were given as part of the routine EPI approximately two and four months later. The report provides no information about the type of vaccine used, the infection status of the infants’ mothers, the GMT of anti-HBs measured, the average duration of storage of the first dose outside the cold chain in the first group, and the average ambient temperature (which varies widely across China during the year). Among the study group of 590 infants aged 10 – 20 months at the time of blood sampling, 358 infants received the first dose of HepB vaccine stored outside the cold chain and 232 received it after cold storage. The prevalence of anti-HBs in the first group was 81.6% and in the second, 81.9%.

Although there are many limitations in the interpretation of this data, it has some value in extending the duration of potential storage of the first dose of HepB vaccine at ambient

temperature up to three months, which would be extremely valuable in certain remote areas of Vietnam and similar nations. The relevant negatives in this report, however, are concerning, as is the fact that although the data is presented as a preliminary report, no follow up was published.

Recombinant DNA vaccine

Two reports of the immunogenicity of heat-treated HepB vaccine produced using recombinant DNA technology have been published.

The first study (Just M & Berger R, 1988) compared the anti-HBs response of 58 healthy volunteers with an average age of 22.5 years, 27 of whom received three doses of Engerix-B vaccine (Smith-Kline Biologicals, Belgium, 20µg/dose) which had been heated at 37°C for one week, using a zero, one and six month schedule; and 31 of whom received the vaccine according to the same schedule, but kept at 4°C as advised by the manufacturer. No other details regarding the recipients were given. The adverse effect profiles were the same in each group and no severe adverse reactions were reported. Overall, rates of seroconversion and GMTs were the same in both groups, and only one subject failed to seroconvert. GMTs were comparable to other studies of this vaccine.

The second study (Van Damme P, Cramm M et al, 1992) took the same concept further, comparing the antibody responses of three groups of healthy adult recipients of HepB vaccine (aged 18 – 30 years, matched for average age and sex, but proportions in each sex not stated). Again, no other details regarding the recipients were given. In particular, as for the previous study, obesity, a known influence on response to HepB vaccine (Averhoff F, Mahoney FJ et al., 1998), was not controlled for. The first group received three doses of Engerix-B, 20µg/dose, stored at 4°C, at zero, one and six months. The second received the same vaccine heated at 45°C for one week for each dose, and the third received the same vaccine heated at 37°C for one month for each dose, according to the same schedule. There were no differences in the rates of seroconversion (above 95% for all groups after three doses), GMT or adverse effect profiles between the groups, and

no severe adverse reactions in any group. GMTs were again comparable to other studies of this vaccine.

These two studies, particularly the latter, offer important information on the potential for using HepB vaccine outside the cold chain. They are significant in that all three doses of vaccine in the “treatment” groups were heat-treated as opposed to only the first dose in the two field studies described above, and yet rates of seroconversion remained very high. There was a non-significant trend in Van Damme’s study for heat-treated vaccine recipients to seroconvert later than controls (Fisher’s exact test, $P = 0.19$), possibly suggesting a slower response to the vaccine. This may have some clinical importance in influencing the PE of vaccine amongst infants of highly infectious carrier mothers as discussed below, but the crude data did not suggest that this was present more in one of these two groups than the other, and such a trend was absent from the first study.

It is unlikely that HepB vaccine in any routine EPI would be exposed to constant temperatures of 37°C for one month as they were for one group of recipients in Van Damme’s study. However, cyclical periods of intense daytime heat followed by cooler night-time temperatures for periods of several months during summer in remote tropical areas might conceivably be required for birth-dosing at village level. Clearly further field research, similar to that conducted in Indonesia, is desirable, with more detailed information about temperatures to which vaccine is exposed, duration of exposure and also the PE of vaccine under these conditions (Chapter 6). However, it is worth noting that Indonesia has taken its field experience with unrefrigerated HepB vaccine and translated it into national policy. There, HepB vaccine in Uniject is now routinely used in several provinces, taken out of the cold chain by midwives for up to one month (if there is no VVM) or until the VVM indicates it should be discarded (for vials with a VVM). Vietnam is keen to introduce a similar strategy when further local studies are complete.

Manufacturers’ data

The final source of information about the heat stability of HepB vaccine comes from the manufacturers of the vaccines themselves. Although pharmaceutical companies are

traditionally cautious in recommending use of their products outside standard conditions, and remain reluctant to endorse wholesale use of their HepB vaccines after storage outside the cold chain given that licensing procedures stipulated cold storage (Mr Michel Zaffran and Dr Nora Dellepiane, WHO Geneva Access to Technologies group, personal communication), these sources also offer encouragement. The data are summarised in a WHO document on thermostability of vaccines (Galazka A, Milstien J et al, 1998), wherein the following is noted:

- the upper limit of HepB vaccine's shelf life if stored at 2 - 8°C has not been determined, but appears to be many years;
- the yeast-derived recombinant DNA Engerix-B vaccine's manufacturer (SmithKline Biologicals, Belgium) consider this product to be stable for 30 days at 20 - 25°C, for one week at 37°C, and for three days at 45°C, with corresponding calculated half-lives of nine months, 31 and 13 days;
- other manufacturers of HepB vaccine (four plasma derived and one recombinant) provided animal-test data for this paper which is summarised in the Table below.

Table 1: Stability of several types of hepatitis B vaccine according to immunogenicity tests on animals

Vaccine type	Parameter used to assess vaccine	Storage temperature (°C)			
		2 - 8	20 - 26	36 - 40	45
Plasma	Longest storage without significant loss of potency	24m.	12m.	3m.	ND
Plasma	Remaining % potency after specified time	100% at 24 m.	70% at 24m.	70% at 24m	ND
Plasma	Longest storage with relative potency upper confidence interval >1	44m.	ND	ND	ND
Plasma	Half-life*	>3y.	4m.	7d.	ND
Recombinant	Longest storage with relative potency upper confidence interval >1	53m.	12m.	7m.	1m.
	Half-life	ND	9m.	1m.	3d.

adapted from Galazka et al., 1998: ND = no data available / y. = years / m. = months / d. = days

* half-life: time at which 50% of original vaccine potency lost

Attention is drawn to the lack of an international standard of HepB vaccine potency in terms of human antigenicity and expressed in micrograms of HBsAg (Department of Vaccines and Biologicals, 2001), and the difficulty in translating manufacturers' laboratory-derived data into a meaningful assessment of a vaccine's performance under field conditions. Loss of 50% of a 20µg/dose vaccine's antigenicity does not mean it will have the antigenicity of another vaccine of 10µg/dose, and one might presume on economic grounds that vaccines are marketed at the minimum dose considered to guarantee acceptable immunogenicity and PE for that product, particularly as the VVM attached to HepB vaccines is the highly-stable variety which does not change colour until 30 days at 37°C. Theoretically, then, any loss of antigenicity due to heat exposure may be important to its PE, although no data to suggest this is the case has been published and presumably manufacturers allow a margin of error adequate to overcome such a possibility. Further complicating the study of HepB vaccines outside the cold chain is the recent finding that differences in the presentation of HBsAg in these vaccines and in anti-HBs assays can influence the quantitation of anti-HBs response (Heijntink RA, van Bergen P et al., 2000). However, this should not impinge upon assessments of PE, which is assessed by measures of infection (presence of HBsAg or anti-HBc), not anti-HBs.

Immunogenicity and protective efficacy

It thus seems reasonable to infer from the studies and data presented above that heat exposed HepB vaccine would be as protective for infants exposed to HBV at or soon after birth as it is immunogenic in studies of unexposed individuals. However, the immunogenicity and PE of vaccine-only regimens are not equivalent (Wong VC, Ip HM et al, 1984), (Xu ZY, Liu CB et al, 1985), (Assateerawatt A, Tanphaichitr V et al., 1991), (Milne A, Rodgers E et al., 1995) and the range of PE (Andre FE & Zuckerman AJ, 1994) in studies of HepB vaccine amongst newborns is wider than the range of immunogenicity (Mahoney FJ & Kane M, 1999). An examination of why this might be the case is germane to this discussion.

In general, the PE of a given HepB vaccine against perinatal exposure probably depends on three factors: its relative potency (in terms of its human antigenicity, which varies by

manufacturer and for which there is no international standard (Department of Vaccines and Biologicals, 2001)), the infectious dose of HBV to which the infant is exposed, usually measured in levels of HBV DNA, presence or absence of HBeAg or titre of HBsAg (Stevens CE, Beasley RP et al, 1975), (Beasley RP, Trepo C et al, 1977), (Lee SD, Lo KJ et al, 1986), (Ip HM, Lelie PN et al, 1989), (Burk RD, Hwang LY et al, 1994), and the timing of the antibody response induced. To my knowledge, even for cold-stored vaccine, there is no published literature examining in detail all three of these issues. Certain reports have addressed them individually and these are reviewed below, but a major problem is that much of the research on HepB vaccine PE has involved both active and passive immunisation, and so does not yield conclusions about vaccine-only strategies. Indeed, several studies have concluded that for best protection, infants of highly infectious mothers (positive for HBeAg) should receive HBIG as well as HepB vaccine (Beasley RP, Hwang LY et al, 1983a), (Wong VC, Ip HM et al, 1984), (Theppisai U, Thanuntaseth C et al, 1987), whilst some authorities consider the benefit of HBIG to be small in terms of population health (Maynard JE, Kane MA et al, 1989) and others have found vaccine alone to be equally or highly protective (Poovorawan Y, Sanpavat S et al., 1990), (Poovorawan Y, Sanpavat S et al, 1992), (Liu Y, Liu X-Z et al, 1996). What is certain is that for many countries, the strategy of screening pregnant women and offering HBIG as well as vaccine to infants of HBsAg + women is not practicable, so maximizing the impact of vaccine-only strategies is important.

With regard to vaccine antigenicity and dose of vaccine antigen, the PE of various types of HepB vaccine for newborns delivered by highly infectious mothers has been reviewed (Andre FE & Zuckerman AJ, 1994), (Mahoney FJ & Kane M, 1999). However, in contrast to numerous comparisons of immunogenicity across doses (Papaevangelou G, Roumeliotou-Karayannis A et al., 1985), (Pongpipat D, Suvatte V et al, 1988), (West DJ, 1989), (Theppisai U, Thanuntaseth C et al., 1990), (Professor Nguyen Thu Van, HepB vaccine producer, NIHE Vietnam, personal communication), few studies (Lee, 1989 and Liu, 1991, quoted in (Andre FE & Zuckerman AJ, 1994)) have compared the PE of a vaccine from the same source over a range of doses (Chapter 5). The reviewers point out the difficulty in comparing the identified PE of one vaccine with that of another on

statistical grounds, but equally, differences in vaccine preparation techniques impinge on the ability to make such comparisons. Nonetheless, on the basis of a relatively small number of studies, it has been concluded that lower rates of PE tend to prevail amongst infants receiving low-dose vaccines (5µg or less) without HBIG (Andre FE & Zuckerman AJ, 1994), (Mahoney FJ & Kane M, 1999), and theoretical support for the use of vaccines with a high antigenic content also exists (Banatvala J, Van Damme P et al., 2000).

With regard to the degree of virus exposure, one relevant report (Lee SD, Lo KJ et al, 1986) strongly suggests that infants of mothers with progressively higher levels of HBV DNA are at progressively higher risk of becoming infected regardless of receiving HepB vaccine or HBIG at birth, presumably because the amount of infection acquired before or at birth overwhelms the capacity of the vaccine to induce a sufficiently rapid and robust active immune response. Other reports have reached similar conclusions, some noting that even co-administration of higher doses of HBIG than used in the above study failed to protect infants exposed to high levels of HBV DNA (Ip HM, Lelie PN et al, 1989), (del Canho R, Grosheide PM et al., 1997). Given these findings, any marked diminution of vaccine antigenicity due to heat exposure may be important in terms of reducing its PE for infants delivered by highly infectious mothers. The literature to date does not address this question, which is discussed further in Chapter 6.

Regarding the timing of the birth-dose, only a small group of studies exist. Early post-exposure vaccination (less than 7 days) amongst infants of highly infectious mothers has been shown to result in higher rates (70 – 95%) of PE than late (Ruff TA, Gertig DM et al, 1995), Lee, 1989 in (Andre FE & Zuckerman AJ, 1994), (Mahoney FJ & Kane M, 1999), (Poovorawan Y, Sanpavat S et al, 1992) and the PE of vaccine-only regimens commencing after the age of one week amongst such infants has been found to be 50 - 57% (Lee, 1989 in (Andre FE & Zuckerman AJ, 1994)), (Lee SD, Lo KJ et al, 1986), (Goudeau A, Lo KJ et al, 1983), (Ruff TA, Gertig DM et al, 1995). One exception was the PE of 75% found in one group of infants of HBeAg + mothers who received vaccine alone in week two (Lo KJ, Tsai YT et al, 1985).

Finally, regarding the timing of antibody responses to HepB vaccine, a wide range has been reported in the literature. In general, protective levels of antibody (>10mIU/ml) are found in only 50 – 80% of individuals approximately one month after one dose (Theppisai U, Thanuntaseth C et al, 1987), (Papaevangelou G, Roumeliotou-Karayannis A et al, 1985), (West DJ, 1989), (Moullia-Pelat JP, Spiegel A et al, 1994) but rates below 22% (Poovorawan Y, Sanpavat S et al, 1989) and as low as 12% (Lo KJ, Tsai YT et al, 1985), and (for both heat-treated and cold-stored vaccine) 10% (Just M & Berger R, 1988) have been found. Obviously it is difficult to compare these figures with rates of PE, not only because of their range but also because the stimulation of immunity after exposure to HBV itself may differ qualitatively from that following exposure to vaccine antigen alone. They also ignore the role of memory B- and T-cell-mediated immunity (Wilson JN & Nokes DJ, 1999). In addition, protective levels of antibody are not always required for prevention of infection after exposure (Centers for Disease Control, 1987), (Hadler SC, 1988), (West DJ, Watson B et al., 1994), (European Consensus Group on Hepatitis B Immunity, 2000), or may protect against clinical infection and carriage but not against subclinical infection (Hadler SC, Francis DP et al., 1986), (Lo KJ, Lee SD et al., 1988), (Wainwright RB, McMahon BJ et al., 1989), (Chotard J, Inskip HM et al., 1992), (Ding L, Zhang M et al., 1993), (Xu ZY, Duan SC et al., 1995), (Jack A, Hall A et al., 1999) making the PE of a particular vaccine difficult to predict based on this kind of immunogenicity data. However, the relative risk of this transient infection (with or without subsequent antiHBc seroreversion) is associated with peak anti-HBs levels after immunisation, and (more closely) with trough levels measured years later (Jack A, Hall A et al, 1999). Presumably these principles apply equally after any number of doses of vaccine, so that the rate of protective levels and titre of anti-HBs after one dose are as important amongst infants in the weeks after vaccination commences as they are years after the course has been completed.

Conclusions on the heat stability issue

In an ideal world, countries considering use of HepB vaccine outside the cold chain, particularly for the birth dose, would be able to draw on performance specifications from suppliers before making a firm decision as to which vaccine to choose. This decision could be based on the conditions according to which they plan to use the vaccine, and would at least include a consideration of the local prevalence of HBeAg + women of child-bearing age (to decide if birth-dosing is of high enough priority and hence whether to give priority to procurement of single-dose vials, or vaccine in Uniject, and HBIG), and the climatic conditions to which vaccine stored outside the cold chain might be exposed. Knowledge of the availability of vials with a VVM guaranteed by the supplier to change colour before loss of potency is also important, although it is anticipated that all HepB vaccines will ship with VVMs appropriate to their degree of heat stability in the near future. Nonetheless, although not supported by field research specifically examining the issue of PE, from this discussion and the Table and data presented above, there appears to be a choice of products suitable for even the most demanding conditions likely to be met within a well-regulated EPI. What remains is the conduct of high quality field research to prove the immunogenicity and PE of HepB vaccine in tropical conditions (and for EPI managers to avoid the potentially bigger threat to the potency of HepB vaccine, freezing en route to the point at which the vial might be removed from the cold chain). It is conceivable that the best strategy might be for HepB vaccine to be shipped at ambient temperature from the time it leaves the manufacturer, or at least from the time it leaves a (well regulated) national EPI storage facility.

Heat stability of the locally produced HepB vaccine

A Vietnamese plasma-derived HepB vaccine was developed in the mid-1990s by Professor Nguyen Thu Van at NIHE. Using a manufacturing method combining both chemical and heat-inactivation, modeled on those developed by Drs Alfred Prince and Seung-il Shin in Korea, and by Merck, Sharpe and Dohme, (now Merck), Professor Van developed her vaccine with assistance from CDC and the Kitasato Institute in Japan.

Local, internal assessment of this vaccine by Professor Van and her staff found it to be eminently immunogenic (Chapter 5) and it has been produced commercially and sold to the government for use in the National EPI since 1997. Approximately 1 million paediatric doses (2.5µg/dose in 2-dose vials) are now purchased by the EPI in Vietnam each year, and until 2002 were available free of charge to infants in a large number of provincial capitals and a small number of rural areas. With the arrival of GAVI-supplied vaccine, the local product is now being used throughout 17, predominantly northern mountainous provinces. The remaining paediatric and adult doses (20µg/dose in single dose vials) produced locally are available for private purchase.

The immunologic stability of heat-exposed samples of this locally produced HepB vaccine was assessed by NIHE in 1997, and the results provided by Professor Van are presented in Table 2 below. As this data derives from mouse studies, it is not clear how it relates to the vaccine's performance in humans, particularly at the low-dose supplied for use in Vietnamese infants. However, based on the very positive human immunogenicity data provided by NIHE (Chapter 5) and on knowledge from previous studies of its heat-stability, SIAMC introduced this HepB vaccine in Thanh Hoa province according to three different strategies (described in detail in Chapter 6) two of which included storage at ambient temperature for up to one month for the first dose.

Table 2: The immunologic stability of plasma-derived HepB vaccine produced at NIHE kept at 37°C for various time periods, in comparison with a WHO-standard HepB vaccine kept at 4 - 8°C.

Number of Weeks	Effective dose 50 (µg)*	Change (%) in immunogenicity of standard vaccine compared to baseline		Effective dose 50 (µg)*	Change (%) in immunogenicity of trial vaccine compared to baseline	
		Incremental	Cumulative		Trial vaccine (NIHE)	Incremental
Baseline	0.33	-	-	0.37	-	-
1	0.35	- 6.1	- 6.1	0.43	- 16.2	- 16.2
2	0.38	- 8.6	- 15.1	0.45	- 4.7	- 21.6
4	0.39	- 2.6	- 18.2	0.49	- 8.8	- 32.4
6	0.41	- 5.1	- 24.2	0.50	- 2.0	- 35.1
8	0.39	4.8	- 18.2	0.50	0	- 35.1

* Dose of vaccine at which 50% of mice produced antibody

Chapter 5: The comparative immunogenicity of a plasma derived hepatitis B vaccine produced in Vietnam, and two recombinant DNA hepatitis B vaccines from Korea

Introduction

As demonstrated already, HBV infection is a major public health problem in Vietnam, with a high rate of virus carriage and, according to local reports, high levels of chronic liver disease and primary hepatocellular carcinoma. Up to 20% of the population, including CBAW, are carriers of the HBV, and almost 80% are infected with HBV in their lifetime (Chapter 3). Reports have shown that up to 90% of chronic infections may be preventable with active neonatal immunisation alone, and 95% if HBIG is also administered (Maynard JE, Kane MA et al, 1989), (Poovorawan Y, Sanpavat S et al, 1992), (Andre FE & Zuckerman AJ, 1994), (Liu Y, Liu X-Z et al, 1996), (Wilson JN & Nokes DJ, 1999), (Mahoney FJ & Kane M, 1999).

At the beginning of 2002 Vietnam, through its EPI, was already administering HepB vaccine in some provincial capitals and a few rural districts, reaching around 20% of the infant population (Appendix 1). However, vaccine remained unavailable to the majority living in rural areas, and for practical and technical reasons, the schedule introduced at this stage did not include a birth dose (Chapter 1). Unfortunately, if the first dose of HepB vaccine is deferred beyond the neonatal period and HBIG is not administered then, vaccine PE drops to 50 – 57% (Goudeau A, Lo KJ et al, 1983), (Lee SD, Lo KJ et al, 1986), Lee, 1989 in (Andre FE & Zuckerman AJ, 1994), (Ruff TA, Gertig DM et al, 1995).

The Vietnamese plasma-derived HepB vaccine is produced at NIHE in Hanoi in two formulations - 2.5µg/0.5ml for children (distributed in two-dose vials), and 20µg/ml (in single-dose vials) for adults. The vaccine has been found to be safe and immunogenic in internal trials conducted by the manufacturer, but has not been evaluated independently

despite over 2 million doses per year being produced by NIHE for use in the Vietnamese EPI and in the private sector.

NIHE cannot produce enough of this vaccine to satisfy national demand because it lacks the raw material, and is producing a recombinant-DNA HepB vaccine, assisted by technology transfer from Korea. However, even with the support from GAVI, until this new vaccine is available en masse (in 2005 at the earliest), Vietnam will continue to rely at least partly on the existing plasma-derived vaccine (Appendix 1). Accordingly, there has been great need for independent hospital- and field-based evaluation of this product.

SIAMC conducted both such evaluations, and this chapter reports on a comparison of the immunogenicity and PE of the NIHE vaccine in two different doses, and two UNICEF-approved recombinant-DNA HepB vaccines produced in Korea, all administered under identical conditions. The field-appraisal of the NIHE vaccine is reported in Chapter 6.

Method

The study was a single-blind, prospective, randomised controlled trial, in which the serologic responses of four groups of infants were assessed after a course of HepB vaccine, stored and administered as much as possible under ideal conditions. Blinding of mothers and serology staff was undertaken, but could not be achieved for the vaccinators because of differences in the appearance and volume of the vaccines used.

Infants in each treatment group each received three doses of one of four types of HepB vaccine: the NIHE vaccine at 2.5 μ g (VN2.5 μ g) (in single dose vials of 0.5ml produced especially for this trial) or 5 μ g/dose (VN5 μ g) (also in 0.5ml), or a recombinant HepB vaccine produced by the then Korean Green Cross Corporation (KGCC) (10 μ g in 0.5ml); or Lucky Goldstar Corporation (LG) (also 10 μ g in 0.5ml, but drawn from vials containing 20 μ g in 1ml). For ethical reasons, there was no placebo (unvaccinated) group. No verification of the antigenic content of the different vaccines could be undertaken.

Recruitment took place at the Thanh Hoa province obstetric hospital, in which approximately 3000 deliveries occur each year, over a period of six months in 1998 - 99. The first dose of all vaccines was scheduled for administration in hospital within 2 days of birth, and doses 2 and 3 either at the hospital or in the infant's home, scheduled at 1 and 2 months of age. All doses were given by deep intramuscular injection in the thigh.

Markers of HBV infection were assessed in the venous blood (taken at recruitment) of mothers whose infants completed follow up, and of infants six months after their third dose of HepB vaccine. HBsAg and total anti-HBc were measured on all samples. A qualitative assessment for anti-HBs was also conducted on all HBsAg-negative maternal samples. At the insistence of the project's provincial counterpart, HBsAg was first assessed in the laboratory at the Preventive Medicine Centre in Thanh Hoa. Specimens found to be HBsAg+ in Thanh Hoa were retested at NIHE, where the HBeAg status of these specimens, and all other markers, were also assessed. A sample of 100 (~17%) of those samples testing negative for HBsAg in Thanh Hoa were retested at NIHE for quality assurance. None tested positive. Infant serum was also tested for HBsAg, anti-HBc and anti-HBs (quantitative analysis) at NIHE. The decision to sample infants only 8 months after birth was a compromise between predicted loss to follow up and problems of interpretation due to antibody decay, on the one hand, and likely contamination by maternal antibody on the other. It was postulated that as the influence of maternal antibody would apply equally to each group, comparison of antibody titres and seroconversion rates between groups remained possible.

All serology was conducted by NIHE or province staff, using ELISA test kits produced by Sanofi Pasteur, France. Although project staff were not present at most of the laboratory testing, during those sessions attended by the author, standard laboratory procedures, initially supervised or conducted by NIHE staff, were followed, with some minor exceptions. Procedures included centrifugation prior to separation of serum from (recycled) glass vials into Nalgene or Eppendorf tubes, use of new micro-pipette tips for each sample, use of manufacturer-supplied controls during ELISA testing (although according to NIHE staff, not for every batch), inactivation of samples after thawing and

storage at 4°C between testing and subsequent refreezing. Haemolysis was again observed for occasional samples. Maternal blood was separated and stored at 4°C pending testing in the province. Samples for retesting and all infant samples were frozen at -20°C before transport to NIHE, where they remained frozen until tested. For this study, QA testing outside NIHE was not conducted, but the quality of testing at NIHE has been discussed in Chapter 3.

The number of infants enrolled was 700 (175 per group). Assuming a 20% dropout and that the null hypothesis would prevail in each case, the study was powered to enable detection of a difference of 10% between the point estimates of the rates of protection (defined as 10mIU/ml or more of anti-HBs) in each group, and a difference of at least 20% in the GMT of anti-HBs between the groups, with 95% confidence.

Infants born more than 3 weeks prematurely (on clinical grounds), requiring intensive care or blood product transfusion at any time during the study, living too far away for follow up or found to have chronic immunosuppressive illnesses or severe malnutrition (as assessed by the study team), were excluded. The study was approved by the leaders of the participating communities, the Provincial Health Service of Thanh Hoa, by NIHE and by the Vietnam MoH.

An experienced neonatal nurse and a doctor from amongst the staff of the hospital were recruited to work for the study and administered all vaccine doses. Hospital staff in the emergency, delivery and post-natal wards received training on the project design and process. Antenatal mothers living within a 15km radius of Thanh Hoa city were invited to allow their infants to enter the study. Those agreeing were given a standard pamphlet containing information about HBV and the study, a small gift upon enrolment, and another after the sampling of their infant six months after the third dose of vaccine. After the first dose an appointment was made for the second, at the infant's home or at the hospital, and so on for the third dose and for collection of the infant blood sample. Demographic information pertaining to the following parameters was kept on each mother-baby pair: follow up status, mother's age, ethnicity, occupation (defined as

farmer, blue collar, white collar, domestic duties and others), parity and mode of delivery, and infant's gender, number of older siblings and birth weight. Analyses were also made for differences in the length of time between birth and each dose of vaccine, and between each dose of vaccine.

Newly recruited infants were allocated to one of the study cells randomly. Block randomization was used, in which each successive infant was allocated a vaccine according to the first of the letters A, B, C and D listed in randomly ordered groups of these four letters.

A numerical coding system was used to blind laboratory staff as to which vaccine each infant had received until completion of all testing. The security of the coding system relied on the nurse and doctor from the hospital, who had access to this information, not to pass the details of which vaccine each infant received on to the laboratory. No guarantee of this security is offered, but the results suggest there was no attempt to manipulate the outcome to favour the local vaccine, as might be expected if the NIHE HBV serology laboratory (which is run by Professor Thu Van, the vaccine manufacturer) had tried to influence the result.

All vaccine for the study was donated by the manufacturers.

Data were again entered and analysed by computer using EpiInfo, version 6.03 (EpiInfo, CDC Atlanta), and STATA (Release 6, STATA Corporation, College Station, Texas).

Careful assessment of the randomisation procedure, using an intention to treat ($n = 700$) and final outcome ($n = 631$) approach, was undertaken to determine whether univariate or multivariate analysis of the data should be undertaken. This was done by assessing for differences across the treatment groups, in most cases using Chi-square or Fisher's exact tests to analyse the frequencies in each group of a number of categorical variables (mothers' parity, ethnicity, occupation (five options) and mode of delivery (three options), infants' gender and number of siblings). However, to assess for differences

between the groups in continuous variables, including mothers' age, infants' birth weight, the between-dose intervals and intervals between birth and each dose, one-way analysis of variance (ANOVA) was used. No analysis for interaction between any of these variables was undertaken.

As very minor differences between certain groups were identified, polytomous logistic regression was additionally used to assess the relative risk ratios (RRRs) of the variables assessed in each vaccine group, in comparison to the group receiving the low-dose, locally produced vaccine (VN2.5 μ g). This was undertaken again in all 700 infants, and then in the 631 who were followed up. For this analysis, independence of each variable was again assumed and no analysis of interaction was undertaken.

Failure risk and risk differences were calculated amongst the groups of infants receiving the different vaccines, with respect to their response to the vaccines.

Results (See Figure for this Chapter in Appendix 8)

Differences between the treatment groups according to the variables listed above were assessed using Chi-square and Fisher's exact tests, analysis of variance and polytomous logistic regression, as described above, using both an intention to treat analysis (n = 700) and also by analysing the status of infants who completed follow up (n = 631) for differences.

There were no differences in the distribution of the mothers' ethnicity (there was only one non-Kinh mother in the entire sample), occupation, parity or mode of delivery, nor the infants' gender, number of older siblings and birth weight. There were very small differences between the mothers' age between the VN2.5 μ g (mean age 26.5 years and 26.5 years in the intention to treat and followed up groups, respectively) and the VN5 μ g (mean age 27.5 and 27.6 years) and the LG (mean age 28.1 and 28.1 years) groups in both the intention to treat (RRR for VN5 μ g = 1.07, P = 0.03; RRR for LG = 1.07, P = 0.03) and followed up (RRR for VN5 μ g = 1.07, P = 0.04; RRR for LG = 1.06, P = 0.07)

groups of infants. There were also small but non-significant differences in infants' weight between the same VN5 μ g and LG groups compared to the VN2.5 μ g group.

The timing of the first dose of vaccine (dose-1) was within 24 hours of birth for 653 infants (93.3%), on day one for another 39 and later for eight. For the second dose (dose-2), the median day of vaccination was 32 days after birth, mean 32.2 and standard deviation 3.9, and for dose-3 the median was 62 days, mean 63.2 and standard deviation 4.5. For each dose, analysis for differences in timing across the groups was conducted using both ANOVA and chi-square analysis of the frequency of dosing before and after certain days. In each case no difference across the groups was found. There was also no difference in the interval between dose-2 and dose-3 across the four groups. The interval between dose-3 and the time of bleeding was not measured, but as recruitment and bleeding did not differentiate infants by vaccine group, and all other median days for dosing and intervals were the same, a difference in this parameter seems unlikely.

From these analyses it was concluded that overall, the randomisation of infants worked well and that loss to follow up generally also occurred in a random fashion.

Table 1 depicts the number of infants successfully followed up in each cell, and separates them according to their maternal HBV infection and antibody status, rates of protection by vaccine type, and GMT.

Table 1: Seroconversion of infants by vaccine type and maternal infection status

<i>vaccine type*</i>	KGCC	LG	KGCC or LG	VN 2.5µg	VN 5µg	Total
Number (#) infants randomised	174	175	349	176	175	700
Infants (%) successfully followed	155 (89.1)	157 (89.7)	312 (89.1)	157 (89.7)	162 (92.6)	631 (91.1)
Number of infants anti-HBs+ at follow up (95% confidence intervals (c.i.))	154 [99.4 (96.5-100)]	155 [98.7 (95.5-99.9)]	309 [99.0 (97.2-99.8)]	139 [88.5 (82.5-93.1)]	155 [95.7 (91.3-98.2)]	
GMT* – all infants (95% c.i.)	828 (709-966)	472.6 (401-557)	625 (556-702)	165.4 (127-216)	161 (122-213)	
Mean difference for failure to detect anti-HBs (95% c.i.) compared to Korean vaccines			-	10.5 (10.0-11.0)	3.4 ^b (3.3-3.5)	
Number of infants of mothers negative for all HBV markers	60 (24.4)	61 (24.8)		71 (28.9)	54 (22.0)	246 (100)
Number of infants amongst these infants (95% c.i.)	948 (758-1187)	487 (380-624)	712 (623-814)	120 (80-180)	88 (56-138)	
Number of seroconversion failures in this group (95% c.i.)	0	0	0	10 [14.1 (7.0-24.4)]	1 [1.9] ^c (0.1-9.9)	
Mean difference for failure to convert to anti-HBs (95% c.i.) compared to Korean vaccines			-	14.1 (12.9-15.2)	1.9 (1.8-1.9)	
Number of infants of anti-HBs+ mothers	66 (25.1)	58 (22.1)		62 (23.6)	77 (29.3)	263 (100)
Number of infants amongst these infants (95% c.i.)	753 (581-975)	480 (352-654)	543 (472-625)	225 (151-336)	257 (172-383)	
Number of infants negative for anti-HBs in this group	0	1 (1.7)	1 (0.8)	2 (3.2)	2 (2.6)	
Number of infants of HBsAg+ mothers	12 (7.7)	21 (13.4)	33 (10.5)	13 (8.3)	15 (9.3)	61/631 (9.7)
Number of infants negative for anti-HBs in this group	1 (8.3)	1 (4.8)	2 (6.1)	6 (46.2)	3 (20.0)	11 (18.0)
Number of HBsAg+ mothers who were anti-HBeAg+	4 (40)	7 (33.3)	11 (35.5)	7 (53.8)	5 (33.3)	23 (37.7)
Number of infections (= HBsAg+) (%) amongst infants of HBsAg+ mothers	2/12(16.7) ^a	1/21 (4.8)	3/33 (9.1)	6/13 (46.2)	2/15 (13.3)	

a. Includes one infant positive for HBsAg and anti-HBs b. raw values = 4.321 – 0.962 = 3.359%
c. Another of these infants failed to produce protective levels of antibody (>9mIU/ml)

*KGCC = Korean Green Cross Corporation; LG = Lucky Goldstar; VN 2.5 = Vietnam vaccine at 2.5µg;
GMT = geometric mean titre in mIU/ml

There were no infections amongst infants of mothers negative for HBsAg or amongst infants of mothers negative for all markers. Amongst infants of 61 HBsAg+ mothers, 9.1% of infants receiving Korean vaccines were HBsAg + (itself a relatively high number albeit from a small sample, possibly suggesting a problem with vaccination technique or

inactivation of vaccine by inadvertent freezing; it also included an infant seropositive for both HBsAg and anti-HBs, who may have been in a stage of recovery from acute infection), as compared to 46.2% and 13.3% of VN2.5 μ g and VN5 μ g recipients, respectively. Ten of the 11 infant infections were observed amongst infants of the 23 mothers who were HBeAg + as well as HBsAg +. The one infection in an infant of an HBsAg + / HBeAg-negative mother was a recipient of the VN2.5 μ g vaccine. Ten of the 11 infected infants (including the three who had received a Korean vaccine) had been vaccinated on the day of birth, and one recipient of the VN2.5 μ g vaccine on the day after birth. The observed difference in HBeAg seroprevalence across the groups was not significant ($\chi^2(3) = 1.69, P = 0.64$).

Absence of anti-HBs was observed amongst only 1.0% (95% c.i. 0.2-2.8) of all recipients of either Korean vaccine. The corresponding rates amongst recipients of the 2.5 μ g and 5 μ g doses of the NIHE vaccine were 11.5% (6.9-17.5), and 4.3% (1.8-8.7) respectively. Compared to Korean vaccine recipients, the failure risk difference for detection of anti-HBs amongst all infants receiving the VN2.5 μ g vaccine was thus 10.5% (10.0-11.0), and amongst those receiving the VN5 μ g vaccine, 3.4% (3.3-3.5). The corresponding figures for infants of mothers lacking all markers of HBV infection were remarkably similar, although the confidence intervals are obviously wider as numbers were smaller. In this group, true vaccine failure occurred in no recipient of a Korean vaccine, but 14.1% and 1.9% of those receiving the VN2.5 μ g and VN5 μ g vaccines respectively. In addition, the anti-HBs titre of another VN5 μ g recipient was below the level considered protective (>9mIU/ml), raising this vaccine's true failure rate using this definition to 3.7% (0.45-13.4).

Compared to infants who received the VN5 μ g vaccine, the relative risk of absence of protection amongst all recipients of the VN2.5 μ g dose (currently used in the local EPI) was 2.65 (= 11.5/4.3) (1.81-3.50). The corresponding risk amongst infants of mothers lacking markers of HBV infection was higher. Compared to those given the VN5 μ g vaccine, the relative risk of this true vaccine failure amongst recipients of the VN2.5 μ g

vaccine was 7.61 (= 14.1/1.9) (5.59-9.63). Including the one VN5 μ g vaccine recipient whose anti-HBs levels were not protective changes this relative risk of true failure to induce protective levels of anti-HBs to 3.81 (= 14.1/3.7) (2.33-5.29).

The Table shows the influence of maternal antibody on both the proportions “apparently protected” and the GMT of anti-HBs amongst recipients of VN vaccines. Amongst recipients of the VN2.5 μ g vaccine whose mothers were anti-HBs+, only 3.2% lacked anti-HBs, as compared to 14.1% of recipients whose mothers were negative for all HBV markers. For recipients of both VN vaccines, the GMTs of anti-HBs were much higher than those for infants of mothers with no HBV markers. The same influence was not apparent for Korean vaccine recipients, which induced high titres of anti-HBs in all groups. In addition, amongst the 630 mothers whose infants completed follow up and for whom results were available, 59.1% were anti-HBc+, and data not shown indicated that 42 (6.7%) of these infants had anti-HBc, but only 11 (1.7%) were HBsAg+. Of those who were anti-HBc+, 37 (88%) of them were delivered by anti-HBc+ mothers. The proportion of anti-HBc+ infants found here to be HBsAg-negative (73.8%) would seem high if it represented true infection in a group of this age, and suggests that much of this anti-HBc was maternal in origin. IgM-type anti-HBc was not measured amongst infants, but would have helped to differentiate maternal from endogenous antibody.

Data pertaining to the immunogenicity of each vaccine, as measured by antibody titre, are also depicted in the Table. There was no difference in GMT between the two doses of the NIHE vaccine, as also evidenced in the graph comparing the centile distribution of the log titres of the two doses amongst infants of mothers lacking HBV markers and who received either of the two doses of the Vietnamese vaccine (see Figure 6, Appendix 8).

Discussion

The goal for most nations' EPI is self-sufficiency, meaning a complete lack of reliance on donor support. This can be interpreted as self-sufficiency in funding all aspects of the EPI, including procurement of local or imported materials, or both funding and actually

producing the program's entire material needs, including vaccines, in country. Vietnam has been able to produce 60% of its DTP and TT and 100% of its oral polio and BCG requirements. Self-sufficiency in vaccine production is a major goal of the nation's EPI leadership, and their decision to start their anti-HBV immunisation program with a locally produced HepB vaccine instead of procuring imported vaccine for the EPI demonstrates their commitment to this goal.

NIHE started producing HepB vaccine early last decade. Internal evaluations of this vaccine considered the issues of dosage, immunogenicity and toxicity, but not vaccine PE. Amongst groups of young adults previously unexposed to HBV, these evaluations found low reactogenicity, and rates of seroconversion for anti-HBs ranging from 93.6% (for 3 doses of 5 μ g vaccine) to 98% (20 μ g vaccine). Using a 0, 1 and 6-month schedule, GMT in adults measured one month after the third dose of the 20 μ g vaccine was 6,818 mIU/ml. For newborns, immunogenicity ranged from 96.2% (using a 2.5 μ g dose) to 98.8% (with a 10 μ g dose). GMT measured one month after the third dose of the 2.5 μ g vaccine was 362mIU/ml (Professor Nguyen Thu Van, NIHE, personal communication).

To my knowledge, this is the first external evaluation of the NIHE vaccine, although strictly speaking the evaluation cannot be said to be completely independent as the laboratory testing of the post-vaccination samples was at NIHE. It is concluded that at 2.5 μ g/dose, it performed less well than the two Korean vaccines in terms of inducing anti-HBs production, in the relative GMT it induced and also probably in its PE against infection amongst infants of HBsAg + mothers. The immunogenicity results are evident both amongst infants of mothers with evidence of previous HBV exposure and amongst infants of mothers with no markers of HBV infection. Moreover, the 2.5 μ g/dose was also inferior to the same vaccine at 5 μ g/dose, again regardless of the mothers' exposure status.

No difference was found between the titre of antibody produced by "true" seroconverters (infants of mothers with no markers of HBV infection) who had received the 2.5 or the 5 μ g dose, but the titres, although comparable to those achieved in a field trial in Indonesia (Ruff TA, Gertig DM et al, 1995) were in both cases rather low. The large

difference in antibody titres between the Korean and Vietnamese vaccines is probably irrelevant from a public health perspective as all vaccines induced production of levels well above that considered protective, particularly in an environment of high endemicity where exposure after successful vaccination rarely yields clinical disease, and chronic infection even less commonly (Hadler SC, Francis DP et al, 1986), (European Consensus Group on Hepatitis B Immunity, 2000), (Xu ZY, Duan SC et al, 1995), (Huang LM, Chiang BL et al., 1999), (Liao SS, Li RC et al, 1999), (Whittle H, Jaffar S et al., 2002).

Based on their own data and to maximise vaccine yield (and, it has to be said, profit) from the scarce supply of human plasma used in production of this vaccine, NIHE elected to produce their paediatric formulation of HepB vaccine at 2.5µg/dose. As indicated above, this may be more important because of the relative failure of the low dose vaccine to induce seroconversion than its failure to induce high levels of antibody. The findings merit an examination of their potential public health consequences.

In Vietnam, the annual birth cohort is approximately 1.6 million infants / year, so that a relative difference in the production of antibody of 12.2% (as identified between true seroconversion to anti-HBs amongst recipients of the low and high dose Vietnamese vaccines) translates maximally into almost 200,000 more infants remaining susceptible to HBV infection, per year. However, only a few of these infants will be exposed to HBV early enough for their risk of chronic infection to be high (McMahon BJ, Alward WL et al, 1985), (Edmunds WJ, Medley GF et al, 1993), (Hyams KC, 1995), and there is no intention nor capacity to use this vaccine nationwide, as the manufacturer lacks sufficient production capacity. If affordable though, it would seem that a higher dose would induce protection of more (>95%) of the infants (in the 17 non-GAVI supplied provinces) still receiving the locally produced vaccine, and virtually all of them if vaccine like the Korean ones tested here could be procured instead.

Depending on the relative costs of the vaccines available, and on the role of national pride and the need to commend and encourage scientific research and possibly vaccine development in a country like Vietnam, some might argue that the differences identified

are rather small. A rate of protection of 85.9% is indeed high, and the anticipated public health benefits of this vaccine are enormous. The data in Chapter 3 suggest strongly that most of the infections with HBV resulting in chronic carriage occur early in life (in fact that around 2/3 of them occur before the age of 18 months). Preventing 85.9% of them, plus the other third acquired later in life, would be a major achievement in the areas where this vaccine is used.

However, another concern about the 2.5 μ g vaccine is its probable low PE. HepB vaccination of infants of seropositive mothers soon after delivery yields varying levels of protection, depending on the degree of exposure, the timing of the first dose, the immunogenicity of the vaccine and whether HBIG is also administered (Chapters 4 and 6) (Andre FE & Zuckerman AJ, 1994). Although the numbers are very small, six of the 13 infants who received this vaccine and were delivered by HBsAg+ mothers were infected at the time of sampling, despite vaccination in the first 48 hours of life. Further, although only 10 infants of the 23 HBeAg+ mothers recruited were infected, five were from the VN2.5 μ g group. A sixth VN2.5 μ g vaccine recipient delivered by an HBsAg+ / HBeAg-negative mother was also infected. It is possible that some of these infants may have been acutely infected at the time of the study (Chapter 6), but at the age sampled, the majority go on to chronic infection.

At the time it was introduced, the internal evaluations conducted by the manufacturer of the NIHE vaccine and reported above gave the MoH confidence that it would be a viable alternative to the costly importing of WHO-certified HepB vaccines. However, the results of this study suggest that the 2.5 μ g dose of the NIHE vaccine is not as immunogenic as a 5 μ g version of the same vaccine, and may not be particularly effective in protecting against chronic HepB carriage resulting from perinatal or horizontally acquired early HBV infection. The contribution of chronically and early-infected infants to persistent horizontal HBV transmission to older children may be substantial. Given the preference for at least some use of the local vaccine (Appendix 1), the findings of this survey would suggest that increasing the dose of the local vaccine to at least 5 μ g is in the public health interests of the communities where it will continue to be used for the next several years.

Further examination of the current vaccine under field conditions is made in the next chapter.

Chapter 6: The introduction of hepatitis B vaccination in Vietnam: scientific issues and operational alternatives in a tropical, developing nation

Introduction

As described in earlier chapters, infection with HBV is a major public health problem in Vietnam, due to the association of chronic infection with cirrhosis of the liver and primary hepatocellular carcinoma. Chronic infection most often results from exposure to the virus early in life, and Vietnam is introducing HepB vaccine for all its infants during 2002 and 2003 (Appendix 1).

Based on the review of available data and the population-based serology survey described in Chapter 3, it is clear that a birth dose of HepB vaccine will reduce rates of chronic infection in Vietnam more rapidly than if the first dose is given with the first EPI contact, which is often after the age of two months. However, delivery of vaccine to all newborns in Vietnam will not be easy, due to the high rate of home birth and difficult geographic access. Furthermore, the scarcity of refrigeration at local health stations militates against the availability of thermolabile vaccines on a daily basis.

As reviewed in Chapter 4, reports from China and Indonesia have confirmed the feasibility (Anonymous, 1991) and success (Sutanto A, Suarnawa IM et al, 1999), (Otto BF, Suarnawa IM et al, 1999) of using HepB vaccine stored outside the cold chain for up to 3 months, and administered within a few days of birth to infants delivered at home. These field studies have made use of the thermostability of HepB vaccine, as demonstrated in controlled animal (Dr D West, personal communication) and human studies (Just M & Berger R, 1988), (Van Damme P, Cramm M et al, 1992).

This chapter reports the results of a second serologic survey designed to evaluate the three strategies of introduction of HepB vaccine piloted by SIAMC in rural Vietnam, two of which included the facility to administer a birth dose with vaccine stored at ambient temperature for up to one month. The aims of the survey were to assess the timing of

HepB vaccination including with the birth dose, the immunogenicity and PE of the indigenous, low-dose, plasma-derived vaccine under field conditions including whether storage outside the cold chain influenced these variables, and to compare infection rates with those obtained at baseline. The data collected also enabled examination of the influence timing of the birth dose had on its PE amongst infants of HBsAg + mothers.

Method

Location and project timing

The survey was conducted as the final evaluation of the research SIAMC conducted to assist Vietnamese authorities with the design of their national strategy of immunisation against HBV. The survey site was the same as described in Chapters 1, 2 and 3, with the addition of some sampling of infants in 8 other Quang Xuong communes as described below.

Field-work for SIAMC ran from early 1998 to late 2000, and as described earlier, comprised phases of information gathering (baseline surveys) (Chapters 2 and 3), implementation (community mobilisation and HW education followed by introduction of HepB vaccine) and evaluation (follow-up surveys) (Chapters 5, 7 and this one). Implementation took place in a step-wise manner, with vaccination beginning in 9 communes in each of Quang Xuong and Ngoc Lac districts in November 1998 and expanding to include all 64 communes in these 2 districts in June 1999.

The vaccine used in the project

The HepB vaccine introduced in these districts was the 2.5µg, plasma-derived vaccine produced at NIHE in Hanoi, which has been internally assessed as safe, immunogenic and heat-stable (Chapter 5), but the PE of which has not been previously documented. No information was available to the project about the lot-to-lot variability of this vaccine, nor whether the vaccine introduced in the field and in the hospital study (Chapter 5) came from the same or different lots. No independent testing for the HBsAg content of the

vaccine was possible, but a semi-independent national regulatory authority was involved in vaccine quality assurance during the project period.

The three project strategies for HepB vaccine introduction

The EPI into which the vaccine was introduced (Chapter 1) is conducted as a monthly activity, and reliable refrigeration stops at district level. In the districts surveyed, EPI day is usually the 15th or 16th of each calendar month. Before SIAMC, infants' first EPI contact was usually not until at least 2 months after birth, and vaccines were not available in hospitals at all. To improve on this, 2 new strategies of vaccination against HBV were assessed:

- *Ideal strategy:* In these communes, a simple new, monthly birth-registration and EPI-recording system was introduced at village-level, to improve accurate recording of the EPI (Appendix 9). Births anticipated in the next month were tallied up by the CHW responsible for the EPI in each commune, based on reports from VHWs there. On EPI day each month, a CHW collected from the district hospital an adequate number of vials of HepB vaccine to immunise the anticipated births for the next month, and stored them at ambient temperature in the CHS. Records of the temperature in each CHS were not kept, but the average minimum and maximum temperatures for the relevant months in the two districts are tabled below (Table 1). VVMs were not available on these vials. Infants born at the CHS received HepB vaccine, usually on the day of birth. Births at home were reported by VHWs to a CHW, who was asked to make a special trip to administer a dose of HepB vaccine in the infant's home as soon as possible after the birth and within the first week of life. Infants born in the district hospital were immunised there before discharge, and a special card including the baby's details and recording the administration of a dose of HepB vaccine was sent with the mother to show the VHW and CHW. The recording of this birth dose and subsequent doses of all vaccines enabled the new register to act as a village-based record of immunisation for mothers, who in general did not have access to a record of their children's EPI status (Chapter 2B), and to VHWs, who also had previously had no formal records to facilitate planning of their assistance in the monthly EPI. Unused HepB vaccine was discarded at the end of each month. To stimulate initial

cooperation and subsequent demand, a small monthly incentive was paid to one CHW (~\$5) in each commune and one VHW (~\$2) in each village, for the first 12 months of this new service, and a community mobilisation and HW education program were undertaken as described below. No incentives were paid after 12 months.

- *Routine strategy:* The system here differed from that in “ideal” communes in several ways. The village-based birth-reporting / EPI recording system was not introduced, and no incentive was paid to CHWs or VHWs. HepB vaccine was collected and stored at the CHS in the same way as described above, but whilst infants born at the CHS could be immunised against HBV before discharge, if a home birth occurred and was reported, CHWs could either visit and vaccinate the infant at home, or request that he or she be brought to the CHS for vaccination (remembering that no incentive was paid to encourage a home visit). The same community mobilisation and HW education program was undertaken in these communes, and promoters of HepB vaccine encouraged mothers delivering at home to take their baby for early immunisation at the CHS. This strategy was thought at the time of project design to most closely resemble what would be feasible in Vietnam, if authorities subsequently chose a birth-dose strategy with storage of vaccine outside the cold chain for the first dose (as indeed they did).

In both these groups of communes, identical community mobilisation strategies (posters, leaflets, roadside billboards, orientation of community leaders and village level health promoters and, where available, loudspeaker broadcasts) were introduced to stimulate awareness of HBV, interest in HepB vaccine and knowledge that immunisation of newborns is important. These activities were evaluated by the project and found to be very effective in achieving these goals (Chapter 7). HWs at district, commune and village level also received education on the importance of HBV and its prevention, injection safety, and on how to improve certain aspects of the EPI. In addition, their EPI activities were regularly monitored by mobile public health teams from the district health service (Appendix 10 and Chapter 7A).

Table 1: Average monthly minimum and maximum temperatures (°Celsius) in Quang Xuong and Ngoc Lac districts during the months of birth of infants surveyed

District		1999						2000						
		Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar
Quang	Minimum	18.9	22.8	23.8	25.8	27.2	25.6	24.6	22.9	19.9	13.5	17.0	15.1	17.4
Xuong	Maximum	24.0	27.0	29.0	31.7	34.5	31.7	31.1	27.9	25.2	19.6	21.2	19.3	21.8
Ngoc	Minimum	19.1	21.3	23.1	25.4	25.4	25.0	24.0	22.5	19.7	12.5	16.9	15.0	18.0
Lac	Maximum	25.7	29.4	29.9	33.8	32.9	31.4	31.4	29.1	25.9	20.9	22.6	20.3	23.1

For comparison, a strategy without the added inputs described above was also implemented:

- *Control strategy:* In these communes HepB vaccine was introduced as had already been undertaken by the National EPI of Vietnam in certain, predominantly urban areas, at that time. Vaccine was only available on EPI day, and birth dosing was not available unless an infant happened to be born on or just before this and attended an EPI session. No incentives were paid, and promotion of HepB vaccine was undertaken only through routine HW meetings and EPI publicity. No additional monitoring of HWs' EPI activity was undertaken in these communes.

In the first phase of the project the allocation of communes to the three project strategies described was not random, such that the ideal and control strategies were implemented in a mixture of the stronger and weaker communes (as subjectively defined by their comparative implementation of the EPI, reported in Chapter 2A, and by their capacity to implement birth dosing for the purposes of this research). At the time, it was expected that this would identify differences in communes' operational capacity to introduce HepB vaccine, in order to highlight potential problems in communes known to be weak in any future expanded introduction of the vaccine. This is discussed further in Chapter 7A. In the phase of expansion, communes were allocated to the 3 strategies randomly, but with one exception described below, communes introducing vaccine in this phase of expansion were not included in any evaluation of the project.

Serosurvey strategy and sample size

Evaluation of the three project strategies was undertaken in two ways. The first, follow up surveys of community and HW KAP regarding liver disease, HBV and the EPI, are reported in Chapter 7. The second was a serology survey of HBV markers amongst infants aged 9 - 18 months, reported here.

The survey took place over 8 days in mid-October 2000 in Quang Xuong and Ngoc Lac districts. Venous blood samples were collected from 1106 infants (583 males and 523 females; 566 in Quang Xuong and 540 in Ngoc Lac) aged 9 – 18 (mean 13.7) months in the 18 original communes where vaccination commenced in November 1998. This comprised the entire vaccinated birth cohort of this age for these communes. An attempt was made to calculate the power of this survey to detect differences in rates of HBsAg across the districts and strategies, using the seroprevalence of HBsAg amongst infants obtained at baseline (Chapter 3), and based on estimates of outcomes that assumed lower rates in ideal communes than in routine and control, and in Quang Xuong than Ngoc Lac. It was clear that with the numbers of infants available, the survey had low power in most cases to evaluate for such differences. For example, the power to detect a 3% difference in the new rates of HBsAg between ideal and control communes (assumed to be 4% and 7% respectively), with a population of 530 and 650 infants in each respectively, was still only 60%. The project sample size was much smaller than this, so power to detect such differences was indeed rather weak, a function of the limited time and money available.

In order to assess the PE of vaccine amongst infants of HBV-infected mothers vaccinated in the first week of life, in addition to sampling infants, the survey also sampled a proportion of their mothers. These women were selected on the basis of their result on a finger-prick screening test for HBsAg (Determine HBsAg, Abbott Laboratories, Tokyo, Japan), conducted on the mothers of all infants vaccinated within 7 days of delivery, the assumed limit for PE of birth-dose HepB vaccine. Mothers whose screening test was positive were bled by venesection for formal testing for HBsAg and HBeAg, as described below.

In addition to these infants and mothers, to increase the power of the testing for PE from its already low base, another small group of infants aged 9 – 16.5 months, and their mothers, were sampled in eight of the additional “ideal” communes in Quang Xuong, where immunisation commenced in June 1999. In these communes, sampling was restricted to those mother-infant pairs in which the infants were vaccinated within a week of delivery, and whose mothers tested positive on the finger-prick screening test for HBsAg. Amongst these mother-infant pairs, the same demographic variables (depicted below) were collected as amongst those in the original 18 communes, enabling their inclusion in analyses of these variables’ influence on rates of infection. From a demographic and socio-economic viewpoint, their inclusion was deemed reasonable because of the homogeneity of the rural population in this district. No qualitative or quantitative comparison of these eight communes’ performance in implementing a birth dose was undertaken.

Finally, mindful of the slight limitation posed on interpretation of the data in the first serology survey because of the gender bias towards males amongst the adult group (Chapter 3), 533 new CBAW (aged 25 – 40 years; 266 in Quang Xuong and 267 in Ngoc Lac) were also surveyed in the 18 original communes. The size of this sample was based on an assumed seroprevalence of HBsAg of $16 \pm 3\%$ (from Chapter 3) with 95% confidence (Lwanga SK & Lemeshow S, 1991). The selection and sampling procedure for these women was identical to that described for the first survey, and the sequence of tests performed also the same as described in Chapter 3 and below.

Informed oral consent for their and their infants’ participation was given by the women and mothers of infants sampled after a community wide publicity campaign prior to this survey. The survey and project strategies were approved by NIHE (a letter to this effect accompanies this thesis), by leaders of the participating communities and by the Vietnam MoH. Mothers and infants who participated were given a small gift in return for their cooperation.

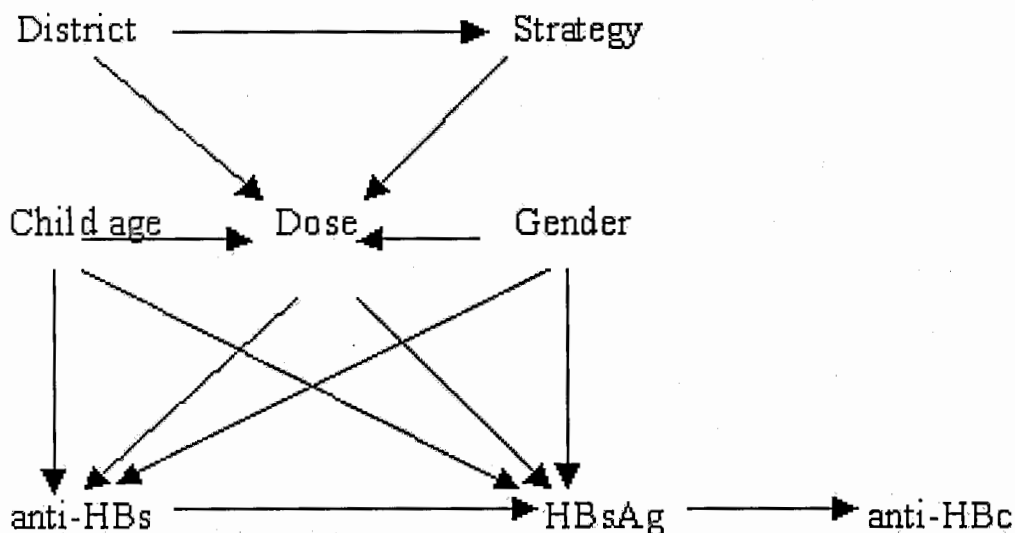
Conduct of the serosurvey

On the evening of collection, blood samples were separated and the serum frozen for subsequent transport to and analysis at NIHE. All sera were assessed by ELISA (Sanofi Diagnostics Pasteur, France) for HBsAg. Infants' samples were tested for HBsAg. If negative, they were tested qualitatively and then quantitatively for anti-HBs (this dual testing was a laboratory error; it was intended for quantitative testing to be conducted at the outset) and for total anti-HBc. Amongst samples from mothers or CBAW, those testing HBsAg + were also tested for HBeAg, and HBsAg-negative samples from CBAW for total anti-HBc and anti-HBs. Repeated thawing and freezing of specimens was avoided. As before, all sera were coded with a unique identifier, but NIHE staff were not blind as to the location from which each sample derived. Standard laboratory procedures were undertaken, as described in Chapters 3 and 5. QA testing was not done on specimens collected in this survey, as laboratory capacity was deemed adequate after the baseline survey (Chapter 3).

Data analysis

Data were entered onto a computer using EpiInfo, version 6.03 (EpiInfo, CDC Atlanta), and analysed using STATA (Release 6, STATA Corporation, College Station, Texas). Chi-square, Z-tests, Wilcoxon rank-sum and t-tests, and linear regression and MLR were used to examine the relationships between independent variables and outcomes of interest.

Backward selection with a cutoff of $P = 0.2$ was again used to initially assess which variables to include in regression analyses, but only the full models are reported. The causal diagram below was used to assess the association between certain variables and the outcomes of interest. Again, the variables were assumed to be independent of each other, and no analysis for interaction was conducted.



The infection status (HBsAg and HBeAg) of mothers was not included because these variables were only available for mothers whose infants were vaccinated in the first week of life. The diagram allows for the fact that infants were not tested for anti-HBs if HBsAg +, and that anti-HBc was not included in regression models examining influences on HBsAg status, as it was not measured (assumed positive) in such infants. For simplicity, mother's age is not included in the diagram, but for the purposes of analysis was included in all assessments of influences on infants' HBsAg status.

For unknown reasons, a value for mother's age was missing in ~13% of cases, predominantly in Ngoc Lac (133 of 149 cases), but there was no reason to suspect that the age of Ngoc Lac mothers differed from those in Quang Xuong. This was easily the commonest missing value amongst all variables examined, and notwithstanding what was described in Chapter 3 about the demographic information system now operating in Vietnam, may represent uncertainty about date of birth in these poorer, older females. To avoid the loss of these infants from regression analyses, imputation was used to estimate values of this parameter for those missing. The mean of mothers whose age was recorded was 26.0 years, median 25, and variance 21.8; corresponding parameters including imputed values were 26.1, 26 and 18.9 years. The median increased because the distribution of mothers' age was slightly skewed to the right, so that imputed values

tended to be higher than the mean of those for whom actual values were available.

Analyses including both actual and imputed values for mother's age are reported, but in general, imputation impinged minimally on all reported analyses.

Only the raw data (usually converted to a geometric mean titre) relating to anti-HBs levels between the groups of infants by district and strategy are compared. However, predicted anti-HBs levels were also estimated for each group, in comparison to the group with the shortest delay between the third dose of vaccine (dose-3) and the time of bleeding, using the spreadsheet at <http://www2.stat.unibo.it/palareti/vaccine.htm> (Honorati MC, Palareti A et al., 1999). For this correction, the group with the shortest delay between dose-3 and bleeding was treated as the baseline, and the titres of groups with longer delays were adjusted by the number of days' delay longer than this group, using the spreadsheet.

Results (See Figures for this Chapter in Appendix 8)

Operational issues relating to introduction of HepB vaccine

There was no association between district and the numbers of infants vaccinated by each strategy (Table 2) ($\chi^2 (2) = 0.7365$, $P = 0.692$). There was also no association between the infants' sex and district or strategy, nor between infants' age or mothers' age and district or strategy.

Table 2: Number of infants vaccinated by each strategy according to district

Strategy	District		Total
	Quang Xuong	Ngoc Lac	
Ideal	172	158	330
Routine	207	211	418
Control	187	171	358
Total	566	540	1106

Coverage with three doses of HepB vaccine varied across the districts and particularly across the strategies (Table 2A).

Table 2A: Percent coverage of infants with HepB vaccine by district and strategy

Strategy	District					
	Quang Xuong			Ngoc Lac		
	Received only 1 dose	Received only 2 doses	Received all 3 doses	Received only 1 dose	Received only 2 doses	Received all 3 doses
Ideal	0	0.6	99.4 (n = 171)	0	3.2	96.2 (n = 152)
Routine	0	0	100 (n = 207)	9.5	6.6	81.5 (n = 172)
Control	1	3.2	95.7 (n = 179)	30.4	12.9	53.8 (n = 92)
Total			98.4 (n = 557)			77.0 (n = 416)

A summary of the timing of vaccine doses by district and strategy is shown in Table 3. Median days are given because the distribution of the first dose of vaccine (dose-1) was heavily skewed, and clearly some infants started their HepB vaccine schedule very late. There were differences in the timing of dose-1 according to strategy both within and between both districts. These differences are also seen on the dot-plot charts of dose-1 by strategy and district (Appendix 8, Figures 7 and 8). In general, in Ngoc Lac vaccine doses were received closer to their scheduled date in ideal than routine and certainly control communes, but these differences were not observed in Quang Xuong where vaccine was administered on schedule (or early, for dose-3) regardless of strategy.

Table 3: Median days for receiving the three doses of Hep B vaccine (dose-1, -2 and -3) by district and strategy

	Ideal			Routine			Control			Total		
	Dose -1	Dose -2	Dose -3	Dose -1	Dose -2	Dose -3	Dose -1	Dose -2	Dose -3	Dose -1	Dose -2	Dose -3
Quang Xuong	0	68	99	1	47	78	15	47	78	1	51	82
Ngoc Lac	4	54	106	39	95	165	65	121	204	16	81	140
Total	2	62	102	4	55	89	23	56	86	5	58	92

Table 3A: Tests for differences in median dose interval within strategies by district

	Ideal			Routine			Control		
	Dose 1-2*	Dose 2-3	Dose 1-3	Dose 1-2	Dose 2-3	Dose 1-3	Dose 1-2	Dose 2-3	Dose 1-3
Quang Xuong	Z = 5.49	Z = -10.6	Z = -2.8	Z = -4.3	Z = -11.3	Z = -10.8	Z = -11.7	Z = -12.4	Z = -12.7
Ngoc Lac	P < 10 ⁻⁵	P < 10 ⁻⁵	P < 10 ⁻²	P < 10 ⁻⁵	P < 10 ⁻⁵	P < 10 ⁻⁵	P < 10 ⁻⁵	P < 10 ⁻⁵	P < 10 ⁻⁵

*The median interval in days between doses-1 and -2

Table 3B: Tests for differences in median dose interval between strategies within districts

	Ideal vs. routine			Routine vs. control			Ideal vs. control		
	Dose 1-2	Dose 2-3	Dose 1-3	Dose 1-2	Dose 2-3	Dose 1-3	Dose 1-2	Dose 2-3	Dose 1-3
Quang Xuong	Z = 10.0	Z = 0.94	Z = 9.9	Z = 12.0	Z = -0.02	Z = 11.6	Z = -14.4	Z = -0.9	Z = 14.3
Ngoc Lac	P < 10 ⁻⁵	P = 0.35	P < 10 ⁻⁵	P < 10 ⁻⁵	P = 0.98	P < 10 ⁻⁵	P < 10 ⁻⁵	P = 0.38	P < 10 ⁻⁵

Amongst infants born in ideal communes, 99% in Quang Xuong and 83% in Ngoc Lac received dose-1 in the first week of life. These figures were virtually unchanged (97% and 86% respectively) for infants born in the 4.5-month period following cessation of payment of an incentive to CHWs and VHWs in these communes. Amongst those born in routine communes, 98% in Quang Xuong and 24% in Ngoc Lac received dose-1 in the first week of life, and in control communes, 33% in Quang Xuong and 6% in Ngoc Lac.

Following the causal diagram above, two proposed major influences on dose-1, district and strategy, were examined more closely. Linear regression showed that both were strongly related to dose-1 (for district, $P < 10^{-3}$; for strategy, $P < 10^{-3}$). The influence of strategy remained when district was removed from the model ($P < 10^{-3}$) and in another model examining whether district was a predictor for strategy, no interaction was observed ($P = 0.96$). These results confirmed that the ideal, routine and control strategies genuinely differed from each other in relation to dose-1, but also that district was an important influence on this variable.

Immunogenicity of the vaccine used

The vaccine produced at NIHE appears to be immunogenic under field conditions. The overall immunogenicity of the vaccine (any anti-HBs detected amongst all 1106 infants) was 81.5 (79.1-83.7)%. Recalling that only HBsAg-negative infants were tested for anti-HBs, on qualitative testing, 901 (87.2 (85-89.2)%) of the 1033 infants so tested had detectable antibody. These 901 were further tested for a quantitative level of anti-HBs. Amongst the 864 for whom there was sufficient serum for this to be possible, 858 (99.3 (98.4-99.7)%) (or 77.6 (75-80)% of all 1106 surveyed) had a protective level of antibody ($\geq 10\text{mIU/ml}$). The GMT of these 858 infants was 121 (95% c.i.: 111.2 – 133.8). Excluding the 37 with insufficient serum to have both types of anti-HBs testing, $858/(1033 - 37 = 996) = 86.1(83.8-88.2)\%$ of non-infected infants had protective levels of antiHBs.

The GMT of anti-HBs levels by group and strategy are presented in Table 4A. Anti-HBs titres are also depicted on two dot-plot graphs (Figures 9 and 10) in Appendix 8. As their distribution was heavily skewed, the natural logarithm of these titres was plotted. There was an upward trend in anti-HBs across the strategies from ideal (GMT = 109mIU/ml) to routine (116mIU/ml) to control (135mIU/ml). Similarly, there were differences between Quang Xuong (100mIU/ml), and Ngoc Lac (150mIU/ml), and differences by strategy within the two districts, and by district within the three strategies. However, differences by strategy within the districts were generally small.

Linear regression analysis of these raw anti-HBs titres confirmed that at the time of sampling, infants in control communes had higher titres than those in ideal ($P = 0.02$), and in control than routine ($P = 0.04$) and those in Ngoc Lac had higher titres than those in Quang Xuong ($P < 0.001$). No other variable (day of dose-1, sex, infant's age or mother's age) was important in this model.

Two known influences on anti-HBs titre were explored: the delay between doses two and three (Table 3) and the delay between dose-3 and sampling. The length of this latter delay is shown in Table 4. In Table 4A, the actual GMT of anti-HBs amongst infants receiving

three doses of vaccine is shown by district and strategy, and also the GMT predicted by extrapolating from the group with the shortest delay (from the spreadsheet at <http://www2.stat.unibo.it/palareti/vaccine.htm>) (Honorati MC, Palareti A et al, 1999). The length of the delays (Table 4) generally reflects the differences in dose interval shown in Table 3. There are differences between the actual and predicted GMT by group (Table 4A).

Differences in the delay between dose-3 and the date of sampling by district and strategy (Table 4) were assessed using t-tests. The mean delay in Quang Xuong was 324 days, and in Ngoc Lac 258 days, leaving less time for antibody decay before the survey ($t = 6.0, P < 10^{-6}$). By strategy, the median delay was not longer in the ideal (311 days) than routine (291 days) ($t = 1.5, P = 0.14$) but tended to be longer in ideal than control (284 days) communes ($t = 1.8, P = 0.07$), but not in routine than control communes ($t = 0.5, P = 0.65$).

More important in explaining the differences in GMT across the groups is the distribution of median dosing times between the two districts and across the three strategies (Table 3). Analyses for differences using the Wilcoxon rank-sum test are tabulated in Tables 3A and 3B. The delays between the first and second doses in routine and control communes, and between the second and third doses and the first and third doses in all communes were significantly shorter in Quang Xuong. The significantly longer intervals (particularly between doses-2 and -3) in Ngoc Lac were the most likely reason for the higher anti-HBs titres in this district (Hadler SC, de Monzon MA et al., 1989), (West DJ, 1993), (Moullia-Pelat JP, Spiegel A et al, 1994). Because of this lack of comparability in gaps between doses across the groups, no attempt was made to apply a correction for the delay between dose-3 and sampling to individual infants' results.

Table 4: Mean delay (in days \pm 95% c.i.'s) between dose-3 and sampling amongst infants who had received three doses of HepB vaccine, by district and strategy

Strategy	District		
	Quang Xuong	Ngoc Lac	Both districts
Ideal	321 \pm 12	300 \pm 14	311 \pm 9
Routine	328 \pm 9	246 \pm 16	291 \pm 10
Control	323 \pm 12	208 \pm 21*	284 \pm 12
All infants in district	324 \pm 6	258 \pm 10	296 \pm 6

*The titre of this group was used as the baseline

Table 4A: Geometric mean titre (GMT) of anti-HBs with 95% c.i.'s and tests for differences in GMT within and between districts and strategies, and predicted GMT, amongst infants who had received three doses of HepB vaccine

District and strategy		GMT (raw)	Predicted GMT [^]	Statistical comparisons (using anti-ln of GMT and c.i.s)	
District	Quang Xuong	100 (88-112)	85	Between (B/w) districts	
	Ngoc Lac	150 (128-175)	124	t = 2.92, P < 0.01	Quang Xuong: ideal - routine
Strategy	Ideal	109 (92-130)	87	B/w districts: ideal	t = 0.72, P = 0.47
	Routine	116 (101-134)	102	t = 1.77, P = 0.08	QuangXuong: routine - control
	Control	135 (111-163)	106	B/w districts: routine	t = 0.53, P = 0.59
Quang Xuong	Ideal	85 (68-106)	87	t = 1.32, P = 0.19	Quang Xuong: ideal - control
Ngoc Lac	Routine	142 (109-186)	96	B/w districts: control	t = 1.18, P = 0.24
Quang Xuong		100 (82-121)	84	t = 1.24, P = 0.22	Ngoc Lac: ideal - routine
Ngoc Lac		141 (114-174)	135	B/w strategies: ideal - routine	t = 0.04, P = 0.97
Quang Xuong	Control	114 (93-140)	86	t = 0.42, P = 0.67	Ngoc Lac: routine - control
Ngoc Lac*		189 (127-283)	189	B/w strategies: routine - control	t = 0.73, P = 0.47
				t = 0.86, P = 0.39	Ngoc Lac: ideal - control
			B/w strategies: ideal - control	t = 0.65, P = 0.52	
			t = 1.1, P = 0.27		

*The titre of this group was used as the baseline for adjustment of others.

[^]Allowing for decay in antibody between dose-3 and bleeding, in comparison to the Ngoc Lac control group, using the spreadsheet at <http://www2.stat.unibo.it/palareti/vaccine.htm>

The effect of exposure to ambient temperature on immunogenicity

The survey also sought to more closely examine the prevalence of anti-HBs and GMT amongst infants receiving heat-exposed vaccine for dose-1 in comparison to infants receiving all doses of vaccine kept in the cold chain, and also whether the duration of storage of dose-1 outside the cold chain affected these outcome variables.

In comparison to infants in control communes, prevalence of a protective level of anti-HBs did not vary either overall across the strategies or between districts or across groups of infants in ideal and routine communes who received dose-1 of vaccine stored for successively longer periods outside the cold chain (Table 5).

Recalling that vaccine was delivered to ideal and routine communes only once a month, usually on the 15th or 16th of the month, Figure 11 shows the anti-HBs titres of all infants in these communes according to the number of days dose-1 had been kept outside the cold chain. It also shows a line representing the median titre for all infants receiving dose-1 on each day. There was no visible decrease in these medians amongst infants who received dose-1 stored outside the cold chain for closer to 1 month than for those who received it closer to the time of vaccine removal from cold storage. The slope of the line of best fit across these daily medians was -0.0045 degrees, confirming no change across the days.

It was not possible to assess for possible differences in GMT amongst infants born in the hot summer months of June – August and those born in the cooler months of December – February (Table 1), because of the obvious difference in the delay between receipt of dose-3 and the time of the survey. However, differences in GMT amongst the same groups of infants are tabulated in Table 5A (raw data). Statistical comparison of GMT between infants in Quang Xuong control communes (who received all three doses of vaccine stored cold) and those in the same district whose vaccine was stored outside the cold chain for at least two weeks revealed no difference. A similar comparison was not attempted for all or only Ngoc Lac infants because of the widely differing median days for each dose, inferred above to impact on anti-HBs levels, and also on the delay in

sampling, which could not be accounted for in this analysis for the same reasons as explained for Table 4A above.

Table 5: Prevalence* (in percent, with 95% confidence intervals) of a protective level of anti-HBs after three doses of HepB vaccine amongst infants in control communes, and amongst infants in ideal and routine communes according to the number of days of heat-exposure for dose-1, and chi-square tests for difference

Denominator	Control communes	Ideal and routine communes: days of storage outside the cold chain		χ^2	P
		1 - 14	15 - 31		
All infants	77.9 (72.4 - 82.7) (n = 271)	83.6 (78.4 - 88.0) (n = 250)	82.7 (78.9 - 86.1) (n = 452)	3.5	0.17
Quang Xuong	78.2 (71.4 - 84.0) (n = 179)	83.7 (77.3 - 88.9) (n = 172)	83.5 (77.7 - 88.3) (n = 206)	2.1	0.35
Ngoc Lac	77.2 (67.2 - 85.3) (n = 92)	83.3 (73.2 - 90.8) (n = 78)	82.1 (76.7 - 86.7) (n = 246)	1.3	0.52

*A positive result was assumed for the small number of infants from whom there was insufficient blood to test quantitatively for anti-HBs; these infants were equally distributed across the groups

Table 5A: GMT (with 95% confidence intervals) of anti-HBs after three doses of HepB vaccine amongst infants in control communes, and amongst infants in ideal and routine communes according to number of days of heat-exposure for dose-1, and t-tests for difference

Denominator	Control communes	Ideal and routine communes: days of storage outside the cold chain		Statistical comparison [^]
		1 - 14	15 - 31	
All infants	135 (111-163)	111 (91-135)	115 (100-131)	B/w QX* infants: control v 15-31 days outside the cold chain t = 0.84, P = 0.40
Quang Xuong	114 (93-140)	93 (73-118)	94 (78-113)	
Ngoc Lac	189 (127-283)	160 (112-231)	136 (113-164)	

*only QX infants are compared as the dose intervals across the three strategies are roughly the same

[^]Using anti-ln of GMT and c.i.'s

Efficacy of the vaccine

Amongst the 1106 infants sampled, 6.5% were HBsAg +, compared to 12.5% amongst 536 same-aged infants in the same communes at baseline, a reduction of 48%. Table 6 shows the overall, district- and strategy-specific rates of HBsAg in this survey, as well as the rates amongst those receiving dose-1 on day 0, days 0 - 2 and 0 - 6 and after day 6, and the reductions since baseline. The crude risk ratio of being HBsAg + for all infants

vaccinated after day 0 as compared to those vaccinated on the day of birth was 2.45 ($Z = 2.41, P = 0.02$). For infants receiving dose-1 on days 0 – 2, this ratio was 1.58 ($Z = 1.56, P = 0.12$), and for those receiving it on days 0 – 3, the ratio was 1.61 ($Z = 1.61, P = 0.11$). Beyond this, the risk ratio decreases. Accordingly, with these crude statistics, this survey could only verify statistically the benefit of a birth dose if dose-1 was given on the day of birth. Although there is a suggestion of benefit for infants vaccinated up to day 3, beyond day 0, there was no “significant” difference in the odds of being HBsAg + amongst infants vaccinated on or before that day, compared to those vaccinated after that day.

Table 6: Comparative rates of infection (percent HBsAg + with 95% c.i.'s^*) at baseline and in this survey, by district, strategy and time of dose-1, and percent decrease compared to baseline

	Overall			Quang Xuong			Ngoc Lac		
	N	HBsAg+	Decrease	N	HBsAg+	Decrease	N	HBsAg +	Decrease
Baseline (Infants)	536	12.5 (9.9-15.7)	-	275	8.7 (5.8-12.8)	-	261	16.5 (12.3-21.7)	-
Routine	1106	6.5 (5.2-8.2)	48*	566	5.0 (3.4-7.2)	43	540	8.2 (6.1-10.9)	51
Ideal	330	5.5 (3.4-8.7)	56	172	4.1 (1.8-8.6)	53	158	7.0 (3.7-12.5)	58
Maternal	418	6.0 (4-8.8)	52	207	4.4 (2.2-8.4)	49	211	7.6 (4.6-12.3)	54
Control	358	8.1 (5.6-11.6)	35	187	6.4 (3.5-11.2)	26	171	9.9 (6-15.6)	40
Dose-1 d.0	259	3.1 (1.5-6.2)	75	236	3.0 (1.3-6.3)	66	23	4.4 (0.2-24)	73
Dose-1 d.0-2	410	4.9 (2.8-7.1)	61	342	4.1 (2.4-6.9)	53	68	9.7 (4.2-19.9)	41
Dose-1 d.0-3	477	5.0 (3.3-7.5)	60	375	4.0 (2.3-6.7)	54	102	8.8 (4.4-16.5)	47
Dose-1 d.0-6	619	6.1 (4.4-8.4)	51	434	4.6 (2.9-7.1)	47	185	9.7 (6-15.1)	41
Dose-1 >d.6	487	7.0 (5-9.7)	44	132	6.1 (2.9-12)	30	355	7.3 (4.9-10.7)	56

*Percent decrease from relevant baseline figure (from Chapter 3) in row one; d. = day after birth

Using more sophisticated statistics further clarified the relationship of timing of the birth-dose and infection, tending to verify its importance. Again referring to the causal diagram, the influence of six variables (day of dose-1, strategy, district, infant’s age, sex and also mother’s age) on infants’ HBsAg status was assessed by MLR. In this case, the three strategies and both districts were included as separate variables, although the analysis omitted the ideal strategy as the one with which routine and ideal were

compared, and omitted Quang Xuong in order to compare children there with those in Ngoc Lac. The results of all the MLR's reported are shown in Tables 7 and 7A.

In the first assessments made, dose-1 was defined as vaccination on day 0. Backward selection was first used to select which might be included in a final model of predictors on HBsAg status. The selection was tried using both the datasets with actual mother's age ($n = 935$) and that including imputed values for missing mother ages ($n = 1104$). In both cases, only dose-1 was associated with child HBsAg status. In full MLR models including all variables, as expected, only dose-1 seemed to be associated with HBsAg, although the small number of HBsAg + children may have played a role in the P-values not reaching significance. For the model using actual mother's age ($n = 957$), the odds of a child being HBsAg + if first vaccinated against HBV on day 0 were 0.47 ($P = 0.10$), compared to if vaccinated later. For the model including imputed mother ages ($n = 1104$) the odds were 0.49 ($P = 0.10$). Mother's age, imputed or actual, was not associated with infant HBsAg status, either in these full models or in simple models examining the association of these values alone with infant HBsAg status ($P = 0.52$ and $P = 0.56$ respectively). In addition, the ORs of all the other variables changed only very slightly between the two full models assessed, so a third model excluding mother's age altogether was assessed, and again confirmed that only dose-1 showed a possible association with infant HBsAg status ($OR = 0.50$, $P = 0.11$). Finally, given that the epidemiology of HBV favours loss of HBeAg and later HBsAg amongst chronic carriers over time, categorising of mothers by actual age rather than including mother's age as a continuous variable in a regression model was attempted. Although the crude frequency of HBsAg amongst HBsAg + infants of mothers aged 20 years or less (9.1%) seemed higher than amongst mothers aged 21 – 30 (5.5%) or >30 years (6.9%) ($P = 0.37$), inclusion of variables for these categories in a regression model with dose-1 = day 0 showed no influence on infant infection. No other variable approached significance in these models (Table 7), and for each, goodness of fit was acceptable ($P > 0.05$).

In considering the influence of dose-1 defined differently, the influence of the same variables on HBsAg was assessed, again using backwards selection first, followed by

MLR, with the same outcome (Table 7). In these MLR models, only the imputed mother age variable was included.

Three models are reported, varying dose-1 from days 0 – 2, days 0 – 3 and days 0 – 6. Again, in each case, the goodness of fit for these models was acceptable. In the first (dose-1 = days 0, 1 or 2), the odds of children being HBsAg + in Ngoc Lac were 1.70 times those in Quang Xuong (P = 0.07), and the odds of this in control communes was 1.54 (P = 0.21).

Table 7: Odds ratios (with 95% c.i.'s) of all infants in the original 18 communes being HBsAg+ according to independent variables in different regression models varying day after birth of first dose of HepB vaccine

Independent variable	Independent variable							
	No. in model	Day of dose-1	Routine strategy compared to ideal	Control strategy compared to ideal	Ngoc Lac compared to Quang Xuong	Male sex compared to female	Age	Mother's age
1 day 0 actual mother's age	957	0.46 (0.9-1.14)	1.14 (0.59-2.21)	1.37 (0.62-3.03)	1.44 (0.77-2.69)	1.23 (0.72-2.11)	0.97 (0.86-1.08)	0.98 (0.92-1.04)
1 day 0 imputed mother's age	1104	0.49 (0.21-1.14)	1.10 (0.53-1.91)	1.32 (0.69-2.52)	1.40 (0.82-2.40)	1.12 (0.69-1.81)	0.95 (0.87-1.04)	0.96 (0.92-1.03)
1 day 0 missing mother's age	1104	0.50 (0.22-1.16)	0.98 (0.52-1.86)	1.29 (0.68-2.44)	1.42 (0.83-2.42)	1.12 (0.70-1.82)	0.95 (0.86-1.04)	
1 day 0-2 imputed mother's age	1104	0.95 (0.48-1.87)	1.10 (0.58-2.09)	1.54 (0.79-3.05)	1.70 (0.96-3.02)	1.13 (0.70-1.83)	0.95 (0.87-1.04)	0.97 (0.92-1.03)
1 day 0-3 imputed mother's age	1104	0.96 (0.50-1.87)	1.10 (0.57-2.11)	1.54 (0.75-3.15)	1.71 (0.96-3.03)	1.13 (0.70-1.84)	0.95 (0.87-1.04)	0.98 (0.92-1.04)
1 day 0-6 imputed mother's age	1082	0.66 (0.34-1.28)	1.32 (0.62-2.60)	2.12 (0.97-4.64)	2.12 (1.22-3.70)	1.14 (0.71-1.85)	0.95 (0.87-1.05)	0.98 (0.92-1.04)
1 day 0-6 missing mother's age	941	0.47 (0.19-1.15)	1.18 (0.61-2.30)	1.39 (0.63-3.08)	1.48 (0.79-2.76)	1.23 (0.72-2.11)	0.98 (0.88-1.09)	0.55* (0.22-1.38) 0.65** (0.22-1.93)

*mother's age 21-30 years, compared to < 21; **mother's age >30 years, compared to < 21.

In the next model (dose-1 = days 0, 1, 2 or 3), corresponding to the interval that the Vietnam EPI has chosen for monitoring birth dosing (within or after three days after birth), the odds of children being HBsAg + in Ngoc Lac were 1.71 times those in Quang Xuong ($P = 0.07$), and the odds of this in control communes were again 1.54 ($P = 0.24$).

Table 7A: Odds ratios (with 95% c.i.'s) of infants delivered by HBsAg+ mothers in all communes being HBsAg+, according to independent variables in different regression models varying day after birth of first dose of HepB vaccine

Regression model*	Number in model	Independent variable							
		Day of dose-1	Routine strategy compared to ideal	Control strategy compared to ideal	Ngoc Lac compared to Quang Xuong	Male sex compared to female	Age	Mother's age	Mother HBeAg+, compared to HBeAg-
Dose-1 = day 0	97	0.95 (0.2-4.1)	2.02 (0.4-10.3)	20.86 (1.2-350.9)	1.93 (0.8-4.6)	1.90 (0.7-5.5)	0.97 (0.8-1.2)	0.97 (0.8-1.1)	19.2 (6.1-60.1)
Dose-1 = day 0,1 or 2	97	0.63 (0.2-1.9)	1.96 (0.4-9.4)	15.95 (1.0-258.2)	1.86 (0.8-4.2)	1.86 (0.6-5.4)	0.96 (0.8-1.2)	0.97 (0.8-1.1)	19.8 (6.-62.7)
Dose-1 = day 0-3	97	0.42 (0.1-3.3)	3.23 (0.5-20.1)	15.49 (0.6-422.2)	3.02 (0.5-19.0)	2.02 (0.4-9.4)	0.97 (0.7-1.3)	0.90 (0.7-1.1)	42.77 (7.6-240.1)
Dose-1 = day 0-6	97	N/A	2.00 (0.4-9.6)	N/A	1.93 (0.8-4.3)	1.90 (0.7-5.4)	0.97 (0.8-1.2)	0.97 (0.8-1.1)	18.85 (6.0-59.0)

* All models used imputed mother's age

N/A: there were too few infants in the comparison group for these variables to be included in this model

Finally, in the model with dose-1 on any of days 0 – 6, the odds of infants first vaccinated on or before day 6 being HBsAg +, in comparison to those first vaccinated on / after day 7, were 0.66, ($P = 0.22$), but again Ngoc Lac infants were more likely to be HBsAg + than those in Quang Xuong ($OR = 2.12$, $P < 0.01$), and control infants more likely than ideal ($OR = 2.12$, $P = 0.06$).

Although, as mentioned, these models did not look specifically for differences between control and routine infants' risk of being HBsAg +, the crude data and the analyses reported above strongly suggest there would be even smaller differences than those already reported for control compared to ideal infants' risks.

Infants in Ngoc Lac seemed to be more likely to be HBsAg + in several of the models reported, including those where the dose-1 variable was 0 – 2, 0 – 3, and certainly 0 – 6 days (Table 7). To examine the influence of the other variables in Ngoc Lac alone, the regression models were run again, removing Quang Xuong infants. In these analyses, none of the independent variables, including strategy and all the different options for dose-1, showed even a mild association with infants' HBsAg status, although numbers of HBsAg + infants in each category were small.

Protective efficacy amongst infants of infected mothers

Using the screening test, a total of 97 HBsAg + mothers of infants vaccinated in the first week of life were identified in the 18 original and 8 additional communes surveyed. Amongst these 97 mothers, 35 (36.1%) were also positive for HBeAg. Table 8 presents the outcome amongst infants of these women. Overall, infants of HBsAg + mothers were not well protected from infection by the vaccine used, particularly if the mother was also HBeAg +. The rate of infection amongst this group was 77.1%, and that amongst infants of HBsAg + / HBeAg-negative women was 19.4%.

Table 8: Infection status amongst those infants of HBV-infected mothers vaccinated in first week of life, according to mothers' HBeAg status, in all 26 communes surveyed

Infant's HBsAg status	HBeAg status amongst HBsAg + mothers		Total
	Positive	Negative	
Positive	27 (77.1)	12 (19.4)	39 (40.2)
Negative	8 (22.9)	50 (80.6)	58 (59.8)
Total	35 (100)	62 (100)	97 (100)

Assuming that 80% of unvaccinated infants of HBeAg + mothers become infected with HBV (Chapter 3), if the 35 such infants in this study had not received any HepB vaccine, 28 infants would have been infected. As 27 of them were in fact HBsAg +, the PE of the vaccine used amongst infants who received a birth dose within a week of delivery was thus $1/28 = 3.6\%$. Similarly, assuming that 40% of unvaccinated infants of HBsAg +

women (regardless of their HBeAg status) will be infected (Chapter 3), and noting the observed infection rates amongst infants in this research (40.2%), the overall PE of the vaccine used in the same group was 0%. Categorisation of infants according to dose-1 explains why a birth dose on day 0 was associated with a lower rate of HBsAg in spite of this poor PE. Only six of 21 infants (28.6%) of HBsAg + mothers in the group vaccinated on day 0 were HBsAg +, resulting in a PE of $([40 - 28.6]/40) = 28.5\%$ - still low, but apparently enough to look different in crude and regression analyses. Categorisation with dose-1 on days 0 – 2 (PE = 13.8%) or 0 – 3 (PE = 9%) yielded progressively lower values, approaching the 3.6% noted overall.

Note that amongst the 8/35 infants of HBeAg + mothers who were not infected, only four (50%) developed anti-HBs (2 had titres between 30 and 70, and 2 above 2,500). The one of these four with the lowest titre was also anti-HBc +, suggesting resolving infection.

Regression analysis (Table 7A) was conducted on infants of all HBsAg + mothers, this time including mothers' HBeAg status as an independent variable. In a model with dose-1 = day 0, the influence of mothers' HBeAg status and control strategy on infants' HBV infection status were confirmed (for HBeAg + mothers, OR for HBV infection amongst their infants = 19.2, $P < 10^{-3}$; for "control infants" compared to ideal, OR = 20.9, $P = 0.04$), regardless of district, infants' age or mother's age. This association of mothers' HBeAg status and infant infection remained across other regression models in which dose-1 varied from 0 – 2, 0 - 3 and 0 – 6. The timing of dose-1 was not significantly associated with infant infection in any of these models. Only control strategy, in comparison to ideal, and being born in Ngoc Lac, showed a possible association with infection in some of the models, although confidence intervals were very wide (Table 7A).

Protective efficacy amongst other infants

The survey was also able to estimate the background risk of HBV infection amongst low risk infants surveyed. Table 9 shows the rate of infection amongst all the infants in the 18 original communes who received dose-1 in the first week of life, according to their

mothers' HBV infection status, assumed negative if their quicktest result was negative. It was not possible to include infants in the 8 other communes in this analysis, as the numbers of HBsAg-negative mothers there were not recorded. In addition, the Table does not differentiate between infants who received all three doses of vaccine or did not. Only 2.8% of infants of HBsAg-negative mothers were infected overall. However, 37.3% of infants of HBsAg + mothers were infected, a similar figure to the 40.2% of infants of HBsAg + mothers vaccinated in the first week of life in all 26 communes surveyed.

Table 9: Infection (%) and anti-HBs status amongst infants vaccinated in first week of life in the 18 original communes, according to mothers' infection status

Infant's HBsAg and anti-HBs status	HBsAg status amongst all mothers		Total
	Positive	Negative	
HBsAg +	22 (37.3)	16 (2.8)	38 (6.1)
HBsAg-negative	37 (62.7)	552 (97.2)	589 (93.9)
Total HBsAg	59 (100)	568 (100)	627 (100)
Anti-HBs + (≥ 10 mIU/ml) (amongst HBsAg-negatives)	24* (66.7)	465 (84.2)	
GMT of all anti-HBs	157	105.3	

*one infant in this group had insufficient serum to test for anti-HBs, so denominator = 36

The effect of exposure to ambient temperature on protective efficacy

In the same way as for immunogenicity, an assessment using MLR was made for the influence of vaccine exposure to ambient temperature on PE amongst infants of HBsAg+ mothers. For this, new variables representing the number of days or weeks vaccine was kept outside the cold chain were included, respectively, in two regression models, which otherwise included the same variables as for the models reported in Table 7A (using actual mothers' age). In both cases, the odds of infection were not significantly affected by exposure of vaccine to ambient temperature (OR for days outside the cold chain = 0.96, $P = 0.164$; OR for weeks outside the cold chain = 0.70, $P = 0.11$). Mothers' HBeAg status was again the strongest predictor of infection amongst infants (in both cases OR = 16.8, $P < 0.001$); indeed in these models no other variables approached significance. Interestingly, the ORs for the two new variables are reported such that the trend was for a

longer period outside the cold chain to be *less* associated with infection. No explanation other than chance is offered for this, although vaccine freezing in control communes may have been responsible.

HBV exposure and possible anti-HBs boosting

Recalling that HBsAg + samples were not tested for anti-HBc, 27/1033 (2.47%) of the HBsAg-negative infants in the 18 original communes were positive for anti-HBc, suggesting either exposure without current infection, or the presence of maternal antibody. Twelve (44.4%) of these infants were also positive for anti-HBs. An attempt was made to use MLR to assess for maternal antibody in these children by examining influences on infants' anti-HBc status, in a model using actual mother's age and assuming perfect correlation between HBsAg and anti-HBc (hence anti-HBc in $72 + 27 = 99$ infants). Recalling that MLR did not show an association between the infants' age and their HBsAg status, this analysis also did not suggest an association between infants' anti-HBc status and age (OR = 0.96, P = 0.41), making it less likely that the anti-HBc was passively acquired maternal antibody. Receiving dose-1 on day 0 was associated with a lower risk of exposure to the virus as measured by anti-HBc (OR = 0.43, P = 0.03), as would be expected given these infants' lower HBsAg + rate.

The possibility of natural boosting of anti-HBs was also assessed amongst the children who were positive for both anti-HBs and anti-HBc, assuming their anti-HBc was naturally acquired, not passively from the mother. Although the number was small, there was no evidence (P = 0.34) of higher anti-HBs titres amongst these infants, compared to those negative for anti-HBc.

Infection amongst CBAW

Table 10 presents the data on HBV infection and exposure amongst the CBAW surveyed. Rates were lower than those measured at baseline (Chapter 3), particularly for HBsAg.

Table 10: Rates of HBV infection and exposure amongst women of child-bearing age by district

	Quang Xuong		Ngoc Lac		Total	
	N	%	N	%	N	%
Total	266	49.9	267	50.1	533	100
HBsAg +	22	8.3 (4.9-11.6)	34	12.7 (8.7-16.8)	56	10.5 (7.9-13.1)
HBeAg +	6	27.3 ^a (7.1-47.5)	13	38.2 ^a (21-55.4)	19	33.9 ^a (21.1-46.7)
Exposure^b	192	72.2 (66.8-77.6)	204	76.4 (71.3-81.5)	396	74.3 (70.6-78)

a: Expressed as percentage of those HBsAg +. b: HBsAg + or anti-HBc+ or anti-HBs+. N= number

Discussion

This is the first report on the outcome of a program of immunisation against HBV in Vietnam. It provides information on the operational feasibility of the program in rural areas as opposed to the predominantly urban areas in which HepB vaccine was at the time of the project available as part of the EPI. It also addresses the feasibility of the administering a birth-dose of HepB vaccine, which has not previously been attempted in this country. The survey also assessed the immunogenicity of the indigenous vaccine under field conditions, including when the first dose is kept outside the cold chain for up to one month, and the relative efficacy of a schedule including a birth-dose of this vaccine in reducing rates of HBV infection, in comparison to delaying the first dose until later in life. More specifically, it examined the relative PE of the vaccine according to how many days dose-1 is delayed after birth and whether exposure of the vaccine to ambient temperature affected its PE. It also identified an interesting disparity between this vaccine's immunogenicity and PE.

Operational issues

This research concludes that in flat, densely populated districts such as Quang Xuong, which characterises a substantial proportion of Vietnam's more heavily populated districts, introduction of HepB vaccine is feasible, and that immunisation at or soon after birth should not be difficult. Even in routine communes, where no incentive was paid but HW education and community mobilisation was undertaken, administration of dose-1 in the first days of life was almost universal, barely differing from ideal communes in which

CHWs and VHWs were initially paid to register newborns, immunise them early and keep a village-based record of infants' EPI status. Moreover, and very interestingly, the median number of days after birth in which infants born in Quang Xuong control communes received dose-1 was only 15, suggesting that most infants in this district got vaccine on the first EPI day after delivery. This is important, as following project training on how to organise their local EPI to ensure highest and timeliest coverage for all antigens, most CHSs in Quang Xuong now conduct the monthly EPI day at the CHS (Chapter 7). Either mothers were bringing very young infants out for vaccination or CHWs were visiting them at home on EPI day to vaccinate them against HBV as early as possible, as required by the new National EPI schedule for HepB vaccine (Chapter 1). This augurs extremely well for a birth dose in a future EPI in which HepB vaccine is available at CHSs every day in such districts, as not only will infants born at the CHS be able to be immunised on the day of birth, but it seems that CHWs are willing to visit infants born at home too, provided the birth is notified and the local community is aware and supportive.

By contrast, it is clear that amongst those of Vietnam's districts represented by Ngoc Lac, in which the population is more dispersed, the terrain more challenging, the rate of home birth much higher (Chapters 2 and 7) and where cultural beliefs may impinge on practices of newborn care, more effort will be required to assure high coverage of a birth dose of HepB vaccine. Although 83% of infants in ideal communes there received a birth dose, the median time of administration was on the fourth day after delivery, no doubt influenced by the high rate of home birth and the delay in notification of the birth to the CHS by the VHW. Further, in routine communes in this district, birth-dose coverage (dose-1 on days 0 – 6) fell to only 24%, suggesting that one or both of the extra inputs (financial and programmatic) made in ideal communes will be required for a successful birth-dose program in such districts. The fact that the rate of early vaccination in ideal communes did not diminish after the incentive was stopped suggests that the programmatic differences, primarily the birth-register / EPI record form (Appendix 9), made a sustained difference to their capacity to follow a birth-dose strategy. In Ngoc Lac control communes, the median for dose-1 was 65 days, reflecting either the lower

frequency of EPI contact there or reluctance of mothers in these communes, which had not benefited from the community mobilisation conducted elsewhere, to take new infants out; or of HWs, who had not had the HBV-specific training conducted elsewhere, to visit them at home. In addition, the long delays between doses and very late administration of dose-3 in these communes attest to the effect of HW education, community mobilisation and regular supervision on the conduct of the EPI in general. If introduction of HepB vaccine is accompanied by some form of refresher training and increased monitoring and supervision of the EPI activities of CHWs (Chapter 7A), as would befit the introduction of such a relatively expensive vaccine, it is likely that there will be spill-over effects on the whole program (Ruff TA, Gertig DM et al, 1995).

Immunogenicity of the local vaccine and the effect of exposure to heat

SIAMC previously evaluated the immunogenicity of the Vietnamese, plasma-derived HepB vaccine in 2 different doses and compared it to that of 2 Korean vaccines (Chapter 5). In that trial, after vaccine storage in experimental (ideal) conditions and administration of all doses to each infant by the same nurse or doctor, and using a 2.5µg dose, a protective level of antibody was found in 88.5% of all infants and 85.9% of infants whose mothers were seronegative for all HBV markers. These were not as high as the percentages amongst those given 5µg doses of this vaccine or the Korean vaccines, but compared well to some (Andre FE & Zuckerman AJ, 1994), (Xu ZY, Liu CB et al, 1985), (Lo KJ, Tsai YT et al, 1985) but not all other trials of low-dose and locally produced (Kyi KP, Oo KM et al., 2002) varieties of HepB vaccine. In the current assessment of the same 2.5µg vaccine under field conditions, with the associated risks of inadvertent freezing of vaccine (which can render it impotent), variable standard injection technique, as was found to be important during a field trial in Thailand (Dr B-A Biggs, co-investigator, personal communication) and a wide variation in scheduling, an overall prevalence of a protective level of anti-HBs was found in 77.6%, and 86.1% if HBsAg + infants were excluded. The comparability of the 85.9% immunogenicity (anti-HBs \geq 10 mIU/ml) in (the 8-month old) infants of completely seronegative mothers in the hospital-based trial (Chapter 5), and the 84.2% amongst the group of (on average, slightly older)

infants whose mothers were known to be HBsAg-negative (Table 9) in this survey, suggests several things:

- that the current study was not affected by the kinds of operational risks listed above
- that the vaccine's measurable immunogenicity is maintained into the second year of life and
- that the use of the vaccine stored outside the cold chain for dose-1 did not impinge on its immunogenicity.

Indeed, the prevalence of anti-HBs in this field trial did not differ by district or strategy, regardless of whether or not and for how long the first dose had been stored outside the cold chain, and regardless of the immunisation schedule (Table 5, Figure 11). It is possible that maternal anti-HBs was present in some of the youngest infants sampled in this survey, but not in more than a few percent.

This encouraging result adds to the existing literature on use of HepB vaccine outside the cold chain (Anonymous, 1991), (Otto BF, Suarnawa IM et al, 1999), (Just M & Berger R, 1988), (Van Damme P, Cramm M et al, 1992), (Galazka A, Milstien J et al, 1998), and expands upon certain parameters not discussed previously. In particular, as well as providing some information about the range of ambient temperatures to which dose-1 of the vaccine was exposed (Table 1), this research has shown that neither the prevalence of anti-HBs nor the GMT induced varied according to the duration of this exposure, up to one month. This would concur with the existing scientific information on heat stability of HepB vaccine reviewed in Chapter 4, and provides further field-based support for the introduction of a birth-dose of HepB vaccine, even in rural areas where refrigeration may not be widely available.

Longer intervals between doses of HepB vaccine, particularly doses 2 and 3, have regularly been shown to yield higher titres of antibody in vaccine recipients (Mahoney FJ & Kane M, 1999), (Hadler SC, de Monzon MA et al, 1989), (West DJ, 1993), (Mouliapelat JP, Spiegel A et al, 1994), although others' findings do not support this (Inskip HM, Hall AJ et al, 1991). A shorter interval between the last dose of vaccine and the collection of blood allows less time for antibody decay. However, this research concludes that the

differences in the titres of anti-HBs observed between the infants vaccinated by the different strategies and in different districts may be explained mainly by differences in the interval between doses, as the differences in GMT between the different groups of infants were greater than could be explained by the delay between dose-3 and sampling.

Protective efficacy of the vaccine and the effects of timing of dose-1 and exposure to heat

The seroprevalence data in this report should be compared to other reports on the introduction of HepB vaccine in countries of high HBV prevalence in Southeast Asia and elsewhere. Many such reports from Taiwan, where HBsAg rates amongst 1 – 2 year olds have fallen from 10.7% at baseline (Hsu HY, Chang MH et al, 1986) to 1.7% amongst a cohort of 6 year olds vaccinated as infants (Hsu HM, Lu CF et al, 1999), attest to the efficacy of their program (Huang K & Lin S, 2000), (Chen HL, Chang MH et al, 1996). A demonstration project in Indonesia (Ruff TA, Gertig DM et al, 1995), which nation is currently phasing in the national introduction of HepB vaccine along lines similar to SIAMC's ideal strategy, achieved a reduction from 6.2% to as low as 1.4% amongst infants vaccinated within 7 days of birth, and another in Thailand where rates of home birth are lower than in Vietnam (Chunsuttiwat S, Biggs BA et al, 1997) achieved a reduction from 5.4 to 0.8%. Similarly, in areas as diverse as the Pacific, China, the Gambia, Alaska and Saudi Arabia, programs of vaccination against HBV have reported excellent success in diminishing the prevalence of infection to rates usually below 2%. As mentioned in Chapter 3, long term follow up of these programs, most of which commenced 10 or more years ago are now appearing in the literature, confirming the durability of this success (Wilson N, Ruff TA et al, 2000), (Mahoney FJ, Woodruff BA et al, 1993), (Ding L, Zhang M et al, 1993), (Liao SS, Li RC et al, 1999), (Viviani S, Jack A et al, 1999), (Harpaz R, McMahon BJ et al, 2000), (Al-Faleh FZ, Al-Jeffri M et al, 1999), (Whittle H, Jaffar S et al, 2002). However, with the exception of the report from Indonesia, there have been no other assessments of how the poorer developing countries of this region, particularly those with high rates of home birth such as Laos, Cambodia, and Vietnam, might best introduce HepB vaccine.

HBV infection in infancy may be considered in 2 phases: perinatal transmission from mother to infant, and post-natal horizontal transmission from mother, father, sibling or another. Many studies have shown the efficiency of mother-baby transmission, particularly if the mother is HBeAg + or has high levels of circulating HBV DNA (Beasley RP, Trepo C et al, 1977), (Lee SD, Lo KJ et al, 1986), (Okada K, Kamiyama I et al, 1976), (Ip HM, Lelie PN et al, 1989), (Burk RD, Hwang LY et al, 1994). However, the exact timing of infection is difficult to ascertain, and hence the theoretical benefit of an at-birth strategy over a control strategy as defined here cannot be precisely quantified. If a vaccine had 100% PE following at birth administration, virtually all HBV infection would be prevented amongst recipients, but the PE amongst others receiving it at a later time would be reduced by their rates of perinatal and post-natal exposure prior to immunisation.

Assuming a mid-range PE of 80% for vaccine-alone (without HBIG) against perinatal infection (Mahoney FJ & Kane M, 1999), (Poovorawan Y, Sanpavat S et al, 1992), (Xu ZY, Liu CB et al, 1985), (Wong VC, Ip HM et al, 1984) and that this applies to all infants immunised by day 6, a fall of around 80% amongst infants receiving dose-1 by then should have been seen, and lower falls for infants vaccinated subsequently. In fact, in comparison to baseline, an overall reduction of HBsAg positivity of 48% was found, ranging from 75% amongst infants vaccinated on day 0, to 61% amongst those vaccinated by day 2 and 51% by day 6 (Table 6). The size of the fall in each strategy was reasonably consistent across the 2 districts, with the exception of the control communes where the fall was greater in Ngoc Lac (40%) than in Quang Xuong (26%). However, although larger falls were seen in Quang Xuong infants vaccinated by days 2 or 6 than in Ngoc Lac, clearly vaccination after day 0 but before day 7 did not yield anything close to the 80% reduction in infection anticipated.

Infection rates for infants vaccinated on days 0 – 2 of life were 36% lower than in control communes in Quang Xuong, but virtually the same (2% lower) in Ngoc Lac. For those vaccinated on days 0 – 6, again there was a moderate reduction (28%) compared to those vaccinated at the first EPI contact in Quang Xuong but virtually no reduction (2%) in

Ngoc Lac. Analysis of these intervals was chosen because of their potential public health significance in various geographic locations of Vietnam. In districts like Quang Xuong, even for infants born at home, delivery of a birth-dose should be possible by day 2 after birth, allowing a day for the VHW to notify the birth and another for the CHW to come and administer it. In those like Ngoc Lac, the allowance for communication and travel must be longer.

To explain the lower than expected protection rates, it is helpful to refer back to the phasing of HBV exposure outlined above, and to consider that the infections observed either represent vaccine failures or infections amongst infants in whom vaccine was administered too late to protect them from exposure already sustained. Accordingly, as the reduction in infection amongst infants vaccinated in the first week of life was only 51%, rather than the 80% anticipated, a higher than anticipated rate of vaccine failure must be the major reason for the lower than anticipated reduction in HBV infection rates seen amongst infants in this study.

However, one major assumption relevant to this issue is that HepB vaccine is 80% effective in preventing infection for perinatal exposures if given any time up to 1 week after birth. In fact, the question of the exact timing dose-1 and the comparative PE of the vaccine after administration at different times after birth has not been assessed in the scientific literature, and most studies of the PE of birth-dose HepB vaccine have involved the additional use of HBIG. However, there is general agreement amongst the few studies including a delayed vaccine-only schedule. Infants in three reports from Taiwan (Lee SD, Lo KJ et al, 1986), Lee, 1989 in (Andre FE & Zuckerman AJ, 1994), (Goudeau A, Lo KJ et al, 1983), and in Indonesia (Ruff TA, Gertig DM et al, 1995) received vaccine alone after 7 days. In each of these 4 studies the PE was 50 - 57%. The only exception to this was a PE of 75% amongst another group of Taiwanese infants of HBeAg + women first vaccinated in their second week of life (Lo KJ, Tsai YT et al, 1985). With only the latter exception, the PE achieved with dose-1 beyond one week of age is well below the 70 - 95% found for vaccine-only regimens commencing in the first week of life (Mahoney FJ & Kane M, 1999), (Poovorawan Y, Sanpavat S et al, 1992), (Xu ZY, Liu CB et al, 1985),

(Wong VC, Ip HM et al, 1984). Accordingly, it appears that delaying dose-1 beyond 1 week reduces its PE against perinatally acquired infection by 13 – 45%. The results in this survey would suggest further that the earlier dose-1 can be given, the better the PE, with best results if it can be given on the day of birth. Although there was a trend downward in PE with increasing delay of dose-1, within the limits of this study, infants who received vaccine during week one but after day 0 were not significantly better off than those receiving vaccine at their first EPI contact. Regression analyses did suggest an influence of vaccination strategy, and also district, on infection rates in infants who received dose-1 after day 0 but before day 7, but the statistics were not impressive. Until further research clarifies this timing issue, this study supports the current WHO recommendation that the birth dose of HepB vaccine should be given “as soon as possible after birth, preferably within 24 hours” (Department of Vaccines and Biologicals, 2001), and questions whether costly and logistically difficult strategies to introduce birth-dosing without HBIG by outreach are worth the effort.

This research has identified a disparity between the Vietnamese vaccine’s apparent reasonable field immunogenicity, measured by the prevalence of anti-HBs and the GMTs achieved, and its PE, indicated by the high rates of infection amongst infants of infected mothers vaccinated in the first week of life. Indeed, the infection rate of 77.1% amongst infants of HBeAg + mothers approximates closely the middle of the 63 – 90% range of perinatal transmission from HBeAg + mothers to unvaccinated infants in the literature (Beasley RP, Trepo C et al, 1977), (Lo KJ, Tsai YT et al, 1985), (Okada K, Kamiyama I et al, 1976), (Stevens CE, Neurath RA et al, 1979), (Beasley RP, Hwang LY et al, 1981b), (Beasley RP, Hwang LY et al, 1983a), (Pongpipat D, Suvatte V et al, 1985). Similarly, the rate of infection amongst infants of HBsAg + / HBeAg-negative mothers (19.4%) also approximates the middle of the range of 0 – 30% (Mahoney FJ & Kane M, 1999), (Smego RA, Jr. & Halsey NA, 1987), and the overall rate (40.2%) is virtually identical to that identified previously, again in unvaccinated infants (Stevens CE, Beasley RP et al, 1975), (Goh KT, 1997). This means that the vaccine used, although immunogenic and effective in reducing infection rates amongst populations of infants (Table 6), has essentially zero PE for post-exposure vaccination in the perinatal context.

As indicated in Chapter 5, it seems rarely to protect infants from infection after very early exposure to HBV. Other studies have identified similar disparity between PE and immunogenicity (Wong VC, Ip HM et al, 1984) (Xu ZY, Liu CB et al, 1985), (Assateerawatt A, Tanphaichitr V et al, 1991), although not to this degree.

As already discussed in Chapter 4, the PE of HepB vaccine in the circumstances applying to infants exposed to the virus at or soon after birth must be a function of the relative antigenicity of the vaccine, the timing of its administration and the burden of infection to which the infant is exposed. This discussion has considered the second of these factors above. Regarding the first, unfortunately no definition for the antigenicity of different varieties of HepB vaccine exists, and because of differences in manufacturing techniques and it is not possible to equate dose in micrograms of HBsAg in a particular vaccine with its "potency" in terms of the rapidity and robustness with which it induces a protective antibody response. However, several previous studies have assessed the PE of vaccine-only regimens of immunisation against HBV including a birth dose (Andre FE & Zuckerman AJ, 1994). Although there is a trend towards higher PE amongst vaccines with a high antigenic mass, this is not universal (Mahoney FJ & Kane M, 1999), (Chotard J, Inskip HM et al, 1992), (Xu ZY, Liu CB et al, 1985).

The third factor influencing PE, the burden of exposure, is not influenced by the timing of dose-1 or the vaccine formulation. As mentioned in Chapter 4, the amount of exposure is usually measured in levels of HBV DNA or titre of HBsAg to which the infant is exposed (Stevens CE, Beasley RP et al, 1975), (Beasley RP, Trepo C et al, 1977), (Lee SD, Lo KJ et al, 1986), (Ip HM, Lelie PN et al, 1989), (Burk RD, Hwang LY et al, 1994). One of these reports (Lee SD, Lo KJ et al, 1986) strongly suggests that infants of mothers with progressively higher levels of HBV DNA are at progressively higher risk of becoming infected, regardless of receiving vaccine or HBIG at birth, presumably because the amount of infection acquired before or at birth overwhelms the capacity of the vaccine to induce an adequately rapid and robust active immune response. Another study (Ip HM, Lelie PN et al, 1989) found that this factor was not important if HBIG was administered, but the dose of HBIG used in that study (100 international units) was

double that used in the first. A third report confirms the relevance of maternal HBV DNA in vaccine PE (del Canho R, Grosheide PM et al, 1997), regardless of the administration of HBIG. In this case, the dose of HBIG given was 200 – 300 units.

Nothing written above suggests that the exposure of the vaccine to ambient temperature in this project has impacted upon its performance. Indeed, as noted in Chapter 5, even in ideal conditions the 2.5µg vaccine had a relatively poor PE, and the fact that its PE and immunogenicity were not affected by heat in the analyses reported in this Chapter argues against this. A more likely explanation for the poor PE reported here must involve a combination of the above 3 factors – vaccine antigenicity, timing of dose-1 (demonstrated here to influence PE) and burden of exposure relative to the first factor. The PE of the vaccine for subsequent exposure is not doubted, as indicated by the fact that overall, and despite the failure of almost 20% of all infants to produce antibody, almost 50% reductions in HBV infection rates were achieved. This supports Vietnam's earlier intention to push on with use of this vaccine until an affordable replacement became available, but in the current milieu of vaccine availability from the Vaccine Fund, it seriously questions the wisdom of Vietnam's intention to continue its use in 17 provinces (Appendix 1). At the least, an increase in the dose of the vaccine, as indicated in Chapter 5, would be recommended.

Methodological issues

Three methodological factors in this survey warrant brief discussion. First, it was assumed that mothers who tested positive on the HBsAg quicktest were positive at the time of delivery of their infant 9 – 18 months previously, and that all mothers who were HBsAg + at that time were still positive at the time of the survey. This test has been independently assessed to have a sensitivity of 99 – 100% and a specificity of 99.4 – 100% (WHO, 2000), (Lien TX, Tien NT et al., 2000). In fact neither of these assumptions is strictly correct, as apart from the possibly imperfect sensitivity of the test in a field situation (for which there is no data), there is a known rate of loss of HBsAg amongst HBV carriers which has been variously estimated at 0.5 - 1% per year (Huo TI, Wu JC et al., 1998), (Alward WL, McMahon BJ et al., 1985). In addition, it is possible

that some mothers who tested positive on the quicktest were in fact suffering from acute infection and were seronegative for HBV at the time of delivery. From the baseline serosurvey, an annual rate of exposure amongst persons aged 16 – 40 years of approximately 1% per year was estimated. Most of these infections would resolve within around 2 months, so on balance these two sources of error favour a net loss of HBsAg amongst mothers from the time of delivery, which would overestimate the rate of infection amongst infants of seronegative mothers and underestimate the PE of the vaccine.

Second, it was not possible to follow the HBsAg + infants identified in this survey for 6 months to determine whether their infection was chronic. HBV infection due to perinatal exposure yields carriage rates of 90%, but those acquired after birth resolve more often than this (Beasley RP, Hwang LY et al, 1981b), (Beasley RP, Hwang LY et al, 1982), (Beasley RP, Hwang LY et al, 1983b), (McMahon BJ, Alward WL et al, 1985), (Roumeliotou-Karayannis A, Tassopoulos N et al, 1985), (Edmunds WJ, Medley GF et al, 1993), (Hyams KC, 1995). From the baseline survey (Chapter 3), it was estimated that approximately 7.8% of infants are exposed to HBV post-natally, before the age of 18 months. Accordingly, some of the HBsAg + infants may have been suffering acute infection of no long-term consequence. Again, this would result in an underestimation of the PE of the vaccine used by a small amount.

Third, the influence of maternal anti-HBs in the above estimations of vaccine immunogenicity has been ignored. Chapter 5 showed previously in a group of younger infants that maternal antibody was certainly still present at 8 months in a proportion, and the literature on HBV serology suggests that a proportion will remain positive for maternally-derived antibody (either anti-HBs or anti-HBc) (Moullia-Pelat JP, Spiegel A et al, 1994), (Chen HL, Chang MH et al, 1996), (Beasley RP, Hwang LY et al, 1981b), (Stevens CE, Taylor PE et al, 1987), (Pongpipat D, Suvatte V et al, 1988), (Poovorawan Y, Sanpavat S et al, 1989), for 12 months or more. Whilst this may be true of some of the infants surveyed, and would have resulted in an overestimation of vaccine immunogenicity, this error will have applied equally to all groups of infants and does not

impinge on conclusions about comparative immunogenicity across groups and strategies. It does, however, result in a potential overestimation of this vaccine's immunogenicity in the field, again justifying an increase in its potency or replacement by a better vaccine.

Conclusion

This research yielded information highly relevant to the National EPI of Vietnam in the planning of its future strategy for immunisation against HBV. It suggested that at-birth immunisation is feasible in a majority of the nation, but that more input, probably both financial and programmatic, will be required in certain districts than others. It demonstrates that storage of the indigenous vaccine outside the cold-chain for up to 1 month for dose-1 does not reduce its immunogenicity nor affect its PE, but that the best results with this vaccine will be achieved if it can be administered on the day of birth. This strongly suggests that vaccine should be available in all hospitals and maternity units, regardless of the availability of refrigeration. In circumstances where immunisation on the day of birth is more difficult, the data suggest that the local vaccine in its current dosage will offer no protection against perinatal infection but will still be immunogenic. The benefits of a delayed "birth" dose with this particular vaccine are likely to be small relative to the potential cost. Follow up studies of the local vaccine in a formulation with higher antigenic mass, or of commercial vaccines considered to be protective and heat stable by their manufacturers, including the PE of other vaccines according to the delay in dose-1, are strongly recommended.

A follow up assessment of immunisation practices in two rural districts of Vietnam**Introduction**

In Chapter 2A, quantitative and qualitative information pertaining to the organisation, conduct and recording of the EPI in Quang Xuong and Ngoc Lac districts was presented. Two HWs in 11 communes were interviewed after one had completed a questionnaire pertaining to technical and programmatic aspects of the EPI. Inconsistency was noted between the responses of the interviewees at several communes, and it was clear that the program had not been reviewed in such depth before. There were major differences in the conduct of the program between the two districts, and serious problems with the planning, organisation, likely efficacy and safety of the EPI were identified in both. Most concerning were the widespread re-use of unsterilised needles and syringes, the conduct of the EPI over more than one day without access to refrigeration, poor monthly planning and very poor recording of activities. There also appeared to be misuse of syringes and needles intended for the EPI in one district, and equipment shortages in both. The conclusion was drawn that the EPI in Thanh Hoa, and probably elsewhere in Vietnam, would benefit greatly from a comprehensive training and refurbishment program.

SIAMC was designed to assist the development of strategies to most effectively introduce HepB vaccine into Vietnam's EPI. To this end, the author and project staff worked in Quang Xuong and Ngoc Lac, conducting the research activities and also a number of training programs for VHWs, CHWs and community leaders.

Based on the problems identified, a set of short (2 – 2.5 day) trainings of CHWs were undertaken, initially in the core group of 18 communes in which HepB vaccine was first introduced, but subsequently for at least one CHW in all communes of the two districts.

The syllabus for the training was developed by project staff, based on local materials and also on documents available on the WHO website (as it was in 1999) at <http://www.who.int/vaccines-documents/DoxTrng/H4IIP.htm>. The selected areas of focus were:

- the aims of the EPI
- the six traditional EPI vaccines, plus HepB vaccine (except in control communes, as defined in Chapter 6)
- the cold chain
- safe immunization (including injection safety, sterile technique and sterilisation of equipment if appropriate)
- organisation and planning of the EPI to maximise timely coverage and
- recording and reporting of the EPI.

Before conducting the training, the syllabus was prepared for the trainers, who came from NIHE, headquarters of the National EPI, and the Thanh Hoa Preventive Medicine Centre. All had previously been trained as EPI trainers by the National EPI and had worked in this capacity. The final training document was revised after considering their feedback, and distributed to every trainer two weeks before the actual courses were conducted. Relevant training materials including posters, EPI equipment, vaccines and disposable needles and syringes were prepared, to enable participants to practise during the lessons.

The trainers were well prepared and most trainees reported that this was the first time they had received specific training on the EPI, including the opportunity to practise during the training. Previous EPI training had apparently been combined with other programs and rarely exceeded half a day in duration, suggesting that it was of poor quality. In general the trainees participated actively and even completed take-home exercises well.

In addition to this specific training, the project made two other inputs to improve the conduct of the EPI at commune level. The first was the purchase and supply of adequate needles and syringes (reusable for Quang Xuong, disposable for Ngoc Lac, in accordance

with policy at the time to use disposable equipment in “mountainous” communes) for the duration of the project, an electric steriliser for most CHSs in Quang Xuong, and also a cold box and / or vaccine carrier for each CHS in both districts. These items were chosen on the basis of needs assessed during the baseline survey reported in Chapter 2A.

The second was the strengthening of semi-regular monitoring and feedback visits by district level public health staff, who worked closely with project staff during the training and on supervisory field visits. In fact, this was not a new initiative, as hygiene and preventive health brigades are an established part of the health sector in rural Vietnam (Appendix 3), but staff on other public health projects and the findings reported in Chapter 2A suggested that the level of good quality monitoring and supervision of HWs at commune level was very poor. SIAMC requested visits by district staff to “ideal” and “routine” CHSs at least 3 monthly on a rotating basis, and required them to complete a monitoring form related to HepB vaccine activities (Appendix 10). In the last 12 months of field activities, the project also took on a staff member whose main responsibility was to supervise data collection and provide feedback to CHWs on their conduct of project activities. It is acknowledged that this level of vertical program monitoring is unrealistic and out of line with health sector reform protagonists’ efforts to integrate the management of primary-level health care programs, but this level of oversight was essential to the conduct of the field research on the local vaccine described in Chapter 6.

This Chapter describes a follow up survey conducted to evaluate the effect of project inputs and changes on the conduct of the EPI in project areas.

Method

Timing, location and strategy

The survey was undertaken over four days in November – December 2000 at 12 project CHSs in Quang Xuong and Ngoc Lac (Chapter 2A). Six communes were selected randomly in each, but in order to avoid the possible influence of having been surveyed before and also of having been a focus area for the project for a longer period of time,

those surveyed at baseline were omitted from the lists of communes before selection. Those surveyed were thus all intended to be those that received training input in March-April 1999, and in which HepB vaccine was introduced in June 1999. One exception was required due to the illness and absence of staff at one CHS in Ngoc Lac. In its place, the survey team returned to one of the worst performing communes from the 1998 survey and re-assessed activities there.

The knowledge and practices of CHWs were again assessed using a structured questionnaire followed by a focussed discussion. The interview strategy was identical to that used at baseline, in which one member of the project's staff, together with a representative of the Thanh Hoa Preventive Medical Centre, interviewed one of the CHWs (usually the one designated as the EPI worker for that CHS), while the author, and/or the representative from NIHE, together with an observer interviewed the head of the CHS. This strategy again enabled inconsistencies to be noted between the accounts given. No assessment of interviewer performance was made, but the two accounts were compared at a collective debriefing session after visiting each site.

Questionnaire and topics surveyed

The same questionnaire and topics for discussion were used as at baseline (Chapter 2A and Appendix 6).

Focussed interview

The interviewing strategy as was the same as used at baseline. This involved separate but simultaneous interviews with two staff.

In Quang Xuong, this interviewing strategy could be undertaken in each of the six communes surveyed. In Ngoc Lac, it was possible in five. In the sixth, the staff at the CHS were absent, so it was only possible to examine the EPI register.

Data analysis and report writing

Qualitative data were recorded by hand at the interviewing site, translated if necessary and analysed using keyword selection and comparison of interviewees' responses by the author. Quantitative data were tabulated.

Results

General comment on the data

The conduct of this survey was a much more pleasurable experience than the preceding one in 1998. Although there were still some inconsistencies between the responses of the two interviewees in some CHSs, in general interviewees agreed with each other and answered questions easily and openly. The quality of the quantitative data was better than before (Table 1), and HWs knew more about the EPI.

Demography and mortality statistics

The same data as in the first survey was sought from each commune regarding certain statistics relevant to the EPI (Table 1).

With only one exception (the relative numbers of under ones and under fives in Ngoc Lien), the data are consistent and believable. The CHS head in Ngoc Lien averred that his data reflect a dropping birth rate in this commune. In addition to this internal consistency, there were reasonably consistent ratios of persons/household, CBAW in the population (except Quang Long) and deliveries relative to the population of CBAW.

The crude birth rate for the 12 month period surveyed was 14.5/1000 in Quang Xuong (virtually unchanged) and 16.4/1000 in Ngoc Lac, a substantial decrease from that calculated for 1998 (19 – 21/1000). The calculated infant mortality rate was 9.7/1000 live births, again very low for a rural population in a developing nation. The causes ranged from congenital malformations to prematurity and bacterial meningitis. One case of possible neonatal tetanus resulting in the death of one infant, delivered by an isolated single mother, was reported in Ngoc Lac.

Deliveries, particularly in Ngoc Lac, tended to be in a health facility or attended by a HW more often than in the first survey (Chapters 2B and 7B), and most deliveries at home were reported to be attended by a traditional birth attendant or trained HW, especially in Quang Hai. However, attention is again drawn to the high rate of home birth in Ngoc Lac communes.

Table 1: Demographic data from 11 communes responding to questionnaire on Expanded Program on Immunisation (EPI), late 2000

Name of Commune	Quang Xuong district						Ngoc Lac district					
	Q. Khe	Q. Phuc	Q. Long	Q. Hai	Q. Hung	Q. Xuong	Phuc Minh	Ngoc Trung	Ngoc Lien	My Tan	Q. Trung	Cao Thinh
Project strategy*	Cont.	Cont.	Rout.	Ideal	Ideal	Ideal	Cont.	Rout.	Rout.	Ideal	Ideal	Ideal
Population	6684	3007	5630	8855	5081	2887	NA	4691	5740	NA	7750	3702
# Villages	6	6	8	11	10	6	NA	9	13	NA	21	8
# Households	1582	620	1225	1783	1089	606	NA	923	1078	NA	1650	803
# Active VHWs	6	6	8	11	10	NA	NA	6/3 ^a	13	NA	15/5 ^a	7/1 ^a
# Inactive VHWs	0	0	12 ^b	0	0	NA	NA	0	0	NA	0	0
# Ethnic groups	1	1	1	1	1	1	NA	2	2	NA	2	2
# Infants < 1y	87	48	64	126	65	36	NA	89	69	NA	97	77
# Children < 5y	493	258	290	501	368	181	NA	455	683	NA	474	450
# CBAW 15-35	1117	716 ^c	618	1521	766	396	NA	859	1191 ^c	NA	NA	622
Women giving birth 6/99-5/00	93	49	70	142	76	36	NA	92	84	NA	81	102
Livebirths	93	49	70	142	76	36	NA	92	84	NA	81	102
Births at CHS	26	46	35	42	47	10	NA	33	41	NA	15	15
Births at other health facility	10	4	8	0	4	26	NA	0	26	NA	10	3
Births at home (% livebirths)	57 (61)	3 (6)	27 (39)	100 (70)	25 (33)	0	NA	59 (64)	17 (20)	NA	56 (69)	84 (81)
Perinatal deaths in this 12 months	3	0	0	1	0	0	NA	0	2	NA	0	0
Infant deaths in this 12 months	1	0	1	0	0	0	NA	0	NA	NA	0	0
Deaths of 1 - 5 year olds	0	0	0	1	1	0	NA	0	2	NA	0	0

Notes: Q. = Quang

NA = not available

* Cont. = control; Rout. = routine

a: all active but only some salaried, others get rice in lieu

b: Retired

c: Aged 15 - 49 years.

Staffing of CHSs and the EPI

As would be expected, this had not changed between the two surveys.

EPI strategy and communication with mothers

The overall strategy (time of the month for collection of vaccine, distribution strategy) for the districts had not changed, apart from more reliable scheduling of the EPI in Ngoc Lac due to more regular transport. At commune level however, the situation had changed remarkably for the better since 1998, and is summarised for the two districts below:

(iii) Quang Xuong:

All 6 communes surveyed now conduct the EPI on one day each month at the CHS only – none conduct outreach. All are assisted by VHWs on the day. Several reported a transition from an outreach to a fixed-point EPI strategy during 1999, but all prefer the latter and reported that mothers were also happy with this arrangement. Most reported the use of printed invitations or reliance on VHWs to notify eligible infants' mothers that the baby was due for vaccine. All prepare lists of infants due for vaccination, including names, vaccines due and some system of checking vaccines given on the list (often changing a “-” to a “+” sign). Several such lists were seen and most were well designed and completed. A template for such a list had even been prepared by the district hospital, but this was only seen in one CHS. All CHSs reported meeting with VHWs on a monthly basis and preparation of a list of new infants born, although the date of this meeting across the month varied widely. The strategy for administering BCG and birth-dose HepB vaccine varied but all were making an effort to administer both on the first EPI day after birth, either at the infant's home or at the CHS. Many reported willingness of new mothers to bring small infants (some even < 1 week old) for vaccination, but others took the vial of BCG or HepB vaccine to the infant at home, particularly in ideal communes. However, there remains the problem of transporting opened, 20-dose ampoules of BCG.

(iv) Ngoc Lac:

HWs from five communes were formally interviewed in this district. The systems used varied but all reported the conduct of the EPI via an outreach strategy, as opposed to the

fixed-point strategy used in Quang Xuong. Three reported that it was conducted on two days each month, one using locally purchased ice to maintain the cold chain. A meeting with VHWs was reported to be held at a particular time each month but the timing varied across the communes. The list of newborns and babies due for immunisation is updated at this time, although one reported simply inviting all children under two to the EPI points and checking their need for vaccination on the day. VHWs were responsible for notifying mothers and, in some communes, for giving vaccine, especially to small infants at home. Invitations were not in use but loudspeakers were used to call infants to an EPI point in some newly electrified communes. A monthly schedule to ensure planned coverage of all villages or outreach points was seen in four out of five CHSs. Three communes planned covering the whole commune every two months, one every 3 months and the other every four or five months. The project birth-register / EPI form was deemed useful in ideal communes, but the design was felt to be cumbersome. In general, the EPI appeared to be more regular and planned with systems to ensure coverage in place, albeit variable from one commune to the next.

Recording and Reporting

The systems in place for this varied widely across the communes surveyed, even within the two districts. As mentioned, invitations were used in some but not other CHSs, as were loose lists, under-five cards, a form developed by the district hospital (in Quang Xuong) and, in one CHS in Ngoc Lac, another developed by the province-based project officer. One CHS in Ngoc Lac reported simply taking the formal EPI register to complete at the outreach point on EPI day (although it looked remarkably clean if this was the case). Nonetheless, much more of a semblance of believability prevailed in the EPI registers of all communes surveyed than at baseline, with few instances of dubious uniformity and none of the fundamental errors noted in Chapter 2A.

Immunisation cards were reported to be in use in several communes and were said to be kept by the mothers, but there was inconsistency between the two interviewees in two communes on this subject (Chapter 7B refers discusses this subject more).

Administration of vaccines and logistics

The changes of strategy in Quang Xuong described above have removed much of the risk previously associated with outreach EPI services there. In addition, all communes now reported using disposable needles and syringes, although none were supplied adequate numbers of these free of charge by the district hospital. In five, the purchase and sale of new needles and syringes to mothers who could afford to pay was conducted by CHWs on EPI day, with the approval of the commune People's Committee. In the sixth, the People's Committee was able to pay for these using local funds. None reported using reusable equipment or sterilisation for the EPI, but some do so for clinical or other services. No HW surveyed admitted re-using the same needle on more than one infant. In fact, when asked, none reported ever having done so, by contrast to what was reported in 1998 (Chapter 2A).

In Ngoc Lac, disposable equipment was in use in all communes and adequate supplies were provided free of charge by the district health service. No HW admitted current or previous re-use of needles or syringes. Equipment was usually reported as being disposed of by burying.

The survey did not specifically assess respondents' sterile technique in vaccine preparation and administration, nor their practices in regard to vaccine heat spoilage. However, a small group of questions to assess their knowledge in these areas were included. Many small errors were made in answering these, but in fact many respondents appeared to have reasonable knowledge of vaccine heat stability and shelf-life once reconstituted. In addition, because of the improved organisation and planning of the EPI, no commune reported the decanting of vaccine from one vial to another, or the preserving of vaccine for use next day. One had a system of rotating access to measles and BCG between villages each month, to ensure coverage without the need to transport opened vials over long distances or to keep the vial beyond its period of stability.

Discussion

This survey identified marked improvements in all aspects of the EPI in the two districts surveyed. Whilst still not perfect and retaining a degree of inconsistency even between communes within the districts, the very alarming practices and deficiencies noted in 1998 have largely disappeared, leaving only some minor problems more characteristic of lack of organisational skill or motivation, or due to geographic difficulties, rather than the fundamental lack of knowledge noted at baseline.

The project inputs described above were, although beyond what is currently affordable for the National EPI in terms of refresher training for CHWs, probably the bare minimum that might be expected to improve the situation in areas similar to Quang Xuong and Ngoc Lac at baseline. However, as mentioned by the HWs trained, it is now unusual for training programs to focus on only one area, and it seems unlikely that those in other areas of Thanh Hoa or elsewhere will benefit from a similar level of input. In defence of the training conducted, however, it seemed that many HWs had never received good basic information on the EPI, and it was not only imperative for the introduction of HepB vaccine that this was improved, but it was also requested by the project donor.

Fortunately, there are some promising large scale primary health care support projects being conducted in Vietnam, funded by the Asian Development and World Banks, and another smaller one by UNICEF, all of which include some EPI training in the activities they support. However, the author is concerned that the extra burden HepB vaccine will place on a weak system may not be supportable, and identifying funding for additional HW training and community mobilisation (Chapter 7B) to assist this is now a priority for Vietnam.

In addition, a better system of monitoring and supervision of the activities of grassroots HWs in rural Vietnam is imperative to improving the standard of their work. The author's impression is that public health work of this kind is not popular with local health staff, perhaps because there are few opportunities to earn money from it and because of the inconvenience it entails. Project staff struggled initially to engender interest amongst

local staff to travel to CHSs to undertake supervision of preventive and clinical activities. Staff on the recently completed, five-province Vietnam-Australia Malaria Control Project noted similar lack of interest. However, the feedback given by CHWs on such visits was positive, particularly if the supervision was sensitive and helpful, rather than prescriptive. Vietnam now trains public health officials who can take on this role at many levels, but it will be important to ensure that their remuneration is adequate to maintain their interest and that their feedback does not stop at district level to ensure that their findings and efforts are recognised and acted upon.

The organisation of the EPI noted in the two districts surveyed is likely to typify the best that can presently be achieved in similar locations. However, improvements will follow if:

- refrigeration can be introduced at the level of the CHS,
- more vials of vaccine can be supplied or
- a higher cost can be tolerated as vial-size is reduced and / or
- a multi-dose vial policy (Appendix 1) is applied (preferably along with the introduction of vaccine vial monitors on all vaccines).

The latter will allow appropriate use of opened vials of DTP, TT, HepB vaccine and OPV kept cold until empty, avoiding the high wastage rates incurred if 10- or 20-dose vials are used on more days of the month, but discarded on the day of opening.

Improving the status of the CHSs in the eyes of their constituency, to encourage the effort required to make a visit, may also be required.

Without such changes the EPI in most places like Ngoc Lac cannot become even a monthly, let alone a daily fixed-point activity in the foreseeable future. Obviously the situation in Quang Xuong is much more promising, due to the greater accessibility of the CHS, and it may be that the first of these improvements (refrigeration) with use of the multi-dose vial policy are all that is required to make the EPI there of high standard indeed.

A follow up study of community perspectives on liver disease, hepatitis B infection and the Expanded Program on Immunisation in rural Vietnam: the influence of a community mobilisation and health worker training program

Introduction

Chapter 2B reported the results of a survey of community KAP with respect to liver disease, HBV and the local EPI, conducted in preparation for the pilot program of introduction of HepB vaccine in Thanh Hoa.

The key findings of that survey included that interviewees in the densely populated, ethnically homogeneous and more easily accessible coastal district (Quang Xuong) were better educated and had better access to electronic mass media than those in the more geographically isolated, semi-mountainous and less crowded inland district (Ngoc Lac), where most people are members of one of Vietnam's ethnic minority groups. Those in Quang Xuong also had better knowledge of the local impact of liver disease, and whether its causes are transmissible. Education level was a predictor of this knowledge, as was membership of one mass organisation, but not access to mass media. Knowledge of the causes of liver disease and familiarity with HBV was generally poor. Understanding the purpose of and target groups for the EPI was good, but access was more regular and more frequent in Quang Xuong. Local HWs and the mass media were sources of information on the EPI, but household records of children's immunisation status were kept infrequently. Most in Quang Xuong reported that the majority of women deliver babies in a government health facility, but only 7.5% did so in Ngoc Lac; the remainder deliver at home. Birth-dosing with HepB vaccine seemed likely to be acceptable to those interviewed.

Following this survey, SIAMC undertook a number of activities to improve community awareness of HBV and acceptance of the need for all infants to receive three doses of

vaccine to prevent it, including preferably a birth-dose administered before the age of one week. These activities were conducted differentially according to project stratum, as outlined in Chapter 6.

This Chapter reports on a follow up survey of community KAP on the same issues assessed at baseline, both to evaluate the success of project inputs and to assist planning of the needs for community mobilisation entailed in the planned national expansion of HepB vaccine.

Method

The method for this survey was virtually identical to that described for the baseline survey (Chapter 2B).

Survey participants, location and timing

SIAMC interviewed the female heads of a new group of randomly selected households in the same communes as were surveyed in 1998. The same, rather than different communes were used because the training and community mobilisation inputs there were conducted by project rather than counterpart staff, and hence their quality and content more reliably defined. One difference was that in this survey, women in three extra "control" communes in Quang Xuong were included, equalising at nine the number of communes included in each district. Interviews were conducted as before over eight days, in November 2000.

Project design and survey sample size

Recalling that project inputs were stratified across different communes, the goal was to compare the responses of householders in the two districts and three project strata on this survey to those obtained at baseline. Comparison within and between each district's performance at baseline and follow up was possible, but the sample size did not allow comparison by strategy within each district. Changes across the surveys were assumed to

forecast the impact elsewhere in Vietnam of future inputs similar to those made by SIAMC.

There were three project strata, each represented by three of the nine communes surveyed per district. Community mobilisation activities were undertaken in two of them, the ideal and routine, as outlined in Chapter 6. For the baseline survey (Chapter 2B), assuming a baseline prevalence of 25%, the number of interviewees required to show an improvement of 50% on six key variables relating to the causes and transmission of liver disease, facts about HBV and maternal access to a record of infant vaccinations at village level was calculated at 300 per district, with a power of 90% and two-tailed alpha level of 5% (Lwanga SK & Lemeshow S, 1991).

The six key variables were:

- whether any causes of liver disease can be transmitted from person to person (survey question 6 – Appendix 11)
- whether any causes of liver disease can be transmitted from mother to infant (question 8)
- whether liver disease can be caused by HBV (question 9A)
- unprompted knowledge that HBV can be transmitted by unclean needles and sexual contact (question 9B, amongst those who answered “yes” to 9A)
- knowledge of the existence of a vaccine against HBV (question 9C, amongst those who answered “yes” to 9A)
- maternal access to a domestic record of infant vaccinations at village level (ideal communes only – question 12)

For this survey, there was also a need to survey 300 households in each stratum, to compare with all the households at baseline. Based on these criteria, in this survey 450 households were sampled in each district, 150 from each of the three project strata. Comparisons of demographic variables and the changes in knowledge on certain sets of questions were made between those obtained at baseline and in this survey across the strata, within and between the two districts.

Sampling method

The selection process for households was described in Chapter 2B. In the baseline survey households were sampled in proportion to the number in each stratum. For reasons of convenience at the time of this survey, a particularly busy time for the project, and also to avoid the cost of collecting data on the number of households in each village before sampling, this time the same number of houses were chosen in each stratum in both districts (150 in each of three strata across the two districts). This meant the sample in each stratum in this survey was less closely related to the total number of households in each group of three communes, but almost certainly this has not impinged on the validity of the conclusions, as where the baseline prevalence allowed it, the intended 50% increase was greatly exceeded for the prevalence of most six variables.

Survey team and instrument

As before, thirty experienced, local interviewers and six supervisors were recruited from within Thanh Hoa city and the two districts surveyed. All were retrained on the survey topics and their interviewing skills upgraded. The use of local interviewers ensured the minimisation of subtle problems with language interpretation. No field-testing of the survey instrument, which was virtually identical to that used at baseline (see Appendices 7 and 11), was conducted, and interviewer reliability was again assumed based on their experience and the outcomes of similar surveys in a non-project district.

Data compilation and analysis

As for the survey chapter 2B, data were entered using Epi Info version 6.03 (CDC, Atlanta) and subsequently analysed using STATA version 6 (STATA Corporation, College Station, Texas) and EpiCalc. Check programs were used to facilitate data entry and reduce errors. Chi-square, Z-, t- and F- tests were used for univariate analyses. Backward selection followed by linear and logistic regression were used for multivariate analyses of the level of association of certain variables on knowledge. Variables were again assumed to be independent and no analysis for interaction was undertaken. No correction for any design effect was undertaken as this was not possible in the backward

selections and therefore in the resulting regression models. Design effects calculated in other surveys were small.

Results (See Figures for this Chapter in Appendix 8)

1. Respondent characteristics

Demographic information

The age distribution of the 900 interviewees was approximately normal, and ranged from 19 – 45 years (mean 33 years 0 months). All were mothers, with 1 – 7 children (mean 2.55). Almost exactly as at baseline, in Quang Xuong, 100% were of Kinh ethnicity, and in Ngoc Lac, 84.8% were Muong, with small numbers of Kinh and other minorities.

Language facility/education level

The claimed education level of interviewees in Quang Xuong was again higher, with 84.2 (80.4-87.4)% reporting more than five years of formal education, compared to 56.0 (51.3-60.6)% in Ngoc Lac (Figure 12). However, again almost all those interviewed could read Vietnamese (99.3 (97.9-99.8)% in Quang Xuong, 87.6 (84.1-90.4)% in Ngoc Lac).

Mass media access, membership of mass organisations and access to health services

Table 1 depicts the differences between the districts in household access to mass media, particularly television (TV) and loudspeakers. It also shows the proportion of interviewees in both districts who were members of the VWU and the VFA, and the difficulty some in Ngoc Lac have in accessing a qualified CHW in the wet season.

Table 1: Access to mass media, and VWU and VFA membership, by district (%)

District	Radio in house	TV in house	Loudspeaker in audible range	VWU membership	VFA membership	Walk to HW in wet season in <2 hours
Quang Xuong	49.4 (44.8-54.1)	59.0 (54.5-63.6)	94.2 (92-96.4)	90.0 (86.8-92.6)	30.0 (25.8-34.5)	100 (100-100)
Ngoc Lac	54.1 (49.5-58.7)	33.0 (28.6-37.2)	53.1 (48.5-57.8)	99.3 (98.1-99.3)	40.0 (35.7-44.9)	86.0 (82.7-89.2)

In both districts there only were minor differences across the strata in possession of a radio. In Ngoc Lac, however, there were substantial differences in possession of a television (TV), with those interviewed in ideal communes (42.3 (34.4-50.6)%) owning one more often than those in routine (32.7 (25-40.9)%) ($\chi^2 = 2.95$, $P = 0.09$) and control (24.0 (17.6-31.8)%) ($\chi^2 = 11.28$, $P=0.001$). Loudspeakers, almost uniformly present in Quang Xuong (range from 89.9 – 97.3% across the strata), were present in 67.3 (59.1-74.6)% of both ideal and routine communes in Ngoc Lac, but only 24.3 (17.8-32.1)% of control communes.

Some of these figures have changed since baseline. In particular and consistent with the trend in economic development and also electrification of rural Vietnam, overall loudspeaker access in Ngoc Lac has improved significantly, from 39.2 (35.4-43.2)% to 53.1 (48.4-57.8)% ($\chi^2 = 20.8$, $P < 10^{-5}$), as has television and radio ownership (by 5 - 8% for each in both districts).

Membership of the VWU in Ngoc Lac increased from 89.9 (87.2-92.1)% to 99.3 (97.8-99.8)% ($\chi^2 = 40.1$, $P < 10^{-6}$), but varied little across the strata in each district. By contrast, there were differences in membership of the VFA, ranging across the strata from 22.7 – 41.3% in Quang Xuong, and 26.7 – 50.7% in Ngoc Lac. Only 4% of interviewees were not members of one mass organisation.

A higher degree of remoteness of those sampled in Ngoc Lac control communes is suggested by the fact that 27.5 (20.7-35.5)% of them cannot access a commune HW in the wet season in < 2 hours, compared to only 6 – 8.7% of those in routine and ideal communes.

2. Liver disease and HBV

Differences between the districts

As before, five survey questions (numbers 3, 4, 6, 7, and 8) were asked to broadly assess interviewees' general knowledge of the impact of liver disease on their community and

whether its causes are transmissible. The mean number of correct responses in Quang Xuong increased from 3.7 at baseline to 4.2 ($t = 6.3, P < 10^{-4}$), and in Ngoc Lac from 3.4 to 4.3 ($t = 10.7, P < 10^{-4}$). There were also clear differences by project strata, and some differences by district within each stratum (Table 2). Unlike at baseline (Chapter 2B), crude analysis showed no difference between the districts at this time ($t = 0.60, P = 0.55$).

Table 2: Mean numbers of correct responses to five questions on liver disease, by stratum and district (with 95% c.i.'s for mean)

District and stratum		Mean number of correct answers	Mean number of correct answers by stratum	Mean number of correct answers by district
QX	Ideal	4.4 (4.3-4.6)	Ideal 4.4 (4.3-4.5)	QX 4.2 (4.1-4.3)
	Routine	4.0 (3.8-4.2)		
	Control	4.2 (4.1-4.3)		
NL	Ideal	4.4 (4.3-4.5)	Routine 4.2 (4.1-4.3)	NL 4.3 (4.2-4.4)
	Routine	4.4 (4.2-4.5)	Control 4.1 (4.0-4.2)	
	Control	4.0 (3.8-4.2)		

These relationships between the districts and strata were first explored using linear regression. In models including only the three strata, the performance of householders in ideal communes was clearly better than those in routine ($P < 0.01$) and control ($P < 10^{-3}$), but the difference between routine and control was not significant ($P = 0.20$). In another model including the three strata separated by district, and comparing each with the ideal stratum in Quang Xuong (which performed best – Table 2), there were again clear differences with the routine ($P < 10^{-3}$) and control ($P = 0.04$) communes in Quang Xuong, and the control in Ngoc Lac ($P < 10^{-3}$) but no difference between the ideal ($P = 0.91$) or routine ($P = 0.52$) communes in Ngoc Lac. These results concur with the means in the Table, and confirm unexpected good performance by the Ngoc Lac ideal and routine, and a relatively weaker performance in the Quang Xuong routine communes.

Influence of certain independent variables on knowledge of liver disease

In a more robust analysis of the associations with knowledge, linear and logistic regression were again used to assess the level to which certain variables predicted

interviewees' scores on these 5 questions. The same 11 possible predictors as were included in the analyses at baseline (Chapter 2B) were assessed. In addition, district and three levels of strategy were included, resulting in a total of 14 such variables after exclusion of comparison groups. Backward selection with cut-off P-values of either 0.20 or 0.25 was again used to select which variables to include in the final regression models.

For the initial analysis, as for the baseline survey, knowledge was again categorised into two levels: good (a score of ≥ 3 out of 5 possible correct responses) or poor (2 or less). Backward selection with P-values of either 0.2 or 0.25 removed the same three variables (access to television, education only to primary level and living in a village with an active VHW) from the 14 possible predictors of good knowledge in each case. The full MLR model, based on the backward selection with $P = 0.20$, thus identified which of the 11 selected variables predicted good knowledge on liver disease, as defined in this model, after project implementation. Secondary or high-school / university education, VWU membership, recognition of HBV as a cause of liver disease, living in Ngoc Lac or an ideal compared to a control commune all predicted good knowledge, as did possibly keeping a record of children's immunisations at home (Table 3). VFA membership, proximity to a loudspeaker and radio ownership were not strongly predictive.

As in Chapter 2B, and given the higher average scores on these five questions in this follow-up survey, the analysis was repeated after increasing the cut off for "good" knowledge to 4 out of 5 questions correct, to determine whether the influence of any of these variables disappeared. Backwards regression with a cut off P-value of 0.25 or 0.2 again dropped TV ownership, proximity of a VHW in the respondent's village and also VFA membership and radio ownership, but included education to only primary school level. The regression model identified high school or university education, having heard of HBV and keeping a record of children's immunisations at home, living close to a loudspeaker, and living in Ngoc Lac or an ideal compared to a control commune as predicting good knowledge (Table 3). Education only to primary school level and VWU membership were not good predictors of knowledge in this model.

Table 3: Variables predicting a good level of knowledge of liver disease, variably defined as at least three, or four, or five correct responses on five relevant questions

Variable	Measures of association	Definition of "good" knowledge in model			Any number correct (linear regression model)
		≥3 questions correct	≥4 questions correct	5 questions correct	
Primary education	OR	2.24	2.03		
	P	0.19	0.12	N/A	0.17
	95 % c.i	0.68 – 7.40	0.83 - 4.98		
Secondary education	OR	3.69	3.11		
	P	0.04	0.01	N/A	0.01
	95 % c.i	1.10 – 12.41	1.27 - 7.63		
High school or university education	OR	8.33	5.99		
	P	< 0.01	< 0.01	N/A	< 0.01
	95 % c.i	1.72 – 40.36	2.00 - 17.98		
VWU membership	OR	3.17	1.83		
	P	0.02	0.13	N/A	N/A
	95 % c.i	1.22 – 8.23	0.83 - 4.04		
VFA membership	OR	0.64			
	P	0.16	N/A	N/A	N/A
	95 % c.i	0.35 - 1.19			
Recognition of HBV as a cause of liver disease	OR	5.09	3.39	2.08	
	P	< 10 ⁻³	< 0.001	< 0.001	< 0.01
	95 % c.i	2.74 - 9.52	2.16 - 5.32	1.47 - 2.95	
Having a record of child's immunisation	OR	1.86	1.61		
	P	0.07	0.04	N/A	0.01
	95 % c.i	0.96 – 3.59	1.02 – 2.52		
Living in a village with a loudspeaker	OR	1.75	1.71	0.90	
	P	0.15	0.05	0.51	N/A
	95 % c.i	0.81 – 3.75	0.99 – 2.95	0.66 – 1.23	
Living in Ngoc Lac, as compared to Quang Xuong	OR	2.73	2.10		
	P	0.009	< 0.01	N/A	< 0.01
	95 % c.i	1.28 – 5.83	1.24 - 3.57		
Living in a routine commune, as compared to an ideal	OR	0.48	0.49	0.78	
	P	0.11	0.02	0.14	0.10
	95 % c.i	0.20 - 1.18	0.27 - 0.90	0.56 – 1.08	
Living in a control commune, as compared to an ideal	OR	0.42	0.42	0.66	
	P	0.05	< 0.01	0.02	0.02
	95 % c.i	0.18 - 1.00	0.23 - 0.75	0.47 - 0.93	

VWU = Vietnam Women's Union; HBV = hepatitis B virus; OR = odds ratio; c.i. = confidence intervals

N/A = After backward selection, not included in this model;

Finally, in a model where “good” knowledge was defined as 5 out of 5 responses correct, only having heard of HBV and living in an ideal as opposed to a control commune remained as predictors of this level of knowledge (Table 3).

Result of backward selection followed by linear regression analysis, in which knowledge (defined by the score out of five) is treated as a continuous rather than a categorical variable, are also shown in Table 3. The same variables were selected regardless of cut off. In general, the results concur with findings of the MLR models presented.

Causes of liver disease and HBV infection

Knowledge in this area had improved markedly since the first survey. When asked, without prompting, what causes of liver disease they knew of, 26.8 (24-29.9)% of interviewees mentioned viruses, up from 1.8% at baseline. Further, as there were 6 missing answers to this question and 333 responded "do not know any causes", of those who responded with any causes, $241/561 = 42.96\%$ mentioned viruses.

In stark contrast to the situation at baseline, when only 36.2% in Quang Xuong and 12.6% in Ngoc Lac had heard of HBV when prompted by its name, in this survey the corresponding figures were 81.6 (77.6-85)% and 77.3 (73.1-81)% ($\chi^2 = 2.46$, $P = 0.12$). These improvements were highly significant in both districts (Quang Xuong: $\chi^2 = 160.7$, $P < 10^{-6}$; Ngoc Lac $\chi^2 = 458.5$, $P < 10^{-6}$).

Analysis of responses to this question by district and project stratum is shown in Table 4. Although some differences exist, particularly between ideal and routine communes ($\chi^2 = 14.58$, $P < 0.001$) and across the districts in the control stratum ($\chi^2 = 13.27$, $P < 0.001$), without exception the frequencies seen are markedly higher than in 1998.

Table 4: Percent of respondents (with 95% c.i.'s) who had heard of the HBV, by district and stratum

Strategy	District		Total
	Quang Xuong	Ngoc Lac	
Baseline	36.2 (30.8-41.6)	12.6 (10.0-15.2)	20.4 (17.8-23.0)
Ideal	88.7 (83.5-93.8)	91.3 (86.8-95.9)	90.0 (86.6-93.4)
Routine	76.7 (69.8-83.5)	80.7 (74.3-87.1)	78.7 (74.0-83.3)
Control	79.3 (72.8-85.9)	60.0 (52.1-67.9)	69.7 (64.4-74.9)
Total	81.6 (78.0-85.2)	77.3 (73.5-81.2)	79.4 (76.8-82.1)

Regarding knowledge of how HBV may be transmitted, amongst those who had heard of the virus in this survey (n = 367 in Quang Xuong, n = 348 in Ngoc Lac), again there were improvements. At baseline, 46 (38.8-53.4)% of such respondents across both districts mentioned blood transfusion, 30 (23.7-37.2)% mentioned needles and 12.7 (8.3-12.3)% sexual contact (see Table 6A for district breakdown of answers on needles and sexual contact). In this survey, in Quang Xuong, these figures were 59.4 (54.1-64.4)%, 58 (52.8-63.1)% and 48.2 (43-53.4)% respectively. Similar but lower figures applied to the first two of these responses in Ngoc Lac 52.9 (47.5-58.2)% for blood transfusion and 54.3 (48.9-59.6)% for needles) but there was significantly lower knowledge (25 (20.6-30)%) of sexual transmission in this district than in Quang Xuong ($P < 10^{-6}$) (Table 6A).

Knowledge of the existence of HepB vaccine had also increased markedly amongst this group, from 62.4 (53.1-71.6)% to 95.1 (92.9-97.3)% in Quang Xuong ($\chi^2 = 85, P < 10^{-6}$) and from 31.2 (20.6-41.8)% to 92.5 (89.7-95.3)% in Ngoc Lac ($\chi^2 = 58.9, P < 10^{-6}$), and from 10% to 74% amongst all interviewees (whether they had heard of the HBV or not).

3. Vaccination and the EPI

General knowledge on vaccination

Again 2 questions were asked on important issues pertaining to immunisation (questions 15 and 15A). Improvement was noted for both, albeit from a relatively high baseline.

Regarding the single most important use of vaccination from a list of proffered alternatives, 760 interviewees (84.6 (82-86.9)%) knew that vaccines are given to prevent disease, compared to 72 (69-74.9)% in 1998 ($\chi^2 = 43$, $P < 10^{-5}$). This improvement was noted particularly in Ngoc Lac, from 67.3 (63.4-71)% to 84.2 (80.4-87.4)% ($\chi^2 = 39.5$, $P < 10^{-4}$), now virtually the same as in Quang Xuong.

Regarding whether even healthy infants need immunisation, virtually all respondents ($n = 865$ or 97.7 (96.4-98.5)%) answered correctly, with some improvement evident in both, but particularly in Ngoc Lac, from 91.5 (88-93.5)% at baseline to 96.4 (94.1-97.9)% in this survey.

Sources of knowledge on the EPI

Some small changes in which people respondents perceived as important sources of information on the EPI were noted. The role of HWs and the VWU, the target groups for education and orientation in this project, seems to have increased, being mentioned by an average of 89.8 (87.6-91.7)% and 73.9 (70.9-76.7)% respondents respectively in this survey, in comparison to 81.8 (79.1-84.2)% and 67.1 (64-70.1)%. There were other small changes in those mentioned less often.

With regard to methods of education about the EPI, again the mass media were clearly important. Over 62 (55.3 -64.5)% mentioned radio or television in both districts (an increase for both media in both districts), and although many also mentioned the local loudspeaker system, the direction of the change in this differed across the districts (Quang Xuong 76.9 (72.7-80.7)%, down from 95.1 (91.9-97.1)%; Ngoc Lac 43.6 (39-48.3)%, up from 34.4 (30.7-38.3)%). Posters, a key means of information dissemination in this project, seemed more important in this survey, mentioned by an average of 46.6% across the districts, up from 26.4 (23.6-29.4)%.

The situation with regard to parental access to their children's EPI record is still poor, but maybe subject to some interpretation. In 1998 only 32.3 (29.3-35.4)% of respondents were familiar with EPI cards (63.8 (58.1-69.2)% in Quang Xuong and 16.7 (13.9-19.9)%

in Ngoc Lac), but only half kept the card in their home. Familiarity with the card increased to 55.6 (52.3-58.9)% in this survey (unchanged in Quang Xuong but up to 50 (45.3-54.7)% in Ngoc Lac), but in Quang Xuong whilst still only 66% of those familiar keep it themselves, an increase of 14%, the corresponding figure in Ngoc Lac decreased from 63.4% to 45.4%, due to an increase in the keeping of the card by HWs. Thus overall only 32 (27.8-36.6)% in Quang Xuong and 21 (17.4-25.1)% in Ngoc Lac keep their child's EPI card at home, barely changed from at baseline. However, in another question an average of 41.1% reported keeping a record of their child's immunisations at home, a significant increase (Table 6 and 6A, averaged across the strata/districts) suggesting some other documents may be considered by mothers as an EPI record.

EPI situation in the two districts

The EPI activity schedule still differs markedly between the two districts (Figure 13). EPI contact for infants in Quang Xuong has changed little from 1998, and remains clearly more frequent and regular than in Ngoc Lac, although improvements are noted there. In particular, perceived monthly contact has increased from 12.8 (10.3-15.7)% to 36.3 (31.9-41)% in Ngoc Lac, and contact less often than every 3 months decreased from 24.3 (21-27.9)% to 7.1 (5-10)%, as did contact at unfixed intervals (from 19.3 (16.3-22.7)% to 13.6 (10.6-17.2)%). Overall, perceived EPI contact every 3 months or less increased in Ngoc Lac from 52.8 (48.8-56.8)% at baseline to 76.6 (72.4-80.4)% in this survey ($\chi^2 = 63, P < 10^{-6}$).

An interesting change in the perceived frequency of EPI contact in Quang Xuong was noted. In contrast to the situation at baseline, when 99 (96.9-99.7)% of respondents in this district answered that an EPI team visits their area, in this survey only 86.7 (83.1-89.6)% answered thus ($\chi^2 = 36.1, P < 10^{-5}$). There was no such change in Ngoc Lac.

Mothers' delivery practices

In comparison to 1998, differences were noted both within and between districts on where women reported delivering babies in this survey. In Quang Xuong, the proportion delivering in the CHS had increased from 83.3% to 96.3%, and in Ngoc Lac from 7.5%

to 34.2% (Table 5). In general, the availability of trained assistance at deliveries has improved significantly, from 92.5% to 98.5% in Quang Xuong ($\chi^2 = 19.4$, $P < 10^{-4}$), and from 38% to 66.6% in Ngoc Lac ($\chi^2 = 89.5$, $P < 10^{-6}$).

Table 5: Mothers' delivery practices in the two districts surveyed

Usual place of confinement	Quang Xuong (%)*		Ngoc Lac (%)	
	1998	2000	1998	2000
At home without help	0.7 (0-1.6)*	0 (0-0)	6.3 (4.4-8.2)	1.8 (1.6-3.0)
At home with help	6.9 (4-9.8)	1.3 (0.3-2.4)	55.7 (51.8-59.6)	31.7 (27.2-35.9)
At home with HW	9.2 (5.9-12.5)	2.2 (0.9-3.6)	30.5 (26.9-34.7)	32.4 (27.9-36.6)
At the CHS	83.2 (79-87.4)	96.3 (94.6-98.1)	7.5 (5.5-9.6)	34.2 (29.7-38.6)

*with 95% c.i.'s

Attitudes to vaccination of newborns

As might be expected given the increases in knowledge about HBV reported above, there was a slight increase (from 93 (91.1-94.5)% to 96.7 (95.3-97.7)%, $P < 10^{-3}$) in the already large number of respondents who considered that mothers would agree to their infants receiving a new vaccine on the first or second day after birth.

Improvement across the six key variables

Mention has been made of some differences in responses to certain questions by district already. Table 6 depicts the changes in frequency of responses across the questions relevant to the six key variables as defined at project commencement, by project stratum, and Table 6A by district.

Table 6: Frequency of responses (percent, with 95% c.i.'s) across the questions relevant to the six key variables defined at project commencement, by stratum

variable	Proportion responding correctly by time of survey				
	1998	2000 – ideal	2000 – routine	2000 – control	
Whether any causes of liver disease are transmissible from person to person	74.0 (71.1-76.8)	95.0 (92.5-97.5)	91.7 (88.5-94.8)	89.0 (85.4-92.6)	
Whether any causes of liver disease can be transmitted from mother to infant	74.3 (71.3-77.1)	96.0 (93.8-98.2)	93.7 (90.9-96.4)	90.7 (87.4-94)	
Whether had heard of liver disease caused by the hepatitis B virus (HBV)	20.4 (17.8-23)	90.0 (86.6-93.4)	78.7 (74-83.3)	69.7 (64.4-78.9)	
Unprompted knowledge about modes of transmission if knew of the HBV	Sexual contact	12.7 (8.3-18.3)	24.0 (19.3-29.2)	40.3 (34.7-46.1)	23.7 (19-28.9)
	Unclean Needles	30.0 (23.7-37.2)	58.7 (52.9-64.3)	41.3 (35.7-47.1)	34.0 (28.7-40)
Whether there is a vaccine against HBV, if knew of the HBV	49.7 (42.5-57)	97.4 (95.5-99.3)	95.8 (93.2-98.4)	87.0 (82.4-91.6)	
Maternal access to a record of infant vaccination at home	20.4 (17.8-23)	47.0 (41.3-52.7)	39.5 (33.9-45)	36.8 (31.3-42.3)	

The goal of 50% improvement was achieved in most variables with a sufficiently low baseline. Although differences by stratum were evident for some questions, in general these were smaller than expected given the lack of relevant community education activities in control communes, and with only one exception (unprompted knowledge about sexual transmission of HBV amongst those who had heard of the virus) differences by district disappeared over the course of the project.

Table 6A: Frequency of responses (percent, with 95% c.i.'s) across the questions relevant to the six key variables as defined at project commencement, by district

Key variable	Proportion responding correctly by time of survey				
	1998 – QX	2000 – QX	1998 – NL	2000 - NL	
1. Whether any causes of liver disease are transmissible from person to person	76.5 (71.7-81.3)	92.2 (89.7-94.7)	72.6 (69.1-76.2)	91.6 (89-94.1)	
2. Whether any causes of liver disease can be transmitted from mother to infant	78.0 (73.3-82.6)	92.4 (90-94.9)	72.5 (68.9-76.0)	94.4 (92.3-96.6)	
3. Whether had heard of liver disease caused by the hepatitis B virus	36.2 (30.8-41.6)	81.6 (78-85.2)	12.6 (10-15.2)	77.3 (73.5-81.2)	
4. Unprompted knowledge about modes of transmission if knew of the HBV	Sexual contact	15.5 (9.3-23.6)	48.2 (43-53.4)	9.0 (3.7-17.6)	25.0 (20.6-30)
	Unclean Needles	40.9 (31.6-50.7)	58 (52.8-63.1)	15.4 (8.2-25.3)	54.3 (48.9-59.6)
5. Whether there is a vaccine against HBV, if knew of the HBV	62.4 (53.1-71.6)	95.1 (92.9-97.3)	31.2 (20.6-41.8)	92.5 (89.7-95.3)	
6. Maternal access to a record of infant vaccination at home	36.2 (30.9-41.7)	43.3 (38.7-47.9)	12.4 (9.8-15.0)	38.9 (34.4-43.4)	

Discussion

At project commencement, the districts surveyed were essentially blank slates with respect to householder knowledge relevant to introduction of HepB vaccine. Although at that time around one-third of those surveyed in Quang Xuong had heard of the virus when prompted, far less in Ngoc Lac had done so and awareness of the existence of a vaccine was very uncommon.

As was likely to have been the case in many developed countries only two or three decades ago, knowledge of the causes of liver disease in the local community was poor, with food or water-borne causes and alcohol mentioned by those who knew any at all (Chapter 2B). However, for the reasons outlined in Chapter 2B and given its importance as a cause of morbidity and mortality (Chapter 3), SIAMC considered it important to

elevate community awareness of HBV as a cause of chronic liver disease in Vietnam prior to the expanded introduction of the vaccine. Accordingly, in the last three years the project introduced a number of simple measures to do just this, with inputs stratified in order to determine how much (or how little) was required to stimulate an adequate level of knowledge.

The inputs included spoken and printed orientation and training activities targeted at health staff and community leaders at district, commune and village levels, and, through trained village-level promoters, ordinary people at grassroots level. As most people in rural Vietnam are busy, the activities rarely took more than half a day and were often combined with information dissemination on other topics, such as neonatal tetanus or malaria, also areas of focus for the project in Thanh Hoa. Verbal orientations or formal training of HWs were supported by leaflets, posters, roadside billboards and broadcasts from local loudspeakers using taped materials prepared by project staff. All of these inputs were made in the project ideal and routine communes, but not in control communes. In these, only some more general inputs on improving the EPI were made – information on HBV was specifically omitted from community education activities in these communes. The other differences between project strata are outlined in Chapter 6, but did not relate specifically to HBV education or community mobilisation.

The results of this survey show the outstanding success of this relatively simple approach, and augur well for its replication elsewhere, assuming funding is identified. Not only did most respondents demonstrate an improved knowledge of the importance of liver disease as a cause of morbidity and mortality, but also that causes of liver disease in their community may be contagious, including from mother to infant and from people who look well to others (data not shown). Moreover, improvements seemed not to be restricted to the ideal and routine strata, with improvements across all communes noted. Clearly the inputs were either being replicated by district health staff through their regular meetings with other HWs, or the education materials produced and distributed in ideal and routine communes either filtered around the districts or were seen by those in control communes too, imparting knowledge more generally than anticipated. This

secondary gain of what was already a rather modest set of inputs by comparison to that which supported Taiwan's HepB vaccine program (Wong WC & Tsang KK, 1994), was a surprising and encouraging finding.

Several specific findings are worthy of comment. The first is the difference between the Ngoc Lac control communes and the rest. In fact, the choice of project stratum for the initial group of nine communes in each district was not random, and did in some cases (of necessity for the scientific research reported in Chapter 6) include consideration of whether staff in those communes were considered capable (either geographically or personally) of delivering vaccine to infants born at home as required by the ideal strategy. Accordingly, it is not surprising that given their apparent isolation and relative socio-economic position (much lower rates of TV ownership and lack of electricity), householders in these communes appeared to have less knowledge in two areas (liver disease and having heard of HBV) than respondents in other strata. Although improvements over baseline were still noted even in these communes, this suggests that inputs may need to be more intense in similar locations to these, which fortunately are usually well known to local leaders and health staff.

There was an interesting finding in the regression models looking at predictors for good knowledge on liver disease. Apart from the predictable variables such as education level, stratum and certain types of knowledge, proximity to a loudspeaker in one model seem to be associated with a better performance on these questions, despite having decreased in the frequency with which it was nominated as a source of awareness about the EPI in Quang Xuong. Although there were concerns about the fidelity of the broadcasts made and whether in fact people were paying any attention to them, the fact that SIAMC did broadcast information relevant to HBV and liver disease and that in this analysis it was significantly associated with knowledge about the latter suggests that used appropriately, these may indeed be a good tool for community mobilisation.

Also interesting in these regression analyses was the reasonably consistent finding that, controlling for all the other variables in the model, Ngoc Lac respondents had better

knowledge than those in Quang Xuong. It is important to remember that residents in this district are poorer, more isolated and less well educated than those in Quang Xuong. Accordingly, it is important for health planners to know that controlling for these and other probably important variables for which those assessed may be proxies, householders in Ngoc Lac had apparently better knowledge than those in Quang Xuong. This belies the commonly held belief that it is more difficult to impart information to ethnic minorities in Vietnam.

The most impressive changes in knowledge were in that pertaining to causes of liver disease and HBV itself. Unprompted mentioning of HBV as a cause of liver disease increased almost 15-fold since baseline, and in total around 80% of all respondents knew when prompted that HBV is one such cause. Furthermore, approximately 74% of all respondents knew that immunisation to prevent HBV infection is possible. These figures compare to around 20% and 10% for these parameters at baseline. There were, however, interesting and unexpected differences in the proportions that responded affirmatively to having heard of HBV across the different strata, favouring particularly the ideal over the routine in both districts, and as mentioned above, the routine over the control in Ngoc Lac. This difference between the two strata where similar education and community mobilisation activities were conducted was not anticipated. It may suggest that the financial incentive initially offered to VHVs and CHVs and the more visible role of the CHVs in promoting HBV prevention through home delivery of HepB vaccine to infants in ideal communes (Chapter 6) were important factors in promoting knowledge.

There were small improvements in the already high regard for and knowledge of respondents on the EPI, but an ongoing low proportion of mothers with access to records of their children's vaccinations. In fact, reflecting the inconsistent distribution of EPI-cards by district and commune health authorities in these two districts at baseline, the project did not give adequate priority to individual under-five or EPI cards for mothers, partly because of the use of the birth register / EPI record form in ideal communes (Chapter 6 and Appendix 9). But clearly this remains an area with great need for improvement. Vietnam's population is now far more mobile and, it would seem, clearly

very aware of the aims and intentions of the EPI, so it seems logical for mothers to keep such a record. Reasons given previously for not using these cards relate to their frequent loss, their lack of durability and lack of knowledge that they exist. These suggest that the cards were poorly promoted, designed and probably prioritised at the outset, and may also be an example of the state-run health system taking responsibility for EPI coverage, rather than allowing mothers to consult their own records and determine their infants' need for vaccination. Personal conversations with the EPI leadership in this country suggest that they are aware that the availability of a home based record of infant EPI status is inconsistent and needs improvement. Introduction of HepB vaccine with a birth dose is just the opportunity to do this.

Two other improvements were noted by this survey. The first relates to the increased frequency of EPI access for mothers in Ngoc Lac, and the perception of Quang Xuong respondents that the EPI is less immediately accessible to them than at baseline. It is postulated that this change has occurred following project training of CHWs on organisation of the EPI to ensure best and timeliest coverage. Most communes in Quang Xuong are now conducting the EPI at fixed points each month, usually at the CHS (Chapter 7A). Thus fewer outreach visits are being made to villages, and for mothers without infants, it may appear that immunisation is less accessible. By contrast, in Ngoc Lac, delivery of vaccines is much more regular, seems to occur to a schedule around each commune and is given more priority by the district health service. These are major changes for these communes, but once again were achieved with relatively small inputs of training of CHWs and discussion at district level.

Finally, increases were noted in the numbers of women delivering babies at the CHS in both districts. Whilst some of this may have been due to the new availability of HepB vaccine at the CHS throughout the month in ideal and routine communes, most likely the arrival of new delivery beds and obstetric equipment as part of the World Bank-funded National Health Strengthening Project was a bigger influence.

In the report on the baseline household survey (Chapter 2B) it was concluded that the introduction of monovalent HepB vaccine requires a comprehensive promotion strategy with appropriate messages targeting particular groups and that appropriate means of communication must accompany the program. The findings of this survey would suggest that in Vietnam at least, this will not be a very difficult task, provided funding is available for the production of relevant materials, community mobilisation and HW education. There are frequent local meetings of mass organisations and relevant professional groups (teachers, HWs) and also informal gatherings at markets, schools and even sporting events which can be used opportunistically to promote HepB vaccine at low cost.

As recommended by UNICEF Vietnam (UNICEF, 2001b) and used in this project, a combination of community mobilisation approaches will be needed to promote the introduction of HepB vaccine. Ideally, to promote its uptake beyond the group targeted by the EPI (to include older children in particular), and so facilitate the more rapid reduction of HBV transmission which has been achieved in the Pacific (Mahoney FJ, Woodruff BA et al, 1993), Alaska (Harpaz R, McMahan BJ et al, 2000) and Taiwan (Chen HL, Chang MH et al, 1996), a multi-media approach should be attempted, as it is for the second-dose measles vaccine campaigns conducted in Vietnam. This is especially the case in inland or more remote areas of the country such as Ngoc Lac, where, as this survey indicates, education and knowledge levels are lower, access to HWs more difficult (both geographically and through less frequent contacts with programs such as the EPI) and some means of mass communication less accessible. The role of demand creation should also be emphasised, to facilitate birth-dosing even of home-born infants by HWs travelling from the CHS specifically to visit newborns and administer vaccine. As was seen in the Ngoc Lac routine communes' poor performance in this area (Chapter 6), and discussed in Chapter 2B, clearly the community has a role in calling for this, which role can only be stimulated by appropriate education and mobilisation.

Chapter 8: The influence of SIAMC on more objective markers of Vietnam's EPI

Introduction

Like any development assistance project, whether or not it has a major research component, SIAMC aimed to have a lasting impact on its main area of focus, the conduct of the EPI and introduction of HepB vaccine, if not throughout the nation then at least in the districts of Thanh Hoa in which it operated.

However, assessment of the conduct of the EPI is fraught with difficulty. Measurement of coverage itself relies on a combination of facility- or parent-held records or maternal memory, the accuracy of which vary greatly (Valadez JJ & Weld LH, 1992).

There are also problems with equating even reliable coverage data with vaccine efficacy. Known causes of vaccine failure, such as thermolability or cold sensitivity, inaccurate dosing, imperfect injection technique, variable immune responsiveness or even child substitution may collectively diminish a given population's degree of protection against vaccine-preventable diseases despite high coverage rates.

The most objective measure of the effectiveness of the EPI involves serological assessment of individuals' responses to vaccination. For example, the presence of measles antibody may be tested using commercially available kits which measure immunoglobulin M or G (IgG), both of which rise after immunisation or natural exposure to the measles virus (Department of Vaccines and Biologicals, 2000). Antibody responses to TT can also be measured, as can antibodies to *Corynebacterium diphtheriae* toxin, vaccine-associated polioviruses and various antigens of *Bordetella pertussis*, albeit less easily. The prevalence of the scar left by BCG vaccine in a population may be another useful indicator.

Although an EPI coverage survey was conducted in Thanh Hoa soon after project commencement, SIAMC did not hold great faith in the results due to disparity between

the reported and identified coverage rates, and based on comments from EPI staff in the province about the large amount of preparation that went into the survey itself. Instead, SIAMC was able to objectively evaluate its impact on the EPI in two districts of Thanh Hoa using two of the more objective indicators mentioned above.

The first evaluation compared the prevalence of BCG scarring amongst a cohort of 2 – 6 year old children (who were participating in another component of SIAMC) assessed for this indicator in July 2000 (effectively measuring EPI performance ~2 – 6 years previous to this) and amongst the infants sampled in the second serology survey (Chapter 6). The second compared the prevalence of IgG-type measles antibody amongst the infants sampled in the first and second serology surveys (Chapters 3 and 6).

It was predicted that the introduction of HepB vaccine and the general focus on the EPI provided by the project would result in increases in these two indicators. This Chapter reports the results of these evaluations.

Method

BCG scars

SIAMC included immunisation, malaria, intestinal parasite and tuberculosis components, each involving surveys and field activities. Although the immunisation component was primarily focussed on HepB vaccine, given the need to strengthen the EPI in general (Chapter 2A), it was decided during the second year of project implementation to assess for improvements in the broader program serologically and using the BCG scar. This was too late to include the recording of BCG scars on infants sampled in the first serosurvey, but early enough to include recording this on a group of 570 children mostly aged between 20 and 70 (mean, 44.4, range 15.1 – 77.3) months, on whom anthropometric and other measurements were made as part of the intestinal parasite component in mid-July 2000.

This survey was conducted in nine communes in Quang Xuong, none of which were in the first cohort of communes in which EPI strengthening and HepB vaccine were introduced in this district. The expanded introduction of HepB vaccine to all communes in Quang Xuong occurred in late June 1999, so that children of the age-range surveyed in mid-July 2000 were all born at least 3 and mostly 8 or more months before any project inputs in their locality. As Vietnam's EPI schedule includes birth-dose BCG, this effectively assessed the prevalence of immunisation with BCG during the period ~15 – 77 months prior to this survey.

Children surveyed resided in those nine communes of Quang Xuong considered by the local health service to be at highest risk for intestinal parasite infection. Lists of all the households containing CBAW and children in the age-range 2 – 5 years were prepared in each commune, and a total of 570 children were selected randomly from these lists.

Children attended the survey site, usually the CHS in each commune, with their mothers. Upon registration, BCG scarring was assessed by a doctor from the district health service and recorded by name. This assessment was repeated on the same children for each of three surveys done in the same communes in July 2000, March 2001 and September 2001. At the repeat surveys, mothers were asked if their child had received BCG since their last assessment.

Measles antibody

The methods for conduct of the first and second serosurveys were described in Chapters 3 and 6. Leftover serum from these two surveys was stored frozen below -20°C at NIHE. Samples were selected for thawing and testing for measles IgG using the Enzygnost Anti-Measles Virus/IgG ELISA (Dade Behring, Marburg, Germany), as recommended by and purchased from the WHO regional office in Manila. Testing was undertaken in the measles laboratory at NIHE, which participates in the WHO quality assurance program and has received on-site support from Dr Mike Catton, a specialist in serology at VIDRL (the regional WHO collaborating centre for virus reference and research). Dr Catton personally verified the quality of testing at this laboratory.

To avoid the possibility of interference from maternal antibody and to allow four weeks for antibody formation after the period during which Vietnamese infants are supposed to receive measles vaccine through the EPI (9 – 11 months of age), samples selected from amongst the frozen sera remaining were restricted to those taken from infants aged 13 – 18 months.

Results

Table 1 depicts the claimed national coverage of Vietnamese infants with BCG and measles vaccines for the years 1986, 1990 and 1996.

Table 1: Immunization coverage of children under 1 year of age, 1986–96

<i>Vaccine type</i>	<i>1986</i>	<i>1990</i>	<i>1996</i>
Tuberculosis (BCG)	54.5	89.9	95.4
Measles	38.8	86.6	96.0

Adapted from (Ministry of Health Vietnam, 1996)

BCG scars

Table 2 depicts the frequency of BCG scarring amongst 15 – 77 month old children surveyed in July 2000, and upon follow up in March and September 2001.

Table 2: Prevalence (in percent with 95% c.i.'s of the bacille-Calmet-Guerin (BCG) vaccine immunisation scar amongst 570 children aged 15 – 77 months in Quang Xuong district, July 2000, and on resurveying in March and September, 2001

Survey date	July 2000 (n = 570)	March 2001 (n = 557)	September 2001 (n = 552)
BCG scar present	64.6 (60.5-68.5) (n = 368)	75.0 (71.2-78.5) (n = 418)	82.6 (79.1-85.6) (n = 456)

Note that 40 children reported BCG vaccination between surveys one and two (10 discordant results as $368 + 40 = 408$, not 418), and 20 between surveys two and three (18 discordant results as $418 + 20 = 438$, not 456), raising the possibility of misinterpretation of scars or child substitution across the surveys.

The frequency of BCG scarring amongst a cohort of infants delivered after the introduction of HepB vaccine and the implementation of measures to improve the EPI in Quang Xuong, assessed during the conduct of the second serosurvey, was 92.2%. Although no baseline figure is available for Ngoc Lac district, amongst 527 infants surveyed there in October 2001, BCG scarring was visible in 77%, also higher than the figure amongst 15 – 77 month old children in Quang Xuong (Table 2). In total, 83% of those surveyed in both districts at follow up had a BCG scar, as compared to 64.6% in Quang Xuong at baseline.

Measles antibody

The presence or absence of measles antibody in serum samples from infants aged 13 – 18 months at baseline (August 1998) and at follow up (October 2000) is depicted in Table 3.

Table 3: Prevalence (percent with 95% c.i.'s) of measles antibody amongst 13 – 18 month-old infants at baseline (August 1998) and follow-up (October 2001)

		Measles antibody level		
		Greater than zero	Zero	Total
Serosurvey	1	57.8 (51.4-63.9) (n = 145)	42.2 (36.1-48.6) (106)	100 (251)
	2	47.9 (42.2-53.6) (147)	52.1 (46.4-57.8) (160)	100 (307)

In fact, the infants sampled in the second survey seemed less likely to have measles antibody than those in the first ($\chi^2 = 3.30$, $P = 0.07$).

Discussion

Assessment of the prevalence of BCG scars and especially measles serology to evaluate the conduct of the EPI is not a common practice in developing countries. Examples exist (Kwamanga D, Githui W et al., 1993), (Fortuin M, Maine N et al., 1995), but in general the expense of such surveys precludes routine evaluation of this program in this way. In addition, there may be reluctance to bleed infants or children in the appropriate age

groups, and uncertainty as to whether, in the case of measles, the presence of antibodies represents a response to immunisation or natural infection. New methods such as measurement of salivary antibody may make such surveys more feasible in future (Nokes DJ, Enquesselassie F et al., 2001), but await further evaluation. Most nations, including Vietnam, rely on coverage surveys, which assume that vaccine administration is equivalent to vaccine efficacy.

The findings reported here verify objectively the problems outlined in Chapter 2, and confirm that despite the improvements observed (Chapter 7), the standard of the EPI in Quang Xuong and Ngoc Lac and, by inference, other Thanh Hoa districts, is well below what is suggested by the coverage data released by the provincial health service (see Appendix 4). The prevalence of BCG scarring at baseline, 64.6%, was well below the rate of 93% reported in the 1998 survey (Appendix 4). In addition, even at follow up, there was a very worrying low level of measles immunity amongst those tested. The better response to SIAMC of BCG-scar rates than measles antibody prevalence verifies that timely and effective access of the communities to the EPI improved during the course of the project, but as identified by many others working at grassroots level in Vietnam and mentioned in Chapter 1, it is difficult to influence service utilisation (Multidonor Health Sector Review Committee, 2001), apparently even by older infants, a critical factor in the campaign against measles (Edmunds WJ, Gay NJ et al., 2001).

There are a number of methodological considerations possibly impacting on the measles data reported here. These include problems with the handling of the specimens (including repeated freezing and thawing), the quality of the laboratory work and that this merely verifies that vaccination is not the same as immunisation. There is also the possibility of poor antibody responses due to residual presence of maternal antibody in some infants (Markowitz LE, Albrecht P et al., 1996). Of greater concern, however, is the likelihood that despite project inputs, this survey has identified a true paucity of measles immunity amongst a group of infants in rural Vietnam at an age by which effective measles vaccination should have been and, according to official reports, has been implemented.

Chapter 9: Summary, final discussion and suggestions for further research

SIAMC was conducted in a milieu of widely acknowledged achievement for the Vietnamese National EPI, including high, published coverage levels, falling incidence of measles and the nation's inclusion as one of a regional group proclaimed polio-free in October 2000. Towards the end of the project, the EPI was expanded to include second dose measles vaccine campaigns, planned use of AD syringes for all vaccinations and the expanded introduction of HepB vaccine for infants beyond certain urban areas. The latter was made possible through Vietnam's successful application to GAVI for a bridging supply of the vaccine, pending the assisted development of its own recombinant DNA vaccine, and is being conducted using strategies demonstrated as feasible by SIAMC.

SIAMC followed the usual project cycle of baseline assessments, implementation of activities with periodic monitoring and evaluation of outcomes at completion. At baseline, the level of knowledge about liver disease was mediocre, and few had heard of HBV as a cause of this common problem in Vietnam. HBV infection was present at high levels in all age groups, and exposure increased monotonously with age. The practices of EPI workers were of an alarmingly low standard, despite the high coverage levels they were reporting. Recording and reporting, injection safety and cold chain issues were major concerns.

Project interventions included HW training, community education to support birth dosing and the need for three more injections for infants in Vietnam, improved supervision and monitoring of CHW activities and a small amount of monetary and material input. The inputs were not considered to be complex or expensive, although at the time of writing, funding to support similar inputs elsewhere in the country is lacking, despite the rapidity with which HepB vaccine is being made available in 44 provinces. It remains to be seen whether birth dosing is feasible in areas similar to Ngoc Lac without the financial incentives and other project inputs SIAMC introduced in the ideal communes there. However, given current EPI reporting practices (Chapters 2A and 8), it is likely that the introduction of HepB vaccine will be "highly successful" and that birth dosing within

three days of delivery will “reach” the high levels “applying” to full EPI coverage. A more open and qualitative examination of the EPI in Vietnam should be conducted to confirm the extent of the problems identified in Chapter 2A and suggested by the findings reported in Chapter 8. Such a survey would hopefully facilitate mobilisation of funds to support the improvements needed and real success in eliminating HBV transmission in Vietnam.

At the time of project design and for much of its duration, given the strong preference for use of local product, the only option for Vietnam to expand the availability of HepB vaccine to its infant population was for the government to increase its purchase of the low-dose, locally produced plasma-derived vaccine. In these circumstances, SIAMC conducted hospital-based and field assessments of this vaccine, as described in Chapters 4, 5 and 6. This vaccine will continue to be used in 17 of Vietnam’s 61 provinces until at least the year 2006. Although adequately immunogenic in a high proportion of recipients, the vaccine performed less well than a higher dose of the same product and two other HepB vaccines imported from Korea, inducing lower rates of production of anti-HBs and possibly being less protective amongst infants of HBV-carrier mothers. SIAMC concluded and has recommended locally that a higher dose of this vaccine be used for infants in these 17 provinces, but no action has been taken by the national EPI.

Vietnam is proceeding with a strategy of HepB vaccine introduction that presumes that its immunogenicity and PE are maintained whether the vaccine is stored cold or at ambient temperature for the first dose. Use after storage outside the cold chain is based on reports of controlled and field-based research (summarized in Chapter 4), but this has only addressed the question of immunogenicity; there is currently no published evidence for or against the PE of HepB vaccine used in this way. SIAMC attempted to address this question but the lack of PE of the local product, whether stored cold (Chapter 5) or “warm” (Chapter 6) for the first dose did not enable it to provide a clear answer. Certainly there was a marked (75%) reduction in the risk of infection amongst infants who received HepB vaccine “stored warm” if it was given on the day of birth, but not beyond this time.

This finding introduces another question not answered by the existing scientific literature - the timing of the birth dose, whether stored cold or “warm”, in regimens lacking HBIG - and which this research attempted to answer (Chapter 6). Unfortunately, the contribution of this thesis to this question is only to confirm its importance and the need for future research amongst infants of HBeAg + mothers. As indicated above, although the findings confirmed that birth dosing in vaccine-only regimens is important and more effective than vaccination at a later date, even if the vaccine is stored “warm”, tentatively it suggests that most of its benefit is achieved amongst infants vaccinated on the day of birth – clearly unrealistic in much of rural Vietnam and similar countries. Most likely, for the reasons discussed in Chapters 4 and 6, there is a continuum of benefit, highest for infants immunised immediately after birth and decreasing thereafter, but it is possible that birth dosing by outreach beyond the day of birth may not be worth the effort. Of course, this ignores the probable benefits of the home visit this would require, if such a visit includes other maternal and child health initiatives. Unfortunately, the vertical organization of Vietnam’s EPI means that although HWs in Vietnam are being encouraged to give a birth dose of HepB vaccine by day 3, no promotion of these other initiatives (such as the conduct of a baby check, assessment of the mother’s TT status, lactation and plans for contraception, and examination for post-partum haemorrhage) is being conducted.

Introduction of HepB vaccine in this project was conducted using three different strategies, two of which included the storage of the first dose at ambient temperature for up to one month and making a birth-dose available to all newborns. SIAMC concluded that local HWs are eminently capable of giving a birth dose of HepB vaccine to newborns in rural Vietnam, particularly in densely populated, flat, coastal areas where most people are of the Kinh ethnic majority. Greater inputs are needed where rates of home-birth are higher and the population is more dispersed, less accessible, less educated and possibly less demanding, although the increase in the level of knowledge of the population in these areas after SIAMC was very encouraging. In addition, the follow up surveys of householders and HWs identified major improvements in most areas of relevance to

introducing HepB vaccine and conducting a safe and effective EPI, suggesting that similar inputs to those of SIAMC would yield a very positive outcome for Vietnam if made across the country.

In summary, SIAMC identified a pleasing capacity amongst rural Vietnamese communities and HWs to absorb new information, accept inconvenient and unfamiliar interventions in the interests of improving the health of their children, and that in large part this has been accompanied by substantial scientific benefits. Although targeting of more remote and socio-economically deprived communities with a greater level of input is still required, thanks to the new supply of vaccine, Vietnam is now on the cusp of dramatically reducing the effects of HBV infection on its future generations.

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Appendix 1

Action Plan For the Introduction of Hepatitis B Vaccine

into Immunization Services

Expanded Program on Immunization

The Socialist Republic of Viet Nam

(co-written by Dr David Hipgrave, University of Melbourne)

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Executive Summary

Hepatitis B (HB) is a serious cause of morbidity and mortality in Viet Nam and the epidemiology of this infection in Viet Nam resembles that in other South-East Asian nations before the introduction of HB vaccine. A 1998, age-stratified seroprevalence study of HB infection in Thanh Hoa province in the Northern Region found a high rate of current, presumed chronic infection amongst over 1500 persons tested, and a rate of exposure approaching 80% in adults. Most of the exposures resulting in chronic infection occurred in infants and young children.

A locally produced plasma-derived HB vaccine was introduced into Viet Nam's routine Expanded Programme on Immunization (EPI) in 1997, but there are insufficient resources to enable expanded use of this vaccine nationwide. The first dose of this HB vaccine is currently given with the first EPI contact, usually several weeks or months after birth, and the second and third doses with contacts for DPT.

Viet Nam has applied to the "new and under-used vaccines sub-account" of the Global Alliance for Vaccines and Immunisation (GAVI) for vaccine and safe injection equipment to enable universal infant HB immunization in this country. Monovalent HB vaccine will be used nationwide. In provinces using GAVI-supplied vaccine, efforts will be made to administer the first dose at birth, or as soon as possible thereafter, at the latest within three days of delivery. In many facilities this will involve storing the vaccine outside the cold chain for up to one month. For infants born at home, a system of birth reporting and home-visits by a qualified health worker to administer the birth dose will be instituted. The second and third doses will be given with DPT1 and DPT3.

In this document, a five-year plan for 2002-2006 is presented, requiring a total of 20,080,154 doses of vaccine from GAVI (as single doses in UnijectTM for the first dose, and 2 dose vials for subsequent doses), plus 12,253,261 auto-disable (AD) syringes and an appropriate number of safety boxes. In the near future, Viet Nam will establish local production of AD syringes, safety boxes and recombinant HB vaccine. Negotiations to establish a Uniject filling line in this country are also proceeding. Pending assurance of quality, funding of these for the EPI will be negotiated within the Immunisation Coordinating Committee mechanism. This will ensure sustainability of HB vaccination in Viet Nam.

Expansion of HB immunisation using vaccine provided by GAVI will commence in January 2002 in 44 provinces, following a small pilot to identify potential operational difficulties, most probably using the local vaccine. In 2002, 50% of the birth cohort will be targeted for vaccination in 39 of these provinces, and 100% in the other five. In 2003 the target group will be extended to 100% of the birth cohort in all 44 provinces. Vaccination coverage targets, with three doses of HB vaccine by 12 months of age, have been set at 85% by 2004, and 90% by 2005. Infants born in the remaining 17 provinces of Viet Nam will receive the locally produced vaccine. As this vaccine has not received local approval for use outside the cold chain, it will be administered as part of the routine EPI, using the existing immunisation schedule.

¹ Uniject is a trademark of the Becton Dickinson corporation

A plan for safe injection was attached to the GAVI application. According to this plan, locally produced AD syringes and safety boxes will be used for all EPI vaccines by 2004, and disposed of by burning. Training in safe immunization practices has commenced and will continue in all future EPI training activities.

The EPI has been using 20 dose vials of DPT, and provinces report wastage rates of approximately 40%. Strategies to reduce wastage, many of them involving substantial improvements to the EPI in Viet Nam, will be implemented. Targets for reduction in wastage from the current level of 40% have been set at 25% in 2002, reducing to 15% by 2005. These targets will apply to the multi-dose vials of HB vaccine supplied by GAVI. Wastage of the local HB vaccine, produced in 2-dose vials, is reported at 22%.

The volume of cold storage at regional, provincial and district levels have been considered in developing this plan. It is calculated that the volume of refrigeration required for EPI vaccines will be adequate at all levels to accommodate the addition of HB vaccine in the formulations proposed.

An appropriate program of health worker education will be conducted, and demand created for HB vaccine through a program of community mobilisation. Administrative forms and immunization cards have already been revised to include the new vaccine throughout the country.

Evaluation of the HB vaccination program will be accomplished through routine monitoring of reported coverage data. Two key performance indicators, the percentage of children receiving the first dose within 3 days of birth, and the percentage receiving the third dose of HB vaccine will be monitored. A follow-up coverage survey will also be undertaken to confirm the results of the routine coverage surveillance. Simplified baseline and follow up surveys of markers of HB infection will be conducted in sentinel sites at the outset, and repeated in 2004.

Background and Purpose

In 1999, the Socialist Republic of Viet Nam, comprising 61 provinces, 623 districts and 10,331 communes, had a population estimated at 76,327,900, 2% aged under 1 year. The population growth rate is 1.5%. The EPI, which began in 1981, includes BCG, OPV, DPT and measles throughout the nation, and HB vaccine in selected districts. The Government of Viet Nam (GOV) was able to fund 67% of vaccines in 2000, the remainder being funded by UNICEF and other donors. All syringes and the maintenance of cold chain equipment are locally funded. All the vaccines used in the EPI, with the exception of measles, can be produced in Viet Nam.

The Ministry of Health (MOH) issued a new vaccination schedule in 1997, and with the assistance of international agencies such as UNICEF and WHO, has improved immunization services and the training of staff. A National EPI evaluation, led by UNICEF and WHO consultants, was conducted in October 1998.

A locally produced plasma-derived HB vaccine was introduced into Viet Nam's routine Expanded Programme on Immunization (EPI) in 1997. Initial use of the vaccine began in the two largest cities, Hanoi and Ho Chi Minh City, and was extended to selected (mainly urban)

districts in 28 of 61 provinces in 1998, and 39 provinces in 1999. However, nationwide use of this vaccine is not possible, as neither sufficient financial resources nor raw material exist to support expanded production. Recently, an agreement has been signed between the Governments of Viet Nam and Korea providing for technical transfer to enable local production of a recombinant HB vaccine in Viet Nam. It is anticipated that production of this new vaccine will commence within three years.

The purpose of this document is to outline Viet Nam's plan for expanded introduction of HB vaccine into the national EPI, using interim support by way of vaccine and safe-injection equipment supplied by GAVI.

The HB Disease Burden in Viet Nam

A survey performed in 1998 on 1579 persons in Thanh Hoa province in the Northern Region examined the seroprevalence of markers of HB infection in four age groups – infants (9-18 months), children 4-6 years, adolescents 14-16 years and adults 25-40 years. The results showed an overall proportion currently infected of 17.2%, increasing from 12.5% in the infants, to 20.5% in the adolescent and 18.8% in the adult groups. Of concern was the presence of HB “e” antigen, which indicates a greatly increased risk of perinatal transmission, in 30% of infected adults. This is in line with data from Taiwan where 35 – 45% of chronic HB infection is estimated to result from perinatal exposure (Maynard, 1989), and where infection rates have fallen dramatically following the introduction of vaccination of newborns.

The survey also found that the prevalence of anti-HBc, indicating exposure to the HB virus, showed a significant upward trend from 18.3% in the infant group to 78.2% in the adult group. Overall, this survey, along with other data collected in Viet Nam, demonstrates a pressing need for universal infant immunization with HB vaccine, to prevent perinatal transmission and provide long lasting protection.

Surveillance for acute viral hepatitis in Viet Nam is based on reports of hospitalized persons with jaundice. As the availability of laboratory testing is limited, diagnosis of acute hepatitis is made based on clinical characteristics. Because clinical features cannot distinguish hepatitis A from HB, the designation of the type of hepatitis in official surveillance reports is likely to be inaccurate. In addition, since the majority of acute HB virus infections, especially among children, are asymptomatic, the burden of disease is greatly underestimated by reports of hospitalized cases of jaundice.

Similarly, a lack of testing or post-mortem examination suggests that surveillance for diseases known to result from chronic HB infection is likely to underestimate their incidence in Viet Nam. Official statistics report 2973 cases of “malignant neoplasms of the liver and bile ducts” (73 deaths), and 6861 cases (250 deaths) due to cirrhosis of the liver in 1999. However, most cases of these disorders probably go undiagnosed.

Goals and Objectives of HB Immunization

The ultimate goal of HB vaccination is to reduce morbidity and mortality associated with chronic HB infection, including liver cirrhosis and hepatocellular carcinoma. However,

because these consequences of HB infection usually do not occur until decades after infection, short-term goals and objectives have been defined. These include:

- Phased introduction of HB immunization for all newborns across the country, beginning in 2002 and completed in 2003
- Delivery of HB and all other EPI vaccines according to safe injection practices;
- Training of EPI staff and sensitization of policy makers and the community about HB infection and HB vaccine;
- Reduction in vaccine wastage by introducing an open vial policy and other measures;
- Coverage with three doses of HB vaccine by 12 months of age of 85% by 2004, and 90% by 2005.

Plan of action for Vaccine Introduction

In the last third of 2001, a small pilot project to assess possible operational difficulties in administering a birth dose of HB vaccine will be implemented. This will build upon a similar project conducted in Thanh Hoa by PATH and other partners over the last 3.5 years. Two districts have been chosen, Soc Son in Ha Noi province (population last year = 248,078 in 26 communes, with ~4116 births per year), and Bien Hoa in Dong Nai (population 470,000 also in 26 communes, with ~8,100 births per year). All commune health stations (CHSs) in these districts have refrigerators and the local vaccine will be used. Alternatively, if available by September, HB vaccine pre-filled in Uniject devices may be used for the first dose. A program of community mobilisation and health worker education, using materials already developed by PATH and the MOH, will be incorporated. Lessons learned from this project will be built into the expansion of HB immunisation using the GAVI vaccine.

In January 2002, introduction of HB vaccine using vaccine supplied by GAVI will begin in 44 provinces. In 39 of these, 50% of the birth cohort will be offered the vaccine, extending to 100% in 2003. In the remaining five provinces (Ha Noi, Thai Binh, Da Nang, BR-Vung Tau and Ho Chi Minh), all newborns will be targeted from 2002. This phasing allows time for adequate supplies of HB vaccine pre-filled in Uniject to become available; for training of health care workers and key local figures about the vaccine, particularly the need for a birth dose; and for a program of community education and mobilization.

From the beginning of 2002, all infants in the remaining 17 provinces will receive the locally produced vaccine, using the existing dosing schedule. No phasing is planned in these provinces. The vaccine will be distributed in 2-dose vials as it is currently.

Vaccination coverage targets, with three doses of HB vaccine by 12 months of age, have been set at 85% by 2004, and 90% by 2005.

This plan for phasing of the expanded introduction of HB vaccine in Viet Nam, separating provinces according to vaccine type, is tabled below (table1).

Table 1. The introduction of HB vaccine into immunization services by province.

GAVI-vaccine provinces		Infants aged under 12 months (allowing for annual increase of 1.5%)					
		2000	2002	2003	2004	2005	2006
1	Ha Noi*	44,222	45,559	46,242	46,936	47,640	48,354
2	Thai Binh*	25,448	26,217	26,610	27,010	27,415	27,826
3	Phu Tho	21,873	11,267	22,872	23,215	23,563	23,917
4	Hai Duong	25,598	13,186	26,767	27,169	27,576	27,990
5	Thanh Hoa	61,116	31,482	63,908	64,866	65,839	66,827
6	Nghe An	51,822	26,694	54,189	55,002	55,827	56,664
7	Bac Ninh	18,036	9,291	18,860	19,143	19,430	19,721
8	Ninh Binh	13,364	6,884	13,974	14,184	14,397	14,613
9	Vinh Phuc	18,654	9,609	19,506	19,799	20,096	20,397
10	Ha Tinh	26,286	13,540	27,487	27,899	28,317	28,742
11	Thua Thien Hue	23,799	12,259	24,886	25,259	25,638	26,023
12	Khanh Hoa	23,177	11,939	24,236	24,599	24,968	25,343
13	Quang Ngai	26,616	13,710	27,832	28,249	28,673	29,103
14	Phu Yen	22,169	11,420	23,182	23,529	23,882	24,241
15	Binh Thuan	23,539	12,125	24,614	24,983	25,358	25,739
16	Long An	23,281	11,992	24,344	24,710	25,080	25,456
17	Dong Nai	44,883	23,120	46,933	47,637	48,352	49,077
18	An Giang	46,084	23,738	48,189	48,912	49,646	50,390
19	Tra Vinh	23,672	12,194	24,753	25,125	25,501	25,884
20	Bac Lieu	19,204	9,892	20,081	20,382	20,688	20,998
21	Tien Giang	36,500	18,802	38,167	38,740	39,321	39,911
22	Lam Dong	24,045	12,386	25,143	25,520	25,903	26,292
23	Can Tho	43,562	22,439	45,552	46,235	46,929	47,633
24	Dong Thap	37,344	19,236	39,050	39,636	40,230	40,834
25	Binh Phuoc	17,448	8,988	18,245	18,519	18,796	19,078
26	Binh Duong	14,699	7,572	15,370	15,601	15,835	16,073
27	Tay Ninh	20,090	10,349	21,008	21,323	21,643	21,967
28	Vinh Long	18,717	9,641	19,572	19,866	20,164	20,466
29	Dac Lac	51,638	26,599	53,997	54,807	55,629	56,463
30	Gia Lai	26,018	13,402	27,206	27,615	28,029	28,449
31	Hai Phong	25,461	13,115	26,624	27,023	27,429	27,840
32	Nam Dinh	33,244	17,124	34,763	35,284	35,813	36,350
33	Thai Nguyen	17,056	8,786	17,835	18,103	18,374	18,650
34	Ha Tay	49,600	25,550	51,866	52,644	53,433	54,235
35	Hung Yen	23,269	11,986	24,332	24,697	25,067	25,443
36	Da Nang*	11,346	11,689	11,864	12,042	12,223	12,406
37	Binh Dinh	32,502	16,742	33,987	34,496	35,014	35,539
38	Soc Trang	27,151	13,986	28,391	28,817	29,249	29,688
39	Ben Tre	19,842	10,221	20,748	21,060	21,375	21,696
40	Kien Giang	34,291	17,664	35,857	36,395	36,941	37,495
41	Ca Mau	29,154	15,018	30,486	30,943	31,407	31,878
42	BR-Vung Tau*	18,260	18,812	19,094	19,380	19,671	19,966
43	HCM*	92,400	95,193	96,621	98,070	99,541	101,034
44	Kon Tum	8,526	4,392	8,915	9,049	9,185	9,323
	Subtotal	1,295,006	765,808	1,354,160	1,374,472	1,395,089	1,416,016

Doses of vaccine to be supplied by GAVI, assuming coverage in tables 4 and 5	In Uniject	806,395	1,264,651	1,230,221	1,322,126	1,341,958
	In 2-dose vials + AD syringes	2,041,643	3,201,862	2,920,752	2,953,124	2,997,422

*provinces where 100% of the birth cohort will be offered vaccine in 2002.

Table 1. The introduction of HB vaccine into immunization services by province (continued).

Provinces where local vaccine will be used	Infants aged under 12 months (allowing for annual increase of 1.5%)					
	2000	2002	2003	2004	2005	2006
45 Ha Nam	14,722	15,167	15,394	15,625	15,860	16,098
46 Tuyen Quang	14,309	14,741	14,963	15,187	15,415	15,646
47 Yen Bai	19,025	19,600	19,894	20,192	20,495	20,803
48 Lao Cai	19,033	19,608	19,902	20,201	20,504	20,812
49 Son La	29,070	29,949	30,398	30,854	31,317	31,786
50 Lai Chau	18,400	18,956	19,240	19,529	19,822	20,119
51 Bac Kan	7,180	7,397	7,508	7,621	7,735	7,851
52 Cao Bang	10,938	11,269	11,438	11,609	11,783	11,960
53 Ha Giang	17,755	18,292	18,566	18,845	19,127	19,414
54 Hoa Binh	16,945	17,457	17,719	17,985	18,255	18,528
55 Quang Ninh	18,355	18,910	19,193	19,481	19,774	20,070
56 Lang Son	18,000	18,544	18,822	19,105	19,391	19,682
57 Bac Giang	30,618	31,543	32,017	32,497	32,984	33,479
58 Quang Nam	28,060	28,908	29,342	29,782	30,229	30,682
59 Ninh Thuan	10,521	10,839	11,002	11,167	11,334	11,504
60 Quang Tri	13,070	13,465	13,667	13,872	14,080	14,291
61 Quang Binh	17,511	18,040	18,311	18,586	18,864	19,147
Subtotal	303,512	312,686	317,376	322,137	326,969	331,873
Doses of vaccine to be supplied by Viet Nam	All in 2-dose vials	938,059	895,763	966,023	1,038,192	1,053,764
Total infants offered HB vaccine	303,512	1,078,494	1,671,536	1,696,609	1,722,058	1,747,889
Total surviving infants	1,598,518	1,646,833	1,671,536	1,696,609	1,722,058	1,747,889

Vaccine delivery - Birth dose of HB vaccine

The feasibility of birth dosing with HB vaccine depends on the proportion of women who are attended during or soon after delivery by a health worker who is legally qualified to administer injectable medication in Viet Nam. This includes all qualified medical and nursing personnel, but not village health workers (VHWs) or traditional birth attendants unless they have received formal training previously. The 2000 multi-indicator cluster survey found that 84% of Vietnamese women received assistance at delivery by professional health workers, such as a doctor or midwife, but that there were large variations between provinces. For example, in highland areas in the north-west and north-east, less than 50% of women had such professional assistance.

In the 44 provinces in which GAVI-supplied vaccine will be used, where delivery occurs in a health facility and/or a health professional is in attendance, it is planned that the birth

dose will be administered using imported vaccine in Uniject, preferably within the first 24 hours, and definitely within 3 days. Where cold chain facilities exist, vaccine will be stored cold, with strict attention to careful ordering, stock rotation and checking of vaccine vial monitors. Particular attention will be paid to ensuring that the HB vaccine is not exposed to temperatures less than 2°C.

Where the birth occurs outside a birth facility, the birth dose will be delivered by a health worker through an outreach program, again using HB vaccine in pre-filled Uniject. Uniject will ensure ease of administration, minimize vaccine wastage and also program and maternal concerns about injection safety for the newborn.

In these 44 provinces, where no refrigeration exists, HB vaccine will be stored out of the cold chain for a maximum period of one month, with careful attention to stock rotation and checking of vaccine vial monitors (VVMs). Uniject vaccine will be ordered every fortnight from the district health office, based on the expected number of births in that period and referring to the stock of vaccine on hand, as has been successfully undertaken in Indonesia (Sutanto, 1999). Negotiations for the local filling of blank Uniject devices have also been proceeding. If successful, this will ensure the sustainability of the model to be introduced with GAVI support.

There is a plan for the introduction of additional refrigeration facilities at some CHSs with support from the government of Luxembourg for which negotiations are still proceeding. This assistance will account for the lack of or inconsistent power supply in parts of Viet Nam by including a mixture of electric and gas-powered refrigerators for use at CHS-level, and will obviously also enable a birth dose using the locally produced HB vaccine to also be introduced in the remaining 17 provinces. The National EPI will co-operate with WHO, UNICEF and/or CVP/PATH in any follow up studies to confirm the efficacy of HB vaccine stored out of the cold chain.

Early registration of births, particularly those occurring at home, will be vital to ensure high coverage and timely administration of the birth dose. This will be achieved along the lines of the successful pilot project undertaken by PATH and its partners in Thanh Hoa, in which the existing network of VHWs and family planning workers were requested to notify the CHS soon after the delivery of an infant, whereupon a qualified health worker would travel to the home to administer vaccine stored for up to one month at the CHS. A key element of this project's success was community awareness of the benefits of and need for the vaccination of newborns against HB, and hence the creation of demand. A major health worker education and community mobilisation campaign will be required to ensure successful, wide scale implementation of this plan. Encouragement of early birth registration will be a key feature of these campaigns. In this plan, three days are allowed for communication of the birth of an infant to the CHS and travel of a qualified health worker to the infant's home to give the birth dose and undertake other perinatal health checks.

Subsequent doses of HB vaccine will be administered at the same time as DPT1 and DPT3. If a birth dose was not given or was given but not recorded, three doses will be given at the same time as DPT1, DPT2 and DPT3. Additional doses of HB vaccine are not harmful.

In the 17 other provinces, as it has not received manufacturer approval for use outside the cold chain, the local vaccine will be administered province wide using the existing EPI

schedule for HB vaccine. In general, the EPI is conducted only on one day per month in Viet Nam, so that unless infants in these provinces are born on or just before the monthly EPI day, and are presented for vaccination on this day, birth dosing will not be possible in these sites. It is anticipated that the new recombinant vaccine will overcome this problem and hence be available for birth dosing according to the schedule outlined above for imported vaccine.

Vaccine formulation

Monovalent HB vaccine will be used. Although the combination DPT-HB vaccine has a number of advantages, monovalent vaccine is the preferred option in Viet Nam for the following reasons:

- the expense of and sustainability issues associated with combination vaccine
- the local preference for indigenous vaccine, coupled with the lack of capacity to produce a combined vaccine in Viet Nam;
- the new arrangement for transfer of recombinant HB vaccine technology;
- the inability to give combined vaccine to newborns, necessitating, given the intention to introduce a birth-dose, a complicated 4-dose strategy with monovalent HB vaccine at birth followed by 3 doses of DPT-HB;
- its scarcity on a global level.

For the birth dose of HB vaccine, for reasons of injection safety, convenience and likely local preference (Sutanto, 1999) Uniject has been selected by the EPI in Viet Nam as the preferred formulation. For subsequent doses, to ensure low wastage, in the 44 provinces supplied with GAVI vaccine 2-dose vials will be used, as will continue for the 17 provinces using the local vaccine.

This plan involves coordinated use of GAVI-sourced monovalent HB vaccine and the locally produced plasma-derived HB vaccine, as tabulated above (table 1). The table shows the phased support for 44 provinces GAVI will provide, totalling 20,080,154 doses of vaccine and 12,253,261 AD syringes. It also shows that around 1 million doses of local HB vaccine will be supplied for use in the remaining 17 provinces each year. In 2002 and 2003, the local product will remain a plasma-derived vaccine. From 2004 onward, it is anticipated that recombinant HB vaccine will be produced locally and will gradually replace the plasma-derived product.

Vaccination Schedule

The current EPI vaccines include BCG, HB, OPV, DPT, and measles, according to the schedule shown in Table 2.

Table 2. Current EPI vaccination schedule

Vaccine	Schedule
BCG	At birth
HBV	At birth, 2 and 3 months
OPV	2, 3 and 4 months
DPT	2, 3 and 4 months
Measles	9 - 11 months

In practice, as the EPI is only conducted once each month, BCG and the first dose of HB vaccine are given either at the first opportunity or with the first dose of DPT (DPT1). This schedule will remain current in the 17 provinces where local HB vaccine will be used. In the 44 provinces in which GAVI-supplied vaccine will be used and a birth dose introduced, monovalent HB vaccine can be added to the current immunization schedule without changing the current number of EPI contacts. The proposed new schedule thus includes HB vaccine given preferably within 24 hours (and definitely within 3 days) of birth, and then along with DPT1 at 2 months of age and DPT3 at 4 months of age (Table 3).

Table 3. Proposed EPI vaccination schedule

Vaccine	Schedule
BCG	At birth
HB	Preferably within 24 hours of birth, 2, 4 months*
OPV	2, 3, and 4 months
DPT	2, 3, and 4 months
Measles	9 months

*Note: * For infants born outside of the health facilities, HBV1 should be given as soon as possible after birth, certainly within 3 days, allowing for notification of the birth and delivery of the vaccine. If the birth dose is missed or has not been recorded, three doses of HB vaccine should be given with DPT1, DPT2, and DPT3.*

Recording of the birth dose and link to subsequent doses

Two important indicators for the evaluation of the program are:

- the percentage of children who receive the first dose within three days after birth and
- the number and percentage of children who receive the third dose of HB vaccine

In order to monitor these indicators, it is important that the first dose given by the health professional attending at or soon after birth is recorded on the child's EPI vaccination or under 5 card. Supplies of these will be made available to all maternity units and midwives, and to reduce the current variable practices noted, a clear, national policy on their use and place of storage will be circulated. The importance of maintaining this parent-held record will be reiterated during the proposed campaigns of health worker training and community education. This is particularly important where the birth occurs in larger health facilities, including hospitals, where midwifery staff are not currently part of the EPI programme.

The vaccination or under 5 card will be the means of communicating a birth dose at another health facility to EPI workers administering later doses of HB vaccine during a subsequent routine EPI contact. An infant's birth dose will be copied into the EPI register held at the CHS, so that assessments of the timeliness of administration of this dose can be made in future surveys thereof. Where births occur in CHS maternity units, staff there can enter the newborn into the EPI register immediately after birth, and will thus already have the record of the birth dose of vaccine at the next EPI contact.

Vaccine logistics

A. Wastage and vial sizes

With regard to wastage of HB vaccine, it is noted that Uniject is a single-dose presentation and the local vaccine is produced in 2-dose vials. Current wastage of the local HB vaccine is reported at 22%, and this is the maximum anticipated initial wastage for 2-dose vials provided for Viet Nam by GAVI, reducing to 15% by 2004. Wastage for the birth dose in Uniject is assumed at ~5%.

For other EPI vaccines, although EPI data shows wastage to be around 40%, it does not appear to be calculated routinely. Wastage of BCG certainly far exceeds this because of low birth numbers and the use of 20-dose vials. The current policy is to use vials of EPI vaccines during one immunization session only.

To help reduce vaccine wastage, for HB, DPT, TT and OPV the WHO open vial policy will be introduced where cold chain facilities allow. The use of VVMs on imported HB vaccine will facilitate this change in policy. Implementation will be preceded by appropriate training of staff on the need for careful stock control and planning, the reading of VVM's and careful checking of the cold chain, taking particular care that HB and vaccines containing tetanus are never frozen. Regular monitoring of vaccine wastage will be incorporated into EPI activities.

Other strategies to reduce wastage will include careful planning of vaccine ordering based on improved commune-level organisation of the EPI, and distribution and maintenance of new cold chain equipment including that from the government of Luxembourg, mentioned above. There is also a plan to change vials of DPT and OPV from the current 20-dose formulation to 10 doses/vial. In-service guidance and supervision of health workers, and community mobilisation to reduce drop out (in areas where relevant) will also be incorporated into community education campaigns.

B. Vaccine requirements

Tables 4 and 5 show the number of doses of HB vaccine required from GAVI over the next five years (2002-2006), as well as the number of AD syringes and safety boxes. The calculations, based on the formulae supplied in the revised GAVI application form, assume increasing rates of coverage after program initiation, and for each birth cohort to receive all three doses of vaccine by one year of age.

The local preference for vaccine supply for doses 2 and 3 (table 5) is for all of these doses in 2 dose vials. Along with Uniject for the first dose, this will enable the EPI to minimize wastage of this relatively expensive vaccine.

Table 6 shows the number of doses of HB vaccine, disposable needles and syringes and safety boxes to be supplied by the GOV over the same period.

Table 4. Estimated number of doses of HB vaccine required in Uniject, assuming 5% wastage each year

Year	2002	2003	2004	2005	2006
Target population for hep B vaccine from GAVI	765,808	1,354,160	1,374,472	1,395,089	1,416,015
No of doses per vaccinated child	1	1	1	1	1
Estimated coverage rate	80%	80%	85%	90%	90%
Target number of children to receive vaccine	612,646	1,083,328	1,168,301	1,255,580	1,274,414
*Buffer stock (25% of that required for new populations)	161,279	123,907	NA	NA	NA
Total vaccine doses required	806,395	1,264,651	1,230,221	1,322,126	1,341,958
Total number of safety boxes required	8,064	12,647	12,302	13,221	13,420

*Buffer stock only calculated for the new populations to receive vaccine.

Table 5. Estimated number of doses of HB vaccine required in 2 dose vials

Year	2002	2003	2004	2005	2006
Target population for hep B vaccine from GAVI	765,808	1,354,160	1,374,472	1,395,089	1,416,015
No of doses per vaccinated child	2	2	2	2	2
Estimated coverage rate	80%	80%	85%	90%	90%
Estimated wastage rate	25%	25%	20%	15%	15%
Wastage factor	1.333	1.333	1.250	1.176	1.176
Target number of children to receive vaccine	612,646	1,083,328	1,168,301	1,255,580	1,274,414
Buffer stock (25% of the required for new populations)	408,329	313,710	NA	NA	NA
Total vaccine doses required	2,041,643	3,201,862	2,920,752	2,953,124	2,997,422
*Total AD syringes required	1,612,791	2,851,861	2,460,442	2,644,251	2,683,916
Total safety boxes required	16,128	28,519	24,604	26,443	26,839

*AD syringes calculated on a wastage rate of 5% of total number of vaccine doses required, excluding the wastage of vaccines.

Table 6: Estimated number of vaccine doses, syringes, and safety boxes required for delivery of monovalent HB vaccine (2002-2006) for 17 locally supplied provinces.

Year	2002	2003	2004	2005	2006
Target Population for HepB	312,686	317,376	322,137	326,969	331,873
# of doses	3	3	3	3	3
Estimated vaccination coverage rate	80%	80%	85%	90%	90%
Target number of children to receive vaccine	250,149	253,901	273,816	294,272	298,686
Estimated wastage rate in %	20%	15%	15%	15%	15%
Buffer stock of 25% additional (for first year)	NA	NA	NA	NA	NA
Total vaccine doses required	938,059	895,763	966,023	1,038,192	1,053,764
Total disposable syringes (including 5% wastage)	790,221	802,073	864,985	929,605	943,549
Total safety boxes (assumes 100 syringes/box)	7,902	8,021	8,650	9,296	9,435

Cold Chain Logistics

The national central storage facility is located in Hanoi and Ho Chi Minh City, and the regional storage facilities in Nha Trang and Buon Me Thuot. EPI vaccines are distributed monthly to the 61 provinces, and then distributed monthly to the 623 districts. Depending on the number of communes or EPI points, there can be up to 20-50 distribution sites from each district centre.

The volume of cold chain storage at the National EPI (NIHE) is 180m³, and 150m³ in Pasteur Institute in Ho Chi Minh City. A 200m³ cold room from Seaprodex in Hanoi is available for use if necessary. For the Central and Central Mountain regions, adequate EPI vaccines for 6 months of the year can be stored in the regional cold rooms which are 40m³/each. At province level, there are at least 3 refrigerators (200 liters each) and 3 freezers (200 liters each) in provinces with populations above 1,000,000. At district level, where populations range from 100,000 to 150,000 inhabitants, there is usually at least 1 refrigerator (200 liters) and 1 freezer (200 liters). EPI vaccines including HB are stored in the cold chain system at provincial and district levels for only 1 or 2 months. It is calculated that the total cold-storage volume required for routine EPI vaccines, including HB, will increase to just over 20 liters at district level, and 200 liters at province level. As each district is also equipped with a car and large cold-boxes used to collect vaccines each month, the cold chain system at all levels is considered to be adequate to accommodate the addition of HB vaccine in the formulations proposed. There is also ample extra space for the anticipated change to 10-dose vials of DPT and OPV. Table 7 summarises the cold chain capacity for Viet Nam's EPI.

Precautions to prevent the freezing of HB vaccine will be emphasized at all levels of the cold chain, through careful monitoring of refrigerator temperatures, allowing ice packs taken from a freezer for use in cold boxes to be kept at room temperature for 5-10 minutes before use, and the use of a barrier of material between the ice packs and the vaccine.

Immunization Safety

A "National Policy for Injection Safety and Safe Disposal of Injection Equipment in the Viet Nam EPI" and a "Plan of Action (2001-2005) to Improve Injection Safety and Safe Disposal of Injection Equipment in the Viet Nam EPI" were prepared in September 2000 (refer to document 10 of the application submitted to GAVI in October, 2000). The EPI currently uses disposable syringes for all vaccines, and will continue to do so for all vaccines procured locally until locally produced AD syringes gradually replace them in 2004, as outlined in the plan. HB vaccines procured in two-dose vials for Viet Nam by GAVI will be administered using the AD syringes with which they will be bundled.

The progressive installation of district incinerators as part of Vietnam's Plan of Action will ensure that the additional waste generated by the addition of HB can be disposed of safely and in accordance with national and WHO policy.

Vaccine Introduction

Vaccine introduction requires training of EPI staff and health care providers, social mobilization and logistical preparation. The EPI will begin training and social mobilization to support the expanded introduction of HB vaccine during 2001. It is expected to take two years to train all EPI staff, beginning at the national level, and working down to the health facility and community levels. Tables 9 and 10 presents the proposed timeline for activities related to the introduction of HB vaccine.

Administrative

All EPI administrative forms have been revised to include HB vaccine, including the:

- Immunization schedule
- Immunization cards
- Vaccination register
- Monthly report forms

Information, Education, Communication (IEC) to support HB vaccine introduction

In all provinces where HB vaccine is being introduced, decision makers, EPI staff at all levels, medical staff of academic institutions, medical and nursing students, and hospital and health centre staff will require education about HB infection and HB vaccine, and some training materials have been revised to include this information with support from UNICEF. A community mobilization campaign in the community is also planned, particularly to support the introduction of a birth dose. Table 8 outlines the target populations that will require education, the type of information they will require, and methods of disseminating this information. As Viet Nam is ineligible to receive support for infrastructure support from GAVI, other sources of assistance are being sought to fund these training and social mobilization activities. The Interagency Coordinating Committee (ICC) mechanism is being used to identify this support, which should include existing health projects funded by UNICEF, the Asian Development Bank (ADB) and the World Bank (WB).

Table 8: Target audiences, information needs, and methods of dissemination

Target Audience	Information Needs	Method
Policy makers	Basic	Sensitization meeting
National and regional EPI staff, provincial, district and commune health staff.	Basic, Technical, Practical	Training courses
Academic physicians, teaching institutions, hospital staff	Basic, Technical, Practical	In-service training courses
Community	Basic	Community education; Women's groups; Youth groups

Basic information

- Description of HB infection
- Consequences of HB infection
- Recipients of HB vaccine
- Vaccination schedule
- Side effects of vaccination

Technical Information

- Epidemiologic data (if available)
- Additional (more advanced) information

Practical information

- How to handle vaccine
- How to administer vaccine
- Open vial policy to decrease wastage
- Safe injection practices; Uniject; safe disposal
- Reporting and documentation requirements
- Adverse events following vaccination

Currently, UNICEF funds community education programmes in health and nutrition in 21 districts of 16 provinces. The ADB funds a province-wide Rural Health Development Project in 13 provinces, and the WB a total of 34 provinces in its province-wide National Health Support, and Population and Family Planning Support Projects. All these projects include extensive health worker training components. Altogether, a total of 51 provinces (allowing for some overlap of the above donors' target provinces) receive partial or province-wide support which can be adapted to provide training for health workers on HB and the introduction of HB vaccine.

In general, however, these projects do not support the community mobilisation required to support the planned birth dose and improved registration of births occurring outside health facilities. Key messages for the community will need to include:

- HB and its consequences
- the safety and efficacy of the vaccine
- the importance of the timely administration of the first dose, and therefore the importance of early birth registration

- the importance of parents keeping the record of the first dose and giving this record to the EPI staff at subsequent immunizations
- the steps being taken to ensure injection safety.

Community mobilization activities for HB can be integrated with existing programmes in some provinces/districts already supported by UNICEF, and also into the activities of the health education unit of the MOH. However, as a priority, additional funding will be sought through the ICC mechanism to support these activities in all areas in which HB vaccine is being introduced, and also for health worker training for those districts and the remaining 10 provinces not covered by the existing projects outlined above. Written materials supporting these activities and the rest of the immunization program will need to be produced or updated.

Monitoring and Evaluation

Integrating a new vaccine into the immunization program will require an evaluation component. Because the consequences of chronic HBV infection are not generally apparent until adulthood, methods for short-term program evaluation are needed.

Routine monitoring

Vaccination coverage will be monitored using monthly reports of the number of children who receive the recommended vaccinations by one year of age. HB vaccine will be included with other EPI vaccines in routine vaccination reporting, and the number of children who receive three doses by one year of age will be collected. The other key indicator will be the percentage of children who receive the birth dose within three days in those provinces where it is being introduced. This indicator will also be able to be monitored through the routine reporting system.

Immunization coverage surveys

The most recent formal survey of vaccination coverage was done in 1998, in consultation with WHO and UNICEF. To monitor the coverage of EPI vaccines, a similar survey will be commissioned in 2003 including HB vaccination coverage. The main indicator of HB vaccination coverage will be HB3 coverage at age 12 months.

Serological surveys for markers of HB infection may also be undertaken. These may comprise formal age-stratified surveys of serum collected at sentinel sites before and 2 – 3 years after vaccine is introduced, or they may involve similarly rigorous but rapid assessments using quick-tests of HB surface antigen, which would be much cheaper and logistically simpler to undertake. A formal plan will be developed to monitor the population prevalence of HB infection in multiple areas of Viet Nam before and after HB vaccination is expanded.

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Table 9. Activities on introduction of hepatitis B vaccine

Activity/Tasks	Budget (US\$)	Time	Output
Workshop and Traing courses			
<u>Activity 1: National and regional training workshops on introduction of HBV</u>			
- One for national regional EPI staff in Hanoi	3,000 (UNICEF)	17-21/9/2001	30 national and regional staff will be trained
- Three for regional and provincial EPI staff, in Hanoi (for 28 provinces in the North), Nha Trang (for 11 central provinces and 3 provinces in High Land) and HCM City (for 19 provinces in the South)	12,000 (UNICEF)	Sep. & Oct., 2001	90 provincial EPI staff will be trained (5 days / course)
- Two for teachers from 60 Secondary Medical Schools in Hanoi and HCM City	6,000 (UNICEF)	Oct. 2001.	60 teachers of SMS will be trained (5 days / course)
<u>Activity 2: Training of trainers on introduction of HBV for district EPI staff</u>			
- 30 training courses for 30 provinces (Hanoi, Thai Binh, Hai Phong, Phu Tho, Hai Duong, Thanh Hoa, Nghe An, Bac Ninh, Ninh Binh, Ha Tinh (Northern provinces); HCM City, Ba Ria - Vung Tau, Long An, Dong Nai, An Giang, Tra Vinh, Bac Lieu, Dong Thap, Kien Giang,... (Southern provinces); Dac Lac, Gia Lai, Kon Tum (High Land provinces); Thua Thien-Hue, Khanh Hoa, Quang Nam, Da Nang and Binh Dinh (Central provinces).	46,000 (UNICEF)	Oct. & Nov., 2001	900 EPI district staff will be trained (3 days / course)
- 31 training courses for 31 provinces (not including 30 provinces with support from UNICEF)	46,500 (GAVI)	Nov. & Dec. 2001	930 EPI districts staff will be trained (3 days / course)

Activity/Tasks	Budget (US\$)	Time	Output
Activity 3: Training courses for commune health worker (CHW)			
- 15 courses for 15 districts (Phu Vang, Duc Pho, Chu Se, Lak, Bu Dang, Tra Cu, Vinh Chau, Districts 10, Phu Quoc, Sapa, Bach Thong, Moc Chau, Van Yen, Ha Long and Mong Cai).	15,000 (UNICEF)	Oct. & Nov. 2001.	450 CHWs will be trained (3 days / course)
- 35 courses for 35 districts	35,000 (GAVI)	Nov. & Dec. 2001.	1,050 CHWs will be trained (3 days / course)
- 300 courses for 300 districts. 2002	300,000 (ADB)	2002	9,000 CHWs will be trained (3 days / course)
- 275 courses for 275 districts	275,000 (ADB)	2003	8,250 CHWs will be trained (3 days / course)
Activity 4: Workshop for advocacy and communication			
- 61 workshops for decision-makers and opinion leaders	35,000 (ADB)	2002, 2003	6,100 local leaders will participant
- 63 workshops for Women Union at national and provincial level	40,000 (ADB)	2002, 2003	6,300 participants (1 day /workshop)
Translation and Printing materials			
Activity 5: Translation, adaptation and printing of materials related to introduction of HBV and safe injection.			
- Translation of Immunization in practice, safe injection WHO policy statement: The use of opened multi-dose vials of vaccine subsequent immunization sessions.	1,500 (UNICEF)	Aug. 2001	Translation

Activity/Tasks	Budget (US\$)	Time	Output
- Adaptation and printing Immunization in practice	15,000 (UNICEF)	Oct. 2001	5,000 copies
- Translation and adaptation of Introduction of hepatitis B vaccine into EPI (Management guidelines, including in formation for health workers and parents	18,500 (GAVI)	Nov. 2001	15,000 copies
- Printing Vaccination register books	15,000 (Gov.)	Nov. 2001	15,000 copies
- Printing Immunization cards	30,000 (Gov.)	Nov. 2001	3,500,000 each
- Printing Immunization schedule	10,000 (AusAid)	2002	15,000 copies
- Printing leaflets on Hepatitis B and the way to prevention Hepatitis B	60,000 (AusAid)	2002	500,000 copies
Mornitoring and Evaluation			
<u>Activity 6:</u> Mornitoring to lower level on introduction of hepatitis B vaccine	200,000 (ADB)	2002 to 2006	National, regional and provincial EPI staff will visit to lower levels quarterly
Activity 7: Annual review meeting	50,000 (ADB)	2002 to 2006	Review all activities in the last year and prepare the plan of action for the next year
Activity 8: GAVI mid term review	50,000 (ADB)	2003	To evaluate immunization coverage To assess the status of safe injection in EPI To evaluate the quality of surveillance of EPI target deaseses
Activity 9: GAVI final review	50,000 (ADB)	2006	To evaluate immunization coverage To assess the status of safe injection in EPI To evaluate the quality of surveillance of EPI target deaseses

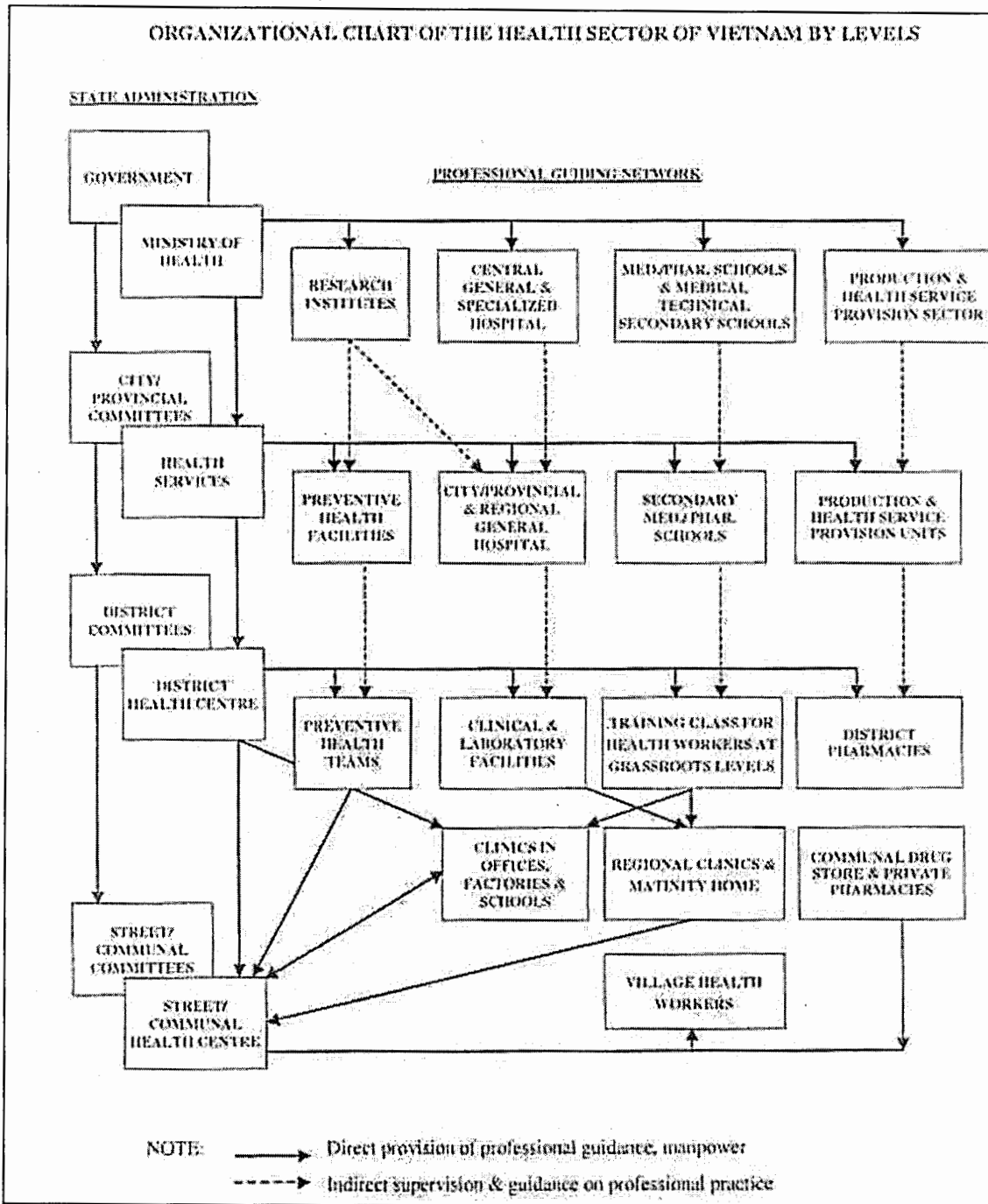
Table 10: Timetable for activities related to introduction of HB vaccine

Year	2001	2002	2003	2004	2005	2006
Procurement of HB vaccine		X				
Revision of training materials	X					
Distribution all immunization forms (immunization card, reporting, etc.)	X	X	X	X	X	X
Training of EPI staff in all provinces and districts	X	X	X			
IEC ¹ campaign for HB vaccine introduction	X	X	X			
Workshop for advocacy and communication		X	X			
Training courses on introduction of HB vaccine using a birth dose in 44 provinces	X	X	X			
Introduction of HB vaccine supported by GAVI		39 prov. (50%) 5 prov. (100%)	44 provinces (100%)			
Monitoring of introduction and feedback		X	X	X		
Review of reported hepatitis coverage data	X	X	X	X	X	X
National coverage survey ²				X		
GAVI mid term review			X			
GAVI final review						X

¹ IEC = information, education, communication

² Similar methodology to 1998 National Immunization Program evaluation done by MOH in consultation with WHO and UNICEF

Appendix 2: Organisational structure of the Vietnamese Health Sector



Appendix 3: Description of government health services in Vietnam

(adapted from: National Documentation for the Certification of Poliomyelitis Eradication, prepared by the National Committee for the Certification of Poliomyelitis Eradication, Hanoi, 1 October, 2000)

Health care in Viet Nam is provided partly through a State-run network of health facilities at central, provincial, district and commune levels. The balance is provided by the private sector. At the central level, management is provided by the Ministry of Health; at the provincial and district levels by the provincial or district health services. At each of these levels the health system management is subject to the authority of the political system: Government at the central level and the People's Committees at lower levels.

1. Central level.

At the central level, the Ministry of Health is the government agency exercising State management in the provision of health care services, including hygiene and prophylaxis, diagnosis and treatment, rehabilitation, production and distribution of pharmaceuticals and medical equipment throughout the country. The central level has direct authority over central level institutions, which include most medical schools of university level, some specialized second-level training schools, various institutes (including the National Institute of Hygiene and Epidemiology, which is responsible for the Expanded Program on Immunisation (EPI)) and several specialized hospitals. The Ministry defines the curricula for all second-level training.

2. Provincial health services.

Each of the 61 provinces has a provincial health service administered by the Provincial People's Committee. They exercise state management over the provincial health services, manage the Provincial Centre for Preventive Medicine (the provincial counterpart for the national EPI), the Centre for Mother and Child Health and Family Planning, the Centre for Health Education, Information and Communication, the Centre for the Quality Control of Pharmaceuticals and cosmetics, polyclinics and special hospitals, district health centres, middle-level medical schools, enterprises producing pharmaceutical and medical equipment and provincial health insurance. The provincial health services also manage private medical practice in the province. In Vietnam's 61 provinces and centrally administered cities, there are 249 provincial and specialized hospitals, including leprosy centres, sanatoriums and rehabilitation centres.

3. District health centres.

District health centres are administered by the provincial health service. District health centres include the district health bureau, the hygiene, prophylaxis and malaria control brigade, the maternal and child health/family planning brigade, the district hospital and the district drug shop.

The hygiene, prophylaxis and malaria control brigade provides preventive services including immunization, control of diarrhoeal diseases, malaria control, control of vitamin A deficiency and control of iodine-deficiency disorders. This brigade plays a supporting role to the commune health stations (CHSs) in the above-mentioned tasks. The brigade consists of technicians including doctors, assistant doctors and laboratory workers, headed by the vice-director of the relevant district health centre.

A district hospital has general practitioners and other doctors specialized in internal medicine, surgery, gynaecology, obstetrics, ophthalmology, dentistry and oto-rhino-laryngology.

In the whole of Viet Nam, there are some 550 district hospitals, which form part of the district health centre, and they support the lower levels of the health services through inter-communal polyclinics and the commune health centres.

4. Commune health stations.

The CHS is the first level of services accessible to the population in the State health network. It has the task of providing technical services in primary health care, early detection and control of epidemics, provision of primary health care and normal deliveries, provision of essential drugs, and education on family planning methods and health promotion.

Viet Nam has 10,457 communes, over 99% of which have a CHS. Each is staffed by 3 to 5 health workers including, at least, one assistant doctor who has undergone 3 years of training and a midwife who has received 2 years training.

After 1975, the health network in many localities collapsed due to economic constraints. By the end of 1995, there were 278 communes without a CHS or commune health workers. The period from 1994 to 1996 saw refurbishment of some 2000 CHSs with State funds and equipment.

Since 1995, the salary of CHS workers has been paid from the State budget. It is expected that by the end of the year 2000, 40% of all CHSs shall be staffed with doctor(s) and all communes shall have either a midwife or assistant doctor specialized in obstetrics and paediatrics, and there will be hamlet health workers. Efforts are being made to improve the activities of CHSs in preventive medicine activities with growing community participation.

In mid-1999 the government introduced a small salary for trained hamlet or village health workers, who have usually had 6 – 9 months training and support health workers from the CHSs in their clinical and public health duties.

Appendix 4

EXPANDED PROGRAMME ON IMMUNIZATION REVIEW VIET NAM

5 - 17 OCTOBER 1998

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EXECUTIVE SUMMARY

Introduction

At the request of the Ministry of Health of Viet Nam, a review of the Expanded Programme on Immunization (EPI) was implemented from the 5th to the 17th of October, 1998. The review teams were composed of international investigators from WHO and UNICEF, in addition to national, regional and provincial level experts. Each team visited one of five provinces to review the EPI and poliomyelitis eradication. The objectives of the review were to identify the achievements and progress of the EPI, the main issues currently facing the program, and to make recommendations to address these issues in order to develop future plans.

Achievements

The EPI in Viet Nam is very robust with much progress made since the last national EPI review, conducted in 1992.

1. Viet Nam first achieved the goal of Universal Childhood Immunization in 1989 and routine immunization coverage has been sustained at a very high level.
2. No polio cases have been reported for more than eighteen months and poliovirus transmission appears to be interrupted. Viet Nam is entering the final stage of preparation for certification of polio eradication.
3. Viet Nam has developed a highly sensitive AFP surveillance system; in the first six months of 1998, 295 AFP cases have been reported, with 94% having two adequate stools. No wild poliovirus cases or polio compatible cases have been identified.
4. NIDs were successfully completed in all review provinces in 1997 and increased efforts were made to reach children belonging to mobile populations and border areas.
5. Neonatal tetanus (NT) has been eliminated at the provincial level and the elimination goal at the district level has almost been achieved; only 19 of 610 districts reported a rate of NT greater than 1 / 1 000 live births in 1997. The surveillance of NT has been integrated into the active AFP surveillance system.
6. Viet Nam has developed a highly effective surveillance system for NT that has applied the Protection at Birth (PAB) methodology and is being integrated with the AFP surveillance system at all levels.
7. New cold chain and injection equipment has been distributed to the commune level.
8. EPI vaccine self-sufficiency has increased and continues to increase every year.

Issues

The EPI in Viet Nam is successfully protecting children from vaccine preventable diseases, and is on the verge of achieving certification of polio-free status throughout the whole country. By any measure, the achievements of the EPI are outstanding, and it is an extremely successful and cost-effective public health program. The following issues are current priorities for the EPI in Viet Nam:

1. Routine EPI: There is a concern that the real target population for the routine EPI may be higher than the official estimates. As a result, high-risk populations such as minorities and unregistered children are at risk of not being immunized.
2. Cold chain: There is a concern that the cold chain is not well maintained at the commune level, in all areas, and that this may result in reduced vaccine potency.

3. Safety of injections: Given the risk of transmission of blood-borne infections, safe injections are a critical problem for the EPI in Viet Nam.
4. AFP Surveillance: There is a risk that political commitment and support given to AFP surveillance may diminish before the global polio eradication target has been met.
5. Supplementary OPV immunization: Targeting of mobile and border populations continues to be a priority but there are still some difficulties in reaching the children most at risk.
6. NT elimination: National policy requires women of child-bearing age (CBAW), 15 – 35 years of age to be immunized with TT in designated high risk districts, but this guideline is not being implemented fully in all areas.
7. Measles: Measles is a significant cause of childhood morbidity and mortality, despite improved routine immunization coverage and surveillance.

Recommendations

In line with the national policies and guidelines, the review team suggests that the conclusions and recommendations of this review provide the background for preparation of a five-year plan for the EPI in Viet Nam.

1. Routine EPI: The National EPI should give priority to find unidentified and unregistered children and hamlets which have been missed by immunization services, to ensure that there are no clusters of unimmunized children. The routine immunization reporting system could be improved in the areas of monitoring and supervision, with data management and analysis at all levels.
2. Cold chain: Potency of vaccines should be ensured through development of a well-maintained cold chain system. All levels should have an adequate supply of cold chain equipment through efficient distribution of available supplies.
3. Safety of injections: Disposable injection equipment should only be used in communes with geographic difficulties, according to national guidelines. These communes should have a backup of a steam sterilizer and reusable injection equipment to ensure continuity of the EPI.
4. AFP surveillance: The immunization status of all AFP cases should be determined as early as possible in the case investigation. If the case is zero-dose or inadequately immunized, an investigation for high risk AFP cases in the local area should be conducted to determine whether there is a cluster of such children, indicating a need for supplementary OPV immunization.
5. Supplementary immunization: There should continue to be a focus on high-risk populations during supplementary OPV immunization to immunize unregistered and mobile children. The strategies of house-to-house and boat-to-boat immunization with mobile teams should continue to be implemented.
6. NT elimination: The provincial level should continue to strengthen the activities of reporting and recording of the neonatal tetanus surveillance system and to intensify efforts to detect all neonatal deaths and then investigate them for NT.
7. Measles: The EPI should focus on improving surveillance and routine immunization coverage for measles as there is still under-reporting and significant morbidity and mortality from this infection.
8. Training: EPI training needs should continue to be identified and priority for training should be given to newly appointed EPI staff and staff in the newly split provinces.

1. INTRODUCTION

The Ministry of Health of Viet Nam implemented a comprehensive review of EPI and poliomyelitis eradication activities in collaboration with international consultants from WHO and UNICEF. This review was undertaken from the 5th to the 17th of October 1998.

Teams consisting of both national staff and international consultants reviewed the Expanded Programme on Immunization (EPI) and polio eradication activities in five provinces of Viet Nam. 30 – cluster surveys assessing routine and supplementary immunization coverage were conducted concurrently. The review teams reported their key findings and recommendations to the Directors of the Provincial Health Service and Provincial Preventive Medicine Centers where they visited, and to the National EPI Unit. A summary of the findings and recommendations was presented to the Ministry of Health on 17 October 1998. The findings of this comprehensive review will be further disseminated at the next National EPI Planning and Review Meeting.

Background

Since the EPI was initiated in Viet Nam in 1981, it has become one of the most successful national priority health programmes. In 1989, for the first time in Viet Nam, the goal of Universal Childhood Immunization (UCI) was achieved with a national coverage of 87%. In 1991, Viet Nam initiated implementation of the National Plan for Poliomyelitis Eradication by the year 2000, and in 1992, the National Plan for Neonatal Tetanus Elimination.

Previous reviews of the national EPI were conducted in 1985, 1987, 1989 and 1992. It was in the context of the plans listed above and the goal of accelerated measles control, that this 1998 review was implemented.

The routine EPI is implemented by Preventive Medicine Centers at the provincial level under the guidance of staff from the regional and national EPI units. Monthly immunization services, conducted through fixed immunization sites, are active in almost all communes. In mountainous areas, mobile teams administer routine vaccines every two or three months. Routine reports indicate that the reported full immunization coverage for children under one year of age reached 95% in 1997. This was the fifth year that overall immunization coverage has been maintained at more than 90%.

There has been greater control of the incidence of vaccine preventable diseases accompanying the improvements in immunization coverage. For example, there were 2 444 reports (with 2 deaths) of pertussis and 167 reports (with 33 deaths) of diphtheria in 1995 and the number of these reports had fallen to 1565 reports (with 6 deaths) of pertussis and 152 reports (with 14 deaths) of diphtheria, in 1997.

Polio eradication

Viet Nam has successfully reduced the circulation of polio cases from 452 clinically confirmed cases and 152 wildvirus cases in 1993 to only two wild poliovirus cases in 1996 and a single wild poliovirus case in 1997. The last poliomyelitis case in Viet Nam was identified in Phu Yen Province and had a date of onset of paralysis on the 29th January 1997.

Supplementary immunization

Viet Nam has implemented five successive years of National Immunization Days since 1993, targeting approximately 10 million children under 5 years of age with 2 rounds of OPV separated by a month. Reported coverage has usually been higher than 95% of children under the age of five years.

Two additional rounds of High Risk Response Immunization were conducted in May and June 1997 in 50 districts of the southern region that were considered to be at high risk for poliovirus transmission. New strategies like use of mobile teams to reach previously unimmunized children were implemented. In addition, Binh Dinh and Phu Yen provinces of the Central Region were included in High Risk Response Immunization in July and August 1997, after identification of a case of wild poliovirus in Song Cau district of Phu Yen Province.

High-risk response immunization in 1998 covered 66 districts of the Southern Region, 5 districts in the Central Region, and a district in the Highland Region

AFP surveillance

Viet Nam first established the AFP surveillance system in 1990. A national AFP system was developed in 1993, together with a computerised database of AFP cases. The national AFP surveillance system has been based on the immediate reporting and investigation of all AFP cases by staff of the Provincial Preventive Medicine Center in collaboration with staff from the Provincial Hospital.

The system has included weekly active surveillance for AFP cases at district hospitals by district level EPI staff and at provincial hospitals by provincial staff (at least weekly). Regular active searches for unreported AFP cases have been conducted since 1994 by national and regional surveillance staff.

By 1996, Viet Nam had achieved the standard of surveillance quality required for certification of polio eradication and the virological case classification criteria for AFP surveillance was applied. The quality of surveillance has continued to improve, so that in the first six months of 1998, 295 AFP case reports have been received, with 94% of AFP cases having had two adequate stools. No poliovirus or polio compatible cases have been identified during 1998.

Neonatal Tetanus Elimination

By the end of 1995, Viet Nam had achieved the target of less than one NT case per 1000 live births for every province in the country, under conditions of improved surveillance. This remarkable progress has been achieved by rapidly increasing routine immunization of pregnant women Nationwide with tetanus toxoid (TT), usually during routine immunization sessions. In addition, campaigns for TT immunization of CBAW have been conducted in high-risk districts, sometimes in conjunction with national immunization days for polio eradication.

57 districts were designated as high risk in 1993 and all it has been aimed to investigate all neonatal deaths with standard case investigation forms since that time. Every year additional districts were added to the original designated high-risk districts, reaching a total of 314 out of 610 districts by 1997. This extended to 384 districts, to cover over half of the country, by 1998. When the performance of these high-risk districts was measured according to the goal of less than one NT case per 1000 live births, only 11 districts in 1996 and 19 districts in 1997 exceeded this rate.

The quality of surveillance for NT has improved with higher rates of immunization coverage. In 1994, 45% of the 2 492 reported neonatal deaths were investigated for NT, in 1995 this had increased to 73% of 2 685 reported neonatal deaths, and by 1996 to 89% of 3, 561 reported neonatal deaths. In 1997, 92% of 3 836 reported neonatal deaths were investigated for NT.

The national EPI reported the coverage of PW, with at least two doses of TT as 82.1% in 1996 and 83.5% in 1997, and the estimated coverage of CBAW in the same period was reported as 96.7% and 91.4%, respectively, in high-risk districts.

The number of NT cases decreased to less than 1 per 1 000 live births by province. The national rate of reported NT cases fell from 0.21 cases per 1 000 live births in 1994, to 0.17 cases per 1 000 live births in 1995 and 0.13 cases per 1 000 live births in 1996 and 1997. The country has achieved the target of NT elimination by province.

Viet Nam is now making progress towards eliminating the disease at the next administrative level (district level) in which the population is approximately 100 000 people. The PAB methodology has been successfully integrated into the surveillance system and each year a higher proportion of neonatal deaths are investigated for NT.

Measles control

In 1995, 6171 measles cases were reported nationwide, associated with 9 deaths and in 1996 5 165 cases were reported, also associated with 9 deaths. In the first 9 months of 1998, 8 390 cases were reported, an increase of 1 883 cases compared with the 6 507 cases reported in 1997. Measles is particularly a problem in mountainous and remote areas where there are weaker routine immunization services. Several outbreaks have been reported during 1997 and 1998 in the Highland Region and in mountainous areas of other regions. There is still significant morbidity and mortality associated with measles and improvements could be made in routine vaccine coverage and surveillance, particularly in remote and difficult areas.

2. PURPOSE AND CONDUCT OF REVIEW

2.1 OBJECTIVES

The overall objective of the review was to identify the achievements and remaining problems and to make recommendations to strengthen the program.

The specific objectives of the review were:

1. To evaluate routine immunization coverage of the six EPI vaccines for children <1 year of age
2. To evaluate supplementary immunization coverage for OPV for children <5 years of age
3. To evaluate TT immunization coverage for pregnant women and the proportion of children protected at birth
4. To evaluate the quality of surveillance of AFP and neonatal tetanus
5. To assess the status of safe injection practices in the EPI
6. To evaluate the cold chain system and management of vaccines in the EPI

2.2 METHODS

A quantitative survey team and a qualitative survey team in each province implemented the review.

Quantitative survey teams

Five interview teams, comprised of two national supervisors and 30 interviewers (for mountainous provinces) and 15 interviewers (in other provinces), were mobilized to

undertake 30 – cluster surveys for immunization coverage (according to standard WHO methodology) in each of the provinces selected for review.

Each cluster (1 cluster = 1 commune) was selected according to the standard methodology and the following children were interviewed:

1. 7 children aged 12 – 23 months of age: birth date from October 1996 to October 1997 (for infant immunization coverage and for supplementary immunization coverage of OPV).
2. 7 mothers of children aged 0 – 11 months: birth date from October 1997 to October 1998 (for TT immunization coverage in pregnant women and the proportion of children protected at birth against neonatal tetanus).

In each of the review provinces, 210 children aged 12 – 23 months and 210 children aged 0 – 11 months of age were selected i.e. a total of 2 100 children.

Qualitative survey teams

Five qualitative survey teams were comprised of one or two international supervisors (from WHO and UNICEF) and a principal national investigator. Each team evaluated the quality of surveillance for AFP and NT, assessed the status of safe injection practices in the EPI and evaluated the cold chain system and the management of vaccines in the EPI in a single province.

Standard forms were prepared as a framework for the evaluation but the investigators did not restrict themselves to these forms. Visits were made to the Provincial Health Service, the Provincial Preventive Medicine Center (including the provincial vaccine stores) and to the Provincial Hospital in each of the review provinces. Two districts and two communes from each district were selected, after consultation with provincial staff, for evaluation of the EPI at the district and commune levels.

2.3 PROVINCES VISITED

Five provinces were at random selected from five geographical categories; Thanh Hoa Province (northern mountains), Hai Duong Province (the Red River delta), Quang Ngai Province (central coast), Dak Lak Province (the western highlands) and Tra Vinh Province (the Mekong delta). The selection was based on the principles that the selected provinces were accessible and representative of the category.

3. FINDINGS

3.1 CLUSTER SURVEYS

Full immunization coverage rate of children under one year of age

Province	# Children	Coverage (%)
Hai Duong	212	95
Thanh Hoa	210	82
Dak Lak	212	53
Quang Ngai	211	86
Tra Vinh	212	83
National	1057	80

Program coverage

Province	# children	# children with BCG scar	% of children with BCG scar	# fully immunized children* (card + history)	% fully immunized children* (card + history)	# fully immunized children* (card only)	% of fully immunized children* (card only)
Hai Duong	212	210	99	210	99	210	99
Thanh Hoa	210	196	93	207	99	202	96
Dak Lak	212	177	83	188	89	175	82
Quang Ngai	211	209	99	211	100	211	100
Tra Vinh	212	198	93	200	94	199	94
National	1057	990	94	1016	96	997	94

*not restricted to children under one year of age

The cluster surveys showed high routine immunization coverage in all provinces and validated the results of routine EPI coverage reports. Coverage was lower in Dak Lak because of the difficult geographic conditions in this province; mobile teams can only implement routine immunization sessions in some areas every few months. Significant progress has been made in implementation of the EPI in Dak Lak; 1992 cluster surveys showed the rate of fully immunized children under the age of one year to be 19 %, compared with a figure of 53 % in 1998.

OPV coverage during the 1997 NIDs

Province	# children	Children receiving 2 doses of OPV (card + history)	% of children receiving 2 doses of OPV (card and history)	Children receiving 2 doses of OPV (card only)	% of children receiving 2 doses of OPV (card only)
Hai Duong	210	209	99.5%	205	97.6%
Thanh Hoa	210	206	98.1%	181	86.2%
Dak Lak	212	203	95.8%	181	85.4%
Quang Ngai	211	211	100.0%	211	100.0%
Tra Vinh	212	207	97.6%	190	89.6%
National	1055	1036	98.2%	968	91.8%

The high rates of coverage found for the 1997 NIDs correlate closely with the high reported results.

TT coverage and protection at birth against neonatal tetanus

Province	# mothers interviewed	# received TT2+	% received TT2+	PAB
Hai Duong	211	206	97.6	95.7
Thanh Hoa	210	202	96.1	88.6
Dak Lak	212	178	84.0	60.9
Quang Ngai	210	210	100.0	97.1
Tra Vinh	211	174	82.5	72.4
National	1054	970	92.0	82.8

The cluster surveys found the coverage of TT2+ among the recently pregnant women surveyed to be 92.0% nationwide, with a range from 82.5% to 100.0% in the provinces surveyed. PAB was also found to be high, with a result of 82.8% nationwide and a range from 72.0% to 97.1%.

Comparison between the reported coverage data and coverage found by 30 – cluster surveys

Province	% fully immunize d < 1 year		% TT2+ coverage PW		% PAB		% OPV coverage 1997 NIDs	
	Report	Survey	Report	Survey	Report	Survey	Report	Survey
Hai Duong	99.97	94.81	98.55	97.63	91.77	95.73	100.00	99.52
Thanh Hoa	99.20	82.38	99.14	96.19	82.04	88.57	98.50	98.10
Dak Lak	95.19	53.30	100.00	83.96	83.81	60.85	99.70	95.75
Quang Ngai	97.70	86.73	80.10	100.00	69.08	97.14	100.00	100.00
Tra Vinh	90.51	85.38	59.37	82.46	53.42	72.04	99.30	97.64
National	96.38	80.51	83.53	92.03	70.35	82.83	99.70	98.20

There was a significant difference between reported coverage and survey results for full immunization coverage and NT surveillance in some provinces.

3.2 EXPANDED PROGRAMME ON IMMUNIZATION

The achievements of the EPI, since its acceleration in 1986, are outstanding and reported immunization coverage for children and PW has been sustained at high levels in all review provinces. As a result, EPI target diseases were effectively controlled and the overall incidence of vaccine preventable diseases was found to be low in the review provinces.

The EPI is implemented by Preventive Medicine Centers at the provincial level under the guidance of the national and regional EPI units. The review team observed that the EPI infrastructure was well developed and functioning at all levels in provinces visited. Monthly immunization services, conducted through fixed immunization sites, were found to be effective. A good achievement of the program was social mobilization and community participation. Very successful social mobilization activities together with widespread use of IEC material were observed during the provincial reviews.

Funding

Funding from the national level is determined by calculations of requirements for injection and cold chain equipment, which are made in consultation with the provinces.

Vaccine logistics

Provinces receive their monthly vaccine supplies from the national level, except for provinces in the Central Region, where supplies are received every 3 months. The required amount is calculated using the estimated target population with a wastage rate of 2.2 for BCG and 1.5 for the other antigens. The review teams observed no shortage of vaccine supply. The provincial EPI distributes vaccine to the districts monthly and the commune health centers usually receive vaccine immediately before routine immunization days.

The wastage rate for BCG was found to be quite high in some provinces because of the scattered population in mountainous areas and the 20 dose vials being used. The unused vaccine is discarded at the end of the day during which the immunization session is held. In most of the provinces it was observed that the supply, storage and distribution of vaccine is monitored, but the stock registry is not always recorded accurately.

Target population

The denominator used for calculation of coverage rate is derived from the crude birth rate estimates of the National Statistics Office. At the annual National EPI Review and Planning Meeting, the National EPI Unit requests regional and provincial staff to determine their provincial targets populations. It was noted that the target populations of some provinces

have been decreasing in recent years, as high as 11% in one province, when compared with previous year. Some provinces maintain their own population figures according to the registries at the commune level, which are frequently greater than estimates.

The review team was concerned that the real target population may be higher than the estimates in some provinces and districts. As a result, high-risk populations such as minorities or unregistered children may be at risk of not receiving routine EPI vaccines.

Immunization coverage

High reported immunization coverage rates with the EPI antigens were noted in all provinces visited. The recorded provincial coverage rates of children consistently exceeded 90% and the TT2+ coverage for PW and CBAW in high-risk areas was high in all provinces. National staff did report, however, that some "white" hamlets exist (villages not covered by the routine EPI) and that these areas sometimes came to the attention of local health authorities after an outbreak of measles. Clusters of unimmunized children and associated measles outbreaks have recently been identified in the Highland and Central Regions. A review of EPI records in most centers visited, however, showed that EPI vaccines were generally given at the right age and at correct intervals.

At the district and provincial levels, full immunization coverage was sometimes reported to be higher than coverage for individual antigens. This can be explained partially by the decrease in the number of immunized children, leaving a large portion of children receiving measles vaccine in the current year, who actually belong to the cohort of previous year. Another possible explanation could be that full immunization coverage was assumed to be equivalent to measles immunization coverage by some commune staff, who reported this figure to higher levels.

Immunization sessions

The review team observed that all provinces conduct monthly immunization sessions on designated dates at fixed immunization sites. This schedule has been practiced for several years and the community is well aware of the immunization days. Planning, reporting, monitoring and logistics are simplified and there is effective social mobilization, publicity and inter-sectoral cooperation.

Vaccine is usually stored in vaccine carriers at the commune level during short immunization sessions, usually one to two days in most provinces. However, in some areas routine immunization sessions are held over a period of three to nine days. The review team was concerned that under these circumstances, especially in difficult to access areas, prolonged storage of vaccine in vaccine carriers may result in poor maintenance of the cold chain and reduce vaccine potency.

Reporting, monitoring and evaluation

The routine reporting system for EPI and vaccine preventable diseases surveillance is well developed and standard forms are being used at all levels. Some problems regarding registers and recording were observed in one province. In most provinces, however, data was well kept for the past two years.

Reports on the number of doses administered are submitted monthly from the communes and districts up to the provincial level. Reporting timeliness and completeness are monitored regularly by the provincial level, and most reports are submitted on time. National data on the number of doses and coverage is usually consistent with provincial data and the provincial level receives regular feedback from the regional and national levels.

It was observed that data analysis and management were weak in some provinces. Monitoring of performance of lower levels, evaluation and supervision were also found deficient in some areas. It was noted that with improved data management, provinces could better identify low performing sites or high-risk areas and populations on which to focus.

Manpower

Apart from one province appearing to be understaffed, there was generally no shortage of personnel at the provincial level. However, a high turnover of EPI staff, especially at the commune level was observed in some provinces. It was also noted that commune health workers were often overworked, not only regarding the EPI, but also with many other programs and tasks.

Training

Provincial EPI staff conduct training on the EPI, surveillance and injection practices at the district level. Most of the staff interviewed from the communes had received training during 1997. Training documents prepared by the national and regional level were available in all of the review provinces.

3.3 COLD CHAIN SYSTEM, LOGISTICS AND SAFETY OF INJECTIONS

Cold Chain

The maintenance of cold chain and vaccine handling, down to district level, was found to be functioning well in all provinces. Vaccine temperature monitoring and recording was being undertaken and EPI vaccines were being stored at the correct temperatures. Cold chain equipment at the provincial and district levels were sufficient to store vaccines in all the provinces, except in one province lacking refrigerators at the district level. Broken freezers or refrigerators were observed in most of the review provinces.

The teams had concerns about the maintenance of cold chain equipment at the commune level. This equipment was found to be old or in need of replacement at the commune level in at least three provinces. A shortage of thermometers was observed in at least two provinces.

Logistics

The teams were generally unable to observe a system to outline the inventory and requirements of cold-chain, sterilization and injection equipment at the provincial, district and commune levels. Also, there was no system to regularly monitor inventory and requirements from higher levels. No specific plan of the replacement of broken cold-chain equipment was elicited at any level surveyed. The amount and timing of equipment supply is determined by the national level, based on a request from the regional EPI management and the availability of supplies.

Generally the teams observed that sufficient amount of syringes and needles were available at facilities offering immunization services. However, in one area there was a shortage of re-usable syringes and needles. In general, re-usable injection equipment used in relatively easy access areas while disposable equipment was used in mountainous areas, according to national policy. It was observed, however, that parents in some delta areas were being asked to bear to cost of disposable injection equipment. Some delta communes were taking the risk of using disposable injection equipment in a situation where they had no backup of reusable injection equipment and steam sterilizers.

Safe injection practices

Immunization of multiple children with a single syringe (but changing the needle) was documented. This practice is particularly dangerous for the transmission of blood-borne infections. Re-sterilization of disposable syringes was also identified in some areas.

EPI staff generally had a good knowledge on sterilization of equipment. In a single province, boiling injection equipment in a cooking pot was still widely practiced due to the shortage of steam sterilizers. This practice does not ensure complete sterilization.

In two provinces, disposable needles were bent after use to avoid reuse, which is a dangerous practice for health staff that can result in needle injury. No system for the collection and destruction of disposable injection equipment under supervision or monitoring was observed.

In most communes, local EPI staff explained that used disposable equipment was burnt and buried. In one area, these wastes were thrown into an old, un-used water well without being burnt. In another commune, the used syringes needles and vials were burnt and buried in a pit in front of the commune health station. During the interview many young children were playing in the area. Sharp objects were seen protruding through the mud, a hazard for all people living in the area. A simple incinerator made by health center was used in some communes.

3.4 POLIO ERADICATION

AFP surveillance

AFP surveillance in Viet Nam is well established and operating effectively; the provincial level and most districts were able to achieve the set targets. Strong commitment and awareness were observed at all levels.

The overall rate of AFP reporting was found to be good with further improvement in 1998. A total of 463 AFP cases were reported in 1997. According to the virological case classification in 1997, only one case was confirmed as poliomyelitis by isolation of wild poliovirus, and only one AFP case was considered compatible with poliomyelitis.

Routine reporting and record keeping was found to be of a high standard in all of the review provinces, with a need for some strengthening in the area of data analysis. Zero reporting has been established in all provinces and is generally monitored regularly by provincial EPI staff.

Almost all past AFP records were complete, with line listing and mapping of all AFP cases is kept at the provincial level.

Case investigation

The standard of case investigation and the rate of two adequate stool sample collection were both found to be high. It was reported in one province that the rate of two adequate stool sample collection had improved markedly after introduction of an 80 000 dong reward paid for full investigation.

In one province, determination of the OPV immunization status of the case is often left until the time of 60 day follow-up. This means that it would be impossible to identify clusters of zero-dose or inadequately immunized children at an early stage and institute supplementary OPV immunization in the local area, if necessary. In some provinces, the review team

considered it that data analysis and management needs strengthening at the provincial level to identify the high-risk areas and populations

Active surveillance and active search

Regular active surveillance was implemented on a regular basis at the district and provincial levels. At the provincial level, the quality of active surveillance depended to a large extent on the relationship between Preventive Medicine Center staff and Provincial Hospital staff.

Provincial hospital staff is required to notify Preventive Medicine Center staff if they identify an AFP case and it is usually their responsibility to collect the necessary stool specimens. In some provinces, Preventive Medicine Center staff does not visit the hospital for active surveillance every month. Nine visits were made during 1997.

All provinces initiated supplementary OPV immunization in 1993. These activities were found by the review teams to be well prepared and implemented, with detailed plans prepared at all levels.

Supplementary immunization

The review teams found consistently high reported rates of supplementary immunization coverage (approaching 100%) during all rounds of the National Immunization Days and the High-Risk Response Immunization campaigns. Master lists of target age group children for supplementary immunization usually were made through a dedicated survey about a month before the campaign. In contrast to other countries in the Western Pacific Region, newborns between the two rounds of immunization were identified and added to the master lists, so that the target population for each round of the campaign was different.

Since the reported number of children immunized during supplementary immunization activities in one province has always been exactly the same with the targeted children, coverage has always been reported as 100% in both rounds in this area.

New strategies have been implemented since 1995 to ensure that no children would be missed: mobile teams, movement from house to house or boat to boat visits, more fixed posts, collection points (moving fixed posts), and improved quality supervision.

In some provinces it was found that the target population for supplementary immunization has fallen in 1998 compared to previous years.

3.4 NEONATAL TETANUS ELIMINATION

NT surveillance

In all of the review provinces NT surveillance has been established and integrated into the AFP surveillance system. Active surveillance of NT cases was conducted, not only at the provincial, but also at the district level on a weekly basis. Clinical staff at one provincial hospital, however, were not fully aware of correct NT case recording and reporting.

Monthly zero reporting for NT cases by the district level has been established and it is monitored by the provincial EPI units. Active surveillance for NT cases is implemented through a similar process as the AFP system.

Using data collected from surveys in the past, the expected neonatal death rate determined by the national level is 7.6 deaths per 1 000 live births. Standard case investigation forms are used for the investigation of neonatal deaths and these forms were complete, together

with line-listings of cases at the provincial level. Some provinces only reported and investigated a proportion of the expected number of neonatal deaths and not all detected deaths were investigated.

The reported TT2+ coverage in the five review provinces ranged from 52% to 99% in 1997, while TT2+ coverage of CBAW in high risk districts was reported to be greater than 95%. PAB ranged from 70% to 92% in the review provinces.

Children protected at birth

The PAB methodology has been shown to be an accurate indicator of protection of children against NT in Viet Nam. It can be used to identify high-risk areas with low levels of protection, and offers an opportunity to identify individual women with inadequate protection and immunize them. All review provinces are using PAB as an important indicator for NT surveillance. However, commune health staff in some areas had not completed the column used for calculating PAB against NT.

4. CONCLUSIONS

The EPI in Viet Nam has been effective in protecting children from vaccine preventable diseases. High coverage rates have been reported for children and pregnant women for several years. The incidence of vaccine preventable diseases remains low and the transmission of wild poliovirus appears to have been interrupted. There is a well-established EPI infrastructure functioning at all levels in provinces visited with regular immunization services conducted through fixed immunization sites.

The routine reporting system for EPI and vaccine preventable diseases surveillance is well developed and standard forms are being used at all levels. One of the strong achievements of the program was social mobilization and community participation. Very successful social mobilization activities, together with widespread use of IEC material were observed during the provincial review. The cold chain system operates well with proper vaccine management and handling and safe injection practices have improved over the last years in most provinces.

A strong commitment has been observed towards eradication of poliomyelitis at every level. The last wild poliovirus associated case was detected in January 1997 and the country is in the final stages of preparation for polio eradication certification. Viet Nam has successfully implemented five successive years of National Immunization Days since 1993, with a reported coverage of more than 95% during both rounds. Two additional High Risk Response Immunization were conducted in 1997 and 1998, using mobile team strategies to reach previously unimmunized children.

Viet Nam has achieved the WHO target of NT elimination and is now making good progress towards eliminating the disease at the district level. At the national level, the quality of NT surveillance has continued to improve with integration into the AFP surveillance. Detected neonatal deaths are investigated to determine the etiology of the death. The routine immunization of pregnant women with TT and campaigns for CBAW in high-risk districts are implemented successfully. The PAB indicator for NT has been introduced and is monitored to identify unprotected newborns.

The surveillance system for NT should be further strengthened with more neonatal deaths detected and investigated. All CBAW should be covered at all communes of the designated high risk districts for NT.

The quality or quantity of services, particularly program management at the provincial level should be further improved. Data analysis and management, monitoring of performance of lower levels, evaluation and supervision should be strengthened to identify high-risk areas and populations. The achievements should be monitored through a more accurate denominator and efforts should be intensified to include all children into the EPI system, especially in difficult to access areas. Using mobile outreach teams to immunize children in difficult to access areas should be continued as a strategy.

Maintenance of cold chain and potency of vaccines should be ensured particularly in difficult to access communes with longer immunization sessions. The policy of using one syringe and needle for every child immunized should be promoted and immunization sessions should be closely monitored to ensure that injections are safe. The national policy of using disposable injection equipment only in difficult to access areas should be promoted. In other areas, the use of disposable injection equipment by the judgement of individual province or parents should be discouraged. In areas using disposable injection equipment, a well-monitored collection and destruction system with the use of safety boxes and proper incineration should be introduced.

Maintaining and improving the EPI is critical to achieve the disease eradication and reduction targets in Viet Nam. The priority given to the program by government should continue and high quality AFP surveillance should be sustained until the global poliomyelitis eradication target is met.

Having drawn these conclusions, the review team considers that the EPI in Viet Nam is successfully protecting children from vaccine preventable diseases, and by any measure the achievements of the EPI are outstanding, and it is an extremely successful and cost-effective public health program.

5. RECOMMENDATIONS

In line with the national policies and guidelines, the review team makes the following recommendations to further improve the program and suggests that the conclusions and recommendations of this review provide the background for preparation of a five-year plan for the EPI in Viet Nam:

Routine EPI

1. The National EPI should provide guidelines for calculation of the target population to the regional level. The number of children registered at the commune level should be taken into consideration for determination of a more accurate target population
2. Efforts to find unidentified or unregistered children, especially in difficult to access areas should be a priority, not only during routine immunization activities, but during supplementary immunization as well. Strategies to reach these children, including house-to-house and boat-to-boat search and registration should be continued.
3. Provinces should continue to conduct monthly routine immunization sessions at all communes, where accessibility is not a problem. Different strategies and policies for difficult to access areas should be defined by the national level. Immunization sessions conducted every two to three months with mobile outreach teams, visiting households to cover all children in the target age group should be considered as a strategy in those areas.

4. Priority should be given to identifying hamlets which have been missed by routine EPI services and ensuring that children and women in these areas are covered by effective surveillance and all EPI antigens, including measles vaccine.
5. In communes implementing routine immunization sessions over a period longer than two days, there should be multiple deliveries of vaccine from the district level to ensure that the cold chain is maintained. Another option is for multiple communes to share a vaccine storage refrigerator and for distribution to take place from the commune level.
6. Data management and analysis should be strengthened at all levels. Data should be collected for immediate action and should be analyzed regularly to identify low performing units or high-risk areas for focus. Analysis needs to be done at all levels with tables, charts and graphs as required by the national level.
7. Supervision of immunization activities by the provincial and district EPI, with the use of standard checklists should be improved and regular supervision visits should be conducted to lower levels, giving priority to problem areas. Priority should be given to new EPI staff and newly split provinces.
8. Improvements are also needed in monitoring. Provincial level staff should evaluate the performance of lower levels and give regular feedback on their performance.

Cold chain and sterilization and injection practices

1. Potency of vaccines should be ensured through development of a well- maintained cold chain system. All levels should have an adequate supply of cold chain equipment through efficient distribution of available supplies.
2. At the commune level, all communes should have enough vaccine carriers with a thermometer and ice packs and / or ice. Replacement of old and broken vaccine carriers is required in many commune health stations.
3. There should be standard policy in calculating annual EPI equipment requirements and the distribution of new equipment for each level. A plan for distribution, particularly of cold chain equipment, should be prepared.
4. Supply of adequate quantity of sterilization and injection equipment needs to be assured to reduce unsafe injection practices.
5. Disposable injection equipment should only be used in difficult access areas, according to national policy.
6. Provincial and district EPI staff to ensure safe injection practices should supervise immunization sessions more closely. The following practices should be discouraged: injecting multiple children with single syringe by changing only the needle, the re-use of disposable syringes and needles, sterilizing injection equipment by boiling in a pot, and bending used disposable needles before discarding. These issues are of particular importance in the development of future plans for supplementary measles immunization campaigns.
7. A supervised system of collection and destruction of disposable injection equipment should be implemented, with the use of incineration boxes.

AFP Surveillance

1. Political commitment and support given to AFP surveillance should continue until after the global polio eradication target has been met.
2. The immunization status of all AFP cases should be determined as early as possible in the case investigation. If the case is zero-dose or inadequately immunized, an investigation for high-risk AFP cases in the local area should be conducted to determine whether there is a cluster of zero-dose or inadequately immunized children. Supplementary OPV immunization should be conducted if such a cluster is identified.
3. Active surveillance for AFP should be further improved to meet the certification criteria of polio eradication. Regional and national staff in all provinces should conduct active search at least once a year.

4. A good working relationship should be developed between Provincial Preventive Medicine Centers and staff at the Provincial Hospital to improve the quality of active surveillance. Provincial EPI staff should visit the provincial hospital at least once a week to perform active search at the Provincial Hospital.
5. Provincial EPI staff should analyze and map AFP surveillance data at the district level, on a regular basis, to identify low-performing areas as early as possible.

Supplementary immunization

1. There should continue to be a focus on high-risk populations during supplementary OPV immunization to immunize unregistered and mobile children. The strategies of house-to-house and boat-to-boat immunization with mobile teams should continue to be implemented.
2. Target population master-lists in all communes should continue to be updated before future supplementary OPV immunization.
3. For evaluation of supplementary immunization, there should be a focus on the absolute numbers of children immunized.
4. Experience from polio supplementary immunization should be applied to the development of future plans for measles supplementary immunization.

Neonatal tetanus elimination

1. The provincial level should continue to strengthen the activities of reporting and recording of the neonatal tetanus surveillance system and to intensify efforts to detect all neonatal deaths and then investigate them for NT.
2. The investigation of NT cases should include an assessment of the immunization status of CBAW and delivery practices in the local area.
3. Supplementary immunization of CBAW and PW should be carried out in response to a report of NT. The national guideline of immunizing all CBAW in the designated high-risk districts should continue. The immediate minimum response to an NT case should be to immunize all CBAW with 2 doses of TT in the commune where the case is detected.

Training

1. EPI training needs should continue to be identified.
2. Training of health staff at all levels on 1) estimation of target populations, 2) monitoring of immunization coverage and surveillance, 3) data analysis, 4) identification of high risk areas and populations, and 5) cold chain, safe injection and sterilization practices, should be conducted accordingly. Priority should be given to new EPI staff and newly split provinces. Provincial EPI staff should receive training on basic epidemiology, surveillance and program management.

6. ACKNOWLEDGEMENTS

The review team members would like to express their appreciation and gratitude to the Minister for Health of Viet Nam and his staff, the National EPI Review Steering Committee, to representatives of the People's Committees, Provincial, District and Commune health staff who gave their time and assistance to ensure that this 1998 National EPI Review was a success.

ANNEX 1. QUALITATIVE REVIEW TEAM MEMBERS AND PROVINCES VISITED

Thanh Hoa Province

- Mr. Kim Mun Dok, Project Officer, Monitoring and Evaluation
UNICEF, Socialist Republic of Viet Nam
Dr Histoshi Murakami, Short Term Consultant,
Western Pacific Regional Office, WHO
Dr Dinh Sy Hien,
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Dak Lak Province

- Dr Nguyen Minh Tuan, EPI Medical Officer,
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Quang Ngai Province

- Dr Nedret Emiroglu, EPI Medical Officer,
Western Pacific Regional Office, WHO
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Hai Duong Province

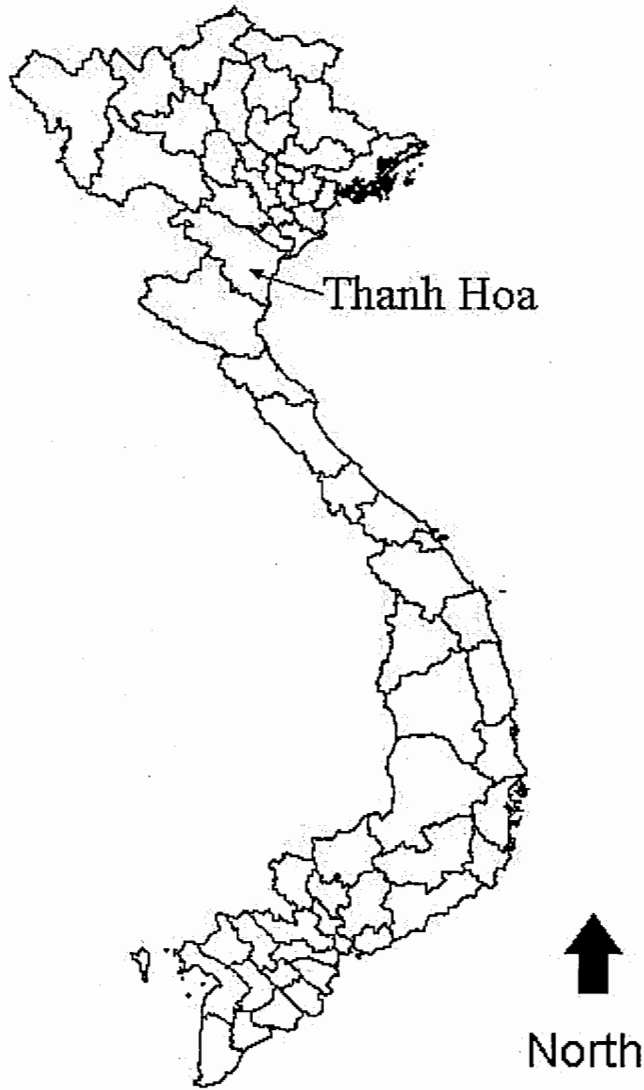
- Dr Yang Bao Ping, EPI Medical Officer,
WHO, PDR Laos
Dr Vu Quoc Ai
Pasteur Institute, Ho Chi Minh City

Tra Vinh Province

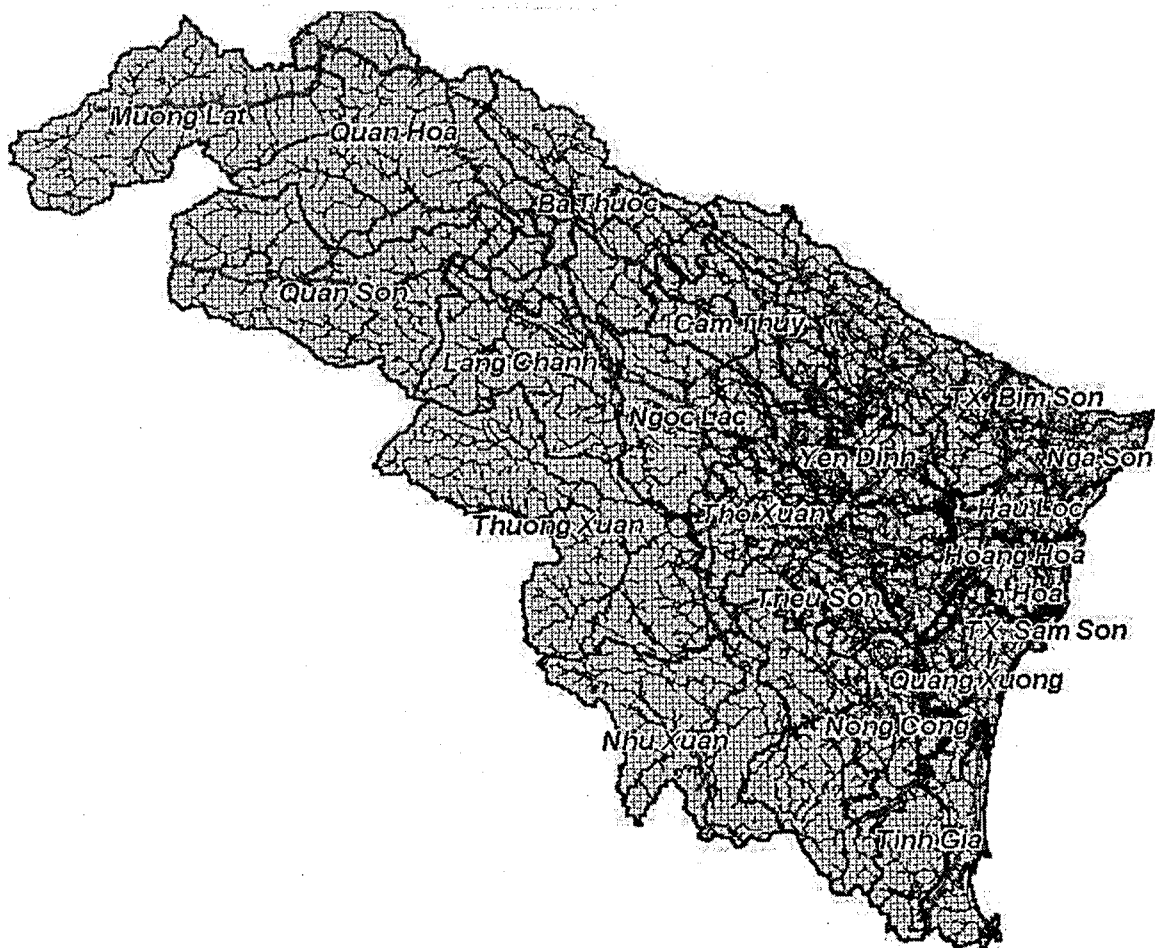
- Dr Marcus Hodge, EPI Medical Officer,
Socialist Republic of Viet Nam
Dr Nguyen Van Cuong
NIHE, Ha Noi

Appendix 5: Maps of Vietnam, Thanh Hoa, Quang Xuong and Ngoc Lac

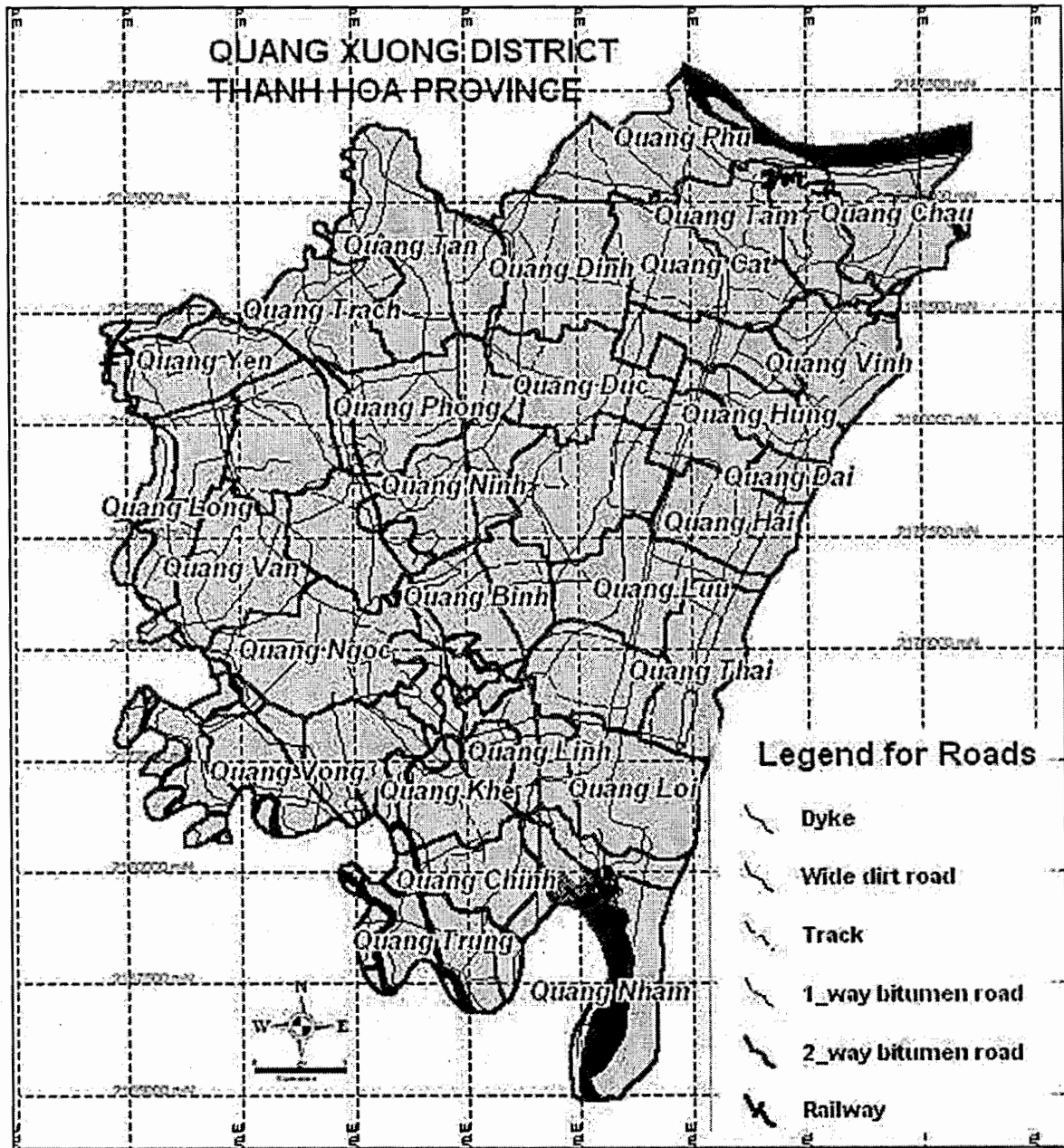
Map of Vietnam's Provinces



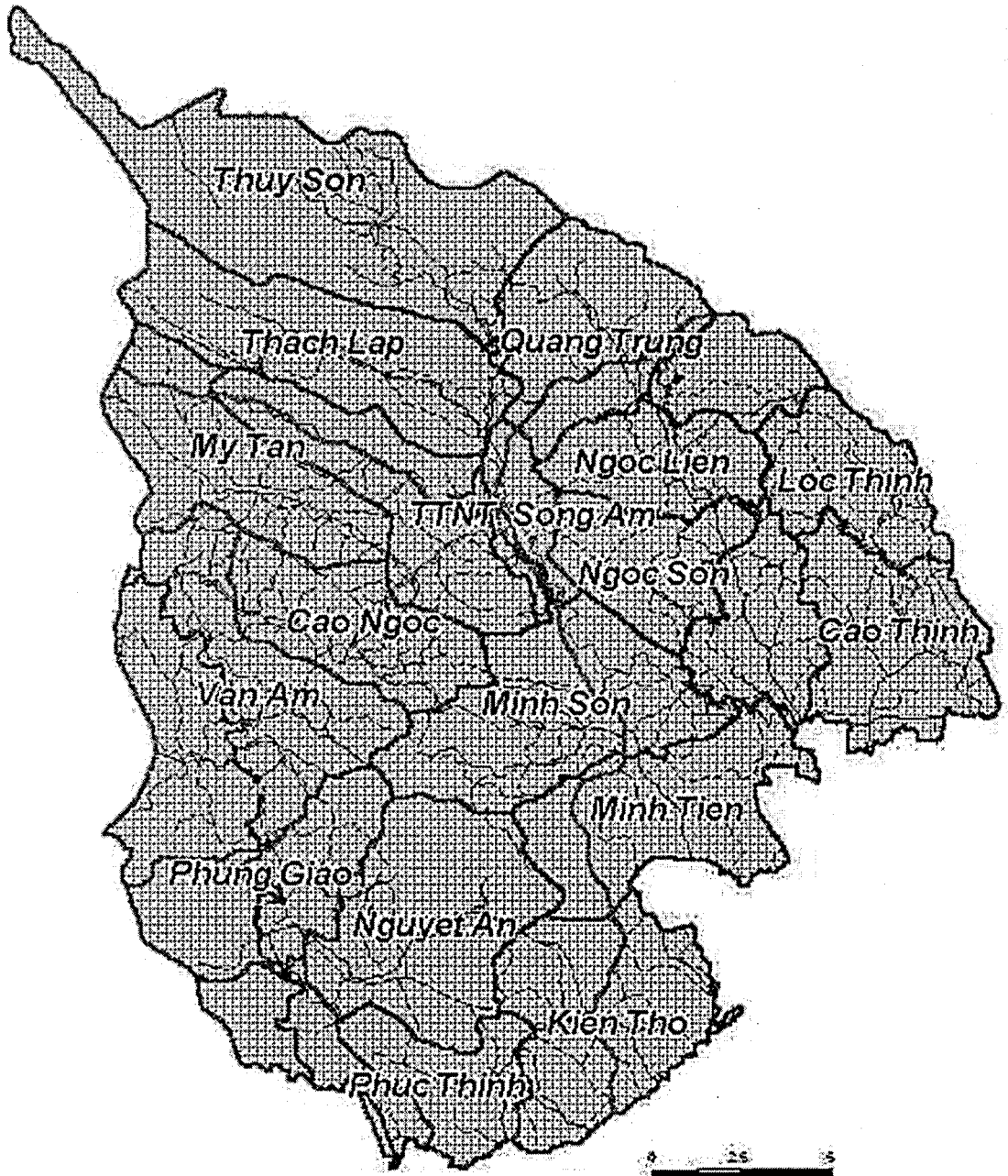
Map of Thanh Hoa province



Map of Quang Xuong district



Map of Ngoc Lac district



Appendix 6: Health Worker Survey Instrument

***EPI ACTIVITIES SURVEY FORM FOR COMMUNE HEALTH CENTRES
QUANTITATIVE COMPONENT – for completion prior to survey team visit***

Province: _____ District: _____ Commune: _____
Name of CHS head: _____

1. GENERAL DESCRIPTION OF COMMUNE:

Population:

No. of villages: _____ No. of households: _____
No. of active village HWs (VHWs): _____ No. inactive VHWs: _____

Ethnic groups present in Commune: _____

No. of children aged under 1 year: _____

No. of children aged under 5 years: _____

No. of women who gave birth in 1997: _____

No. of women aged 15 - 35 years: _____

No. of babies born in commune in 1997:

- No. born at CHS: _____
- No. born at other health facility (district or province hospital, polyclinic): _____
- No. born outside a health service (at home, at traditional birth attendant): _____

No. of perinatal deaths (infants born alive at >24 weeks gestation but dying aged < 28 days) in 1997: _____

No. of infant deaths (infants dying aged 28 days – 1 year): _____

No. of deaths amongst children aged 1 – 5 years: _____

2. EPI ACTIVITIES IN THIS COMMUNE DURING 1997:

No. of trained HWs at CHS: _____ No. involved in usual EPI activity? _____

Doctors: _____ Doctors: _____

Assistant doctors/Nurses: _____ Assistant doctors/Nurses: _____

Others: _____ Others: _____

Any VHWs or other helpers assisting EPI activities?.....

Number/cadres of staff formally trained in EPI:

Number of staff who received refresher training in 1997:

How often do CHS staff conduct EPI activities?

Monthly: _____ No. of EPI points each month (give range if varies): _____

2 monthly: _____ No. of villages per EPI point (give range): _____

Quarterly: _____ No. of EPI tables at each EPI point (give range): _____

During NIDs only: _____ No. of campaigns in 1997 (excluding NIDs): _____

Frequency of EPI contact with each village (circle one):

Monthly 2 monthly 3 monthly Less often or give range if varies

3. EPI ACHIEVEMENTS IN 1997:

BCG – doses given (number):
 DPT3 – doses given (number):
 Children fully vaccinated:
 TT2+ (amongst women who delivered in 1997):
 TT2+ (amongst women aged 15 – 45 years):
 Percentage of mothers of children with DPT1 vaccinated to TT2 and TT3+

OPV3 – doses given (number):
 Measles – doses given (number):

No. of newborn babies who received BCG/OPV-O in first 4 weeks of life in 1997:

Number of cases in 1997:

Poliomyelitis	Neonatal tetanus	Tetanus
Diphtheria	Whooping cough	Measles

4. COLD CHAIN AND EPI EQUIPMENT (specify quantity in storage at the CHS):

Electricity available at this CHS?	Yes ... No ...
Document re safe injection technique at CHS?	Yes ... No ...
Document re safe disposal of needles and syringes at CHS?	Yes ... No ...
Container for safe disposal of needles and syringes at CHS?	Yes ... No ...
Do you use disposable needles and syringes?	Yes ... No ...
Do you use reusable needles and syringes?	Yes ... No ...

	In use	In store	Damaged	Remark
Vaccine thermos				
Cold Boxes				
Ice blocks				
Thermometer				
Pressure steriliser – 1 tier				
- 2 tier				
Spare gasket				
Spare valve				
Stove or fuel cooker				
Fuel, if no electricity				
Source of fuel				
Amount of fuel/month				
Reusable syringe 1 ml				
Reusable syringe 0,5 ml				
Reusable syringe 0,1 ml				
Needle 24G				
Needle 26G				
Disposable needles and syringes				
Forceps				
Mode of transport for EPI owned by CHS?				
Own transport used?				
Mode of keeping vaccines cold from CHS to EPI point?				
In 1997, which equipment was in short supply?				

Source of EPI equipment: Province: District: EPI program:... Other

How many days per month do you do EPI?

If >1 day, how do you ensure cold chain is maintained?

5. OTHER EPI-RELATED ACTIVITIES:

Current IEC materials:

Poster (specify type and quantity):

Booklets (specify type and quantity):

Other publicity materials (specify type and quantity):

Number of EPI cards (not yet used – at CHS) : vaccination for children:

tetanus vaccination cards for women:

combined U5/TT card (blue):

Which card do you prefer?

Report form (type and quantity):

EPI progress diagram in use?

Major difficulty in conduct of EPI?

QUALITATIVE COMPONENT – issues for survey team to discuss with CHS staff

During interview, surveyor also to assess:

- Source of information re babies born other than at CHS:.....
- Source of information re perinatal/under 5 deaths:

Does this CHS hold a regular weekly Antenatal Clinic: Yes No

If yes, what is the average number of patients attending?

If yes, is TT available at this Clinic? Yes No

If no, how are pregnant women at village-level assessed for their TT status before delivery?

Source of information re EPI performance/case numbers:.....

How CHS knows about newborns to be vaccinated?

Whether any newborns ever come for OPV/BCG? Yes No

How village women know about EPI schedule of CHS?

Whether invitations are in use? Yes No

How EPI-workers know number of children to be vaccinated each month?

How EPI-workers divide up vaccines into cold boxes by number?.....

Knowledge of sterilisation techniques?.....

Knowledge re reusable/single use equipment?

Knowledge of principles of cold chain & which vaccines should/should not be frozen?

Record keeping – vaccinations recorded on site or back at CHS? Rely on memory or records kept (?cards ?loose sheet)?

Role of multi-dose vials in missed opportunities?

No. of new-born babies protected against tetanus (i.e.mother covered by TT2):

Where are vaccination cards kept?

Why?

Whether interviewee believes it is OK to change only the needle for a second injection?

Ask HW to describe how to sterilise needles and syringes. Check answer includes:

- flushing needles and syringe?
- Separation of needle and syringe in the steriliser?
- steam sterilising, not boiling?
- sterilisation for 20 minutes after steam starts to come out of the steriliser?

Day month year 199

Name of surveyor:

Appendix 7

KAP Questionnaire on Liver Disease and the EPI – For Householders - Thanh hoa province, 1998

Date: day:.....month:..... year:.....

Time of interview(tick one): Morning: [] Afternoon: [] Evening: []

Name of surveyor:.....

Number of cluster:

Number of household:

Name of interviewee:..... Age:..... Sex: Male: [] Female: []

Address of interviewee: - Village:.....

- Commune:

- District:

Duration from village to CHS by foot, in hours:

- Dry season: <2: [] 2 - 4: [] 4 - 8: [] >8: []

- Wet season: <2: [] 2 - 4: [] 4 - 8: [] >8: []

Ethnicity of household (tick one): Kinh: [] Muong: [] Other:.....

Able to understand language spoken by CHW? Yes: [] No: []

Able to read Vietnamese? Yes [] No []

Qualification/Title (if any):

- Did not go to school: []

- Primary school (First degree): []

- Primary school (Second degree): []

- Secondary school: []

- Tertiary or higher: []

TV in house? Yes: [] No: [] Radio in house? Yes: [] No: []

Is there a VHW in this village (tick one)? Yes: [] No: []

Does this village have a loudspeaker? Yes: [] No: []

Q1. Which of the following social organizations do you belong to? (tick if answers yes)

- Communist Youth member: []

- Communist Party: []

- Women's union: []

- Farmer's union: []

- None: []

- Others (specify):

Q2. Do you know people in your community who have ever had liver disease?

- Yes: []

- No: []

- Unsure: []

Q3. Does liver disease ever cause long term illness in your locality?

- Yes: []

- No: []

- Unsure: []

Q4. Does liver disease ever cause death?

- Yes: 1
- No: 2
- Unsure: 9

Q5. Do many people have long term illness or die of liver disease?

- Yes: 1
- No: 2
- Unsure: 9

Q6. Can any causes of liver disease be transmitted from person to person?

- Yes: 1
- No: 2
- Unsure: 9

Q7. Can a person who does not look sick transmit any causes of liver disease to another person?

- Yes: 1
- No: 2
- Unsure: 9

Q8. Can causes of liver disease be transmitted from mother to baby?

- Yes: 1
- No: 2
- Unsure: 9

Q9. What causes of liver disease do you know?

Q9A. Have you heard of liver disease caused by the hepatitis B virus?

- Yes: 1
- No: 2 If no, go to Q10.

Q9B. By what means does this virus pass from person to person? (do not list – tick only if mentioned)

- Blood transfusion: 1
- Food or water: 2
- Sex: 3
- Needle: 4
- Razors: 5
- Toothbrushes: 6
- Casual contact: 7
- Don't know 9

Other (specify)

Q9C. Is there a vaccine against the hepatitis B virus?

- Yes: 1
- No: 2
- Unsure: 9

Q10. Does an immunisation team visit your area?

- Yes: 1
- No: 2
- Unsure: 9

Q10A. *If yes*, how often does the team reach your village, or a place convenient for you?
(do not list, tick one only. If variable, tick option 5)

- Monthly: 1
- 2 monthly: 2
- 3 monthly: 3
- Less often: 4
- No fixed schedule 5
- Don't know 9

Q11. Which of the following people have told you about the EPI? (list each and tick if interviewee agrees)

- Health worker: 1
- Women's union representative: 2
- Family planning worker: 3
- At a public meeting: 4
- Friend/family 5
- Other (specify): 5

.....
Q11A. By which of the following methods did you learn about the EPI? (list each and tick if interviewee agrees)

- Radio/television/video: 1
- Loudspeaker 2
- Posters: 3
- Newspaper: 4
- Other (specify): 5

.....
Q12. Do you keep a record of your baby's immunisations at your home?

- Yes: 1
- No: 2

Q13. Who tells you, or how do you know when your baby needs to go for immunisation?
.....
.....

Q13A. How many days before the EPI team arrives do you know they are coming?

Q13B. If your baby missed a dose of vaccine, would someone come to remind you that the baby needs vaccination?

- Yes: 1
- No: 2
- Unsure: 9

- Q14. Do you know about the under 5 card? - Yes: [] 1
 - No: [] 2
 - Unsure: [] 9

Q14A. *If yes*, which of the following people keep it? (list, then tick only one)

- You [] 1
- The village health worker [] 2
- The village headman [] 3
- You, but it is lost [] 4
- Don't know [] 5
- Other (specify).....

Q15. What is the most important use of vaccination? (list, then tick only one)

- Treat diseases: [] 1
- Prevent diseases: [] 2
- Improve baby's health: [] 3
- Don't know: [] 4
- Other/don't know (specify):.....

Q15A. Do you believe healthy infants need vaccination?

- Yes: [] 1
- No: [] 2
- Unsure: [] 9

Q15B. Do you always take your babies for vaccination?

- Yes: [] 1
- No: [] 2

Q16. Which of the following do you think are common reasons for mothers not bringing their babies for vaccination? (list each, tick if interviewee agrees)

- Vaccine side effects: [] 1
- Baby is too sick at the time: [] 2
- They forget: [] 3
- They are too busy: [] 4
- They are too far away: [] 5
- They dislike the waiting: [] 6

Remember, I am asking about common reasons mothers don't take a baby for vaccination

- They dislike the EPI team: [] 7
- The explanations are poor: [] 8
- The EPI team ask for money: [] 9
- They don't know the team are coming [] 10
- They think the team will not arrive: [] 11
- They think there may not be enough vaccine: [] 12
- They do not know about vaccination: [] 13
- They do not know the schedule of doses: [] 14
- They do not believe in vaccination: [] 15
- There are bad rumors about vaccination: [] 16
- Other (specify):.....

Q16A. Which are the most important? (show interviewee and write numbers)

Q17. Is there a trained village health worker in your village?

- Yes: [] 1
- No: [] 2
- Unsure: [] 9

Q17A. *If yes*, do they help on EPI day?

- Yes: [] 1
- No: [] 2
- Unsure: [] 9

Q18. In your village, where do the majority of women deliver their babies? (tick one)

- At home without help: [] 1
- At home with help: [] 2
- At home with a health worker: [] 3
- At the commune health station: [] 4
- Somewhere else (specify):

Q18A. Who usually helps women to deliver their baby?

Q19. If a new vaccine required infant vaccination on the first or second day after birth, do you think mothers would agree to their new baby receiving the vaccine at this time?

- Yes: [] 1
- No: [] 2
- Unsure: [] 9

Q19A. If not, why not?
.....
.....

Q20. Are you aware of any cases of tetanus amongst newborns or women of child bearing age in your village in the last 2 years? - Yes: [] 1

- No: [] 2
- Unsure: [] 9

Thank you very much for your help!

Signature of surveyor

Chapter 2A

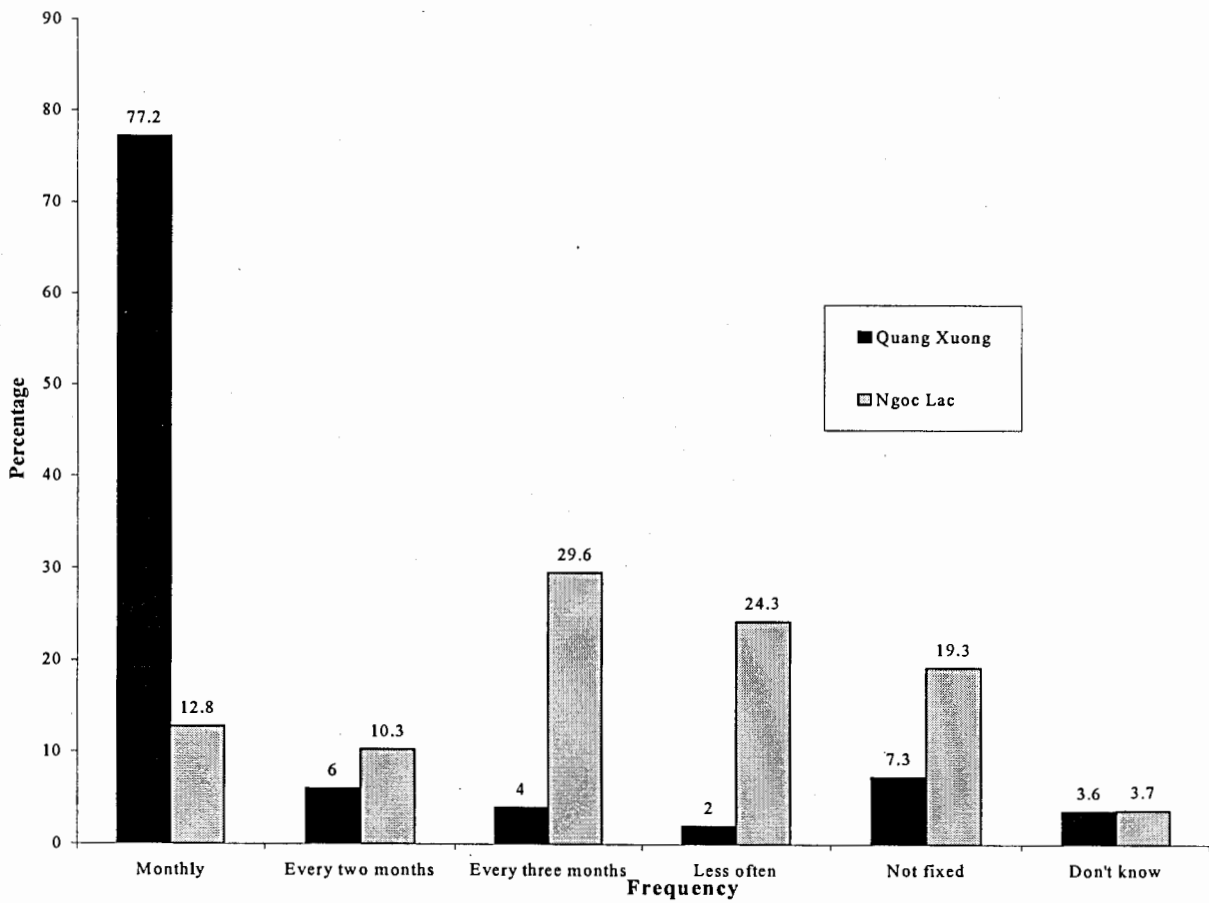


Figure 1: Frequency of convenient availability of the Expanded Program on Immunisation (EPI) to interviewees within the two districts at baseline

Chapter 2B

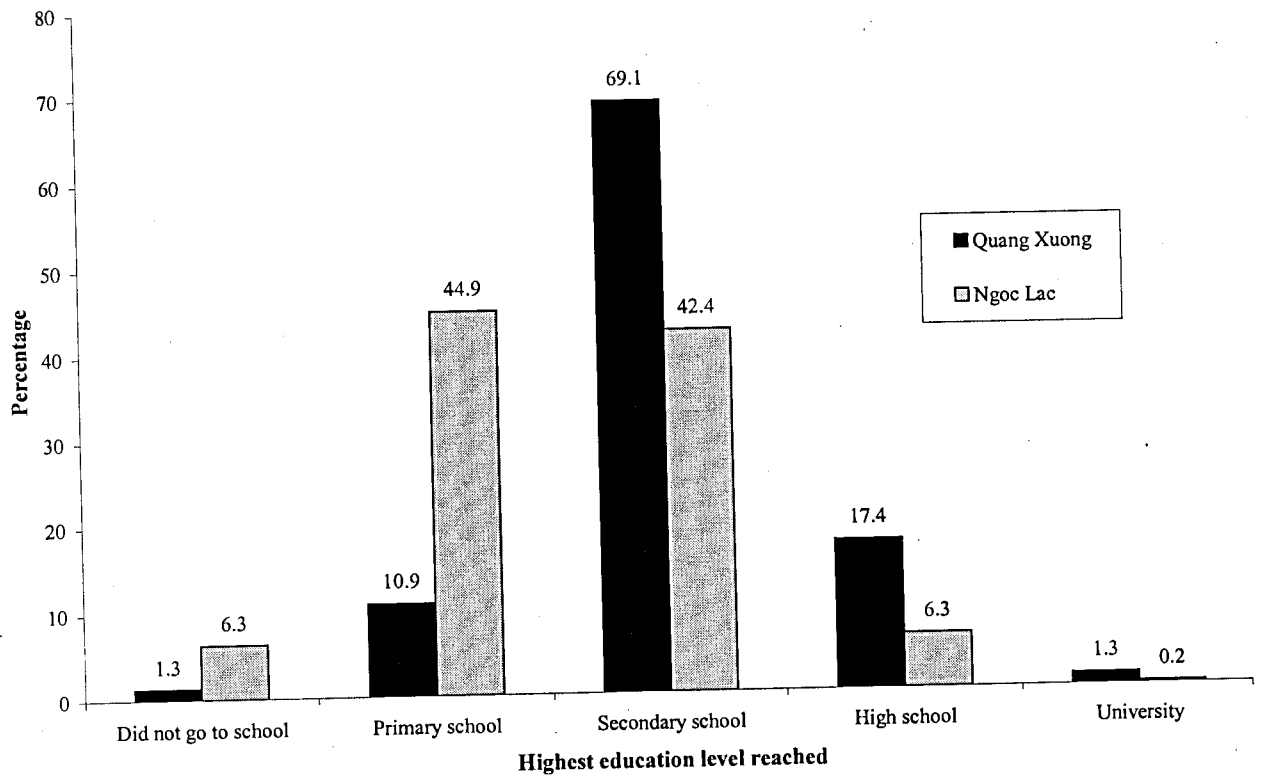


Figure 2: Highest education level reached by all interviewees depicted by district at baseline

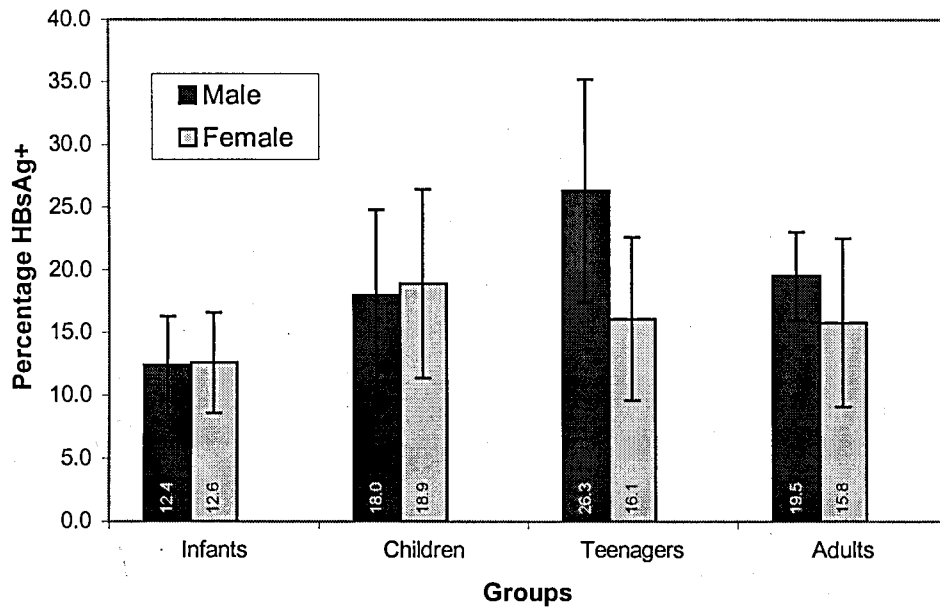


Figure 3: Prevalence of infection (hepatitis B virus (HBV) surface antigen positive (HBsAg+)) and 95% confidence intervals (c.i.) depicted by sex and age group

Chapter 3

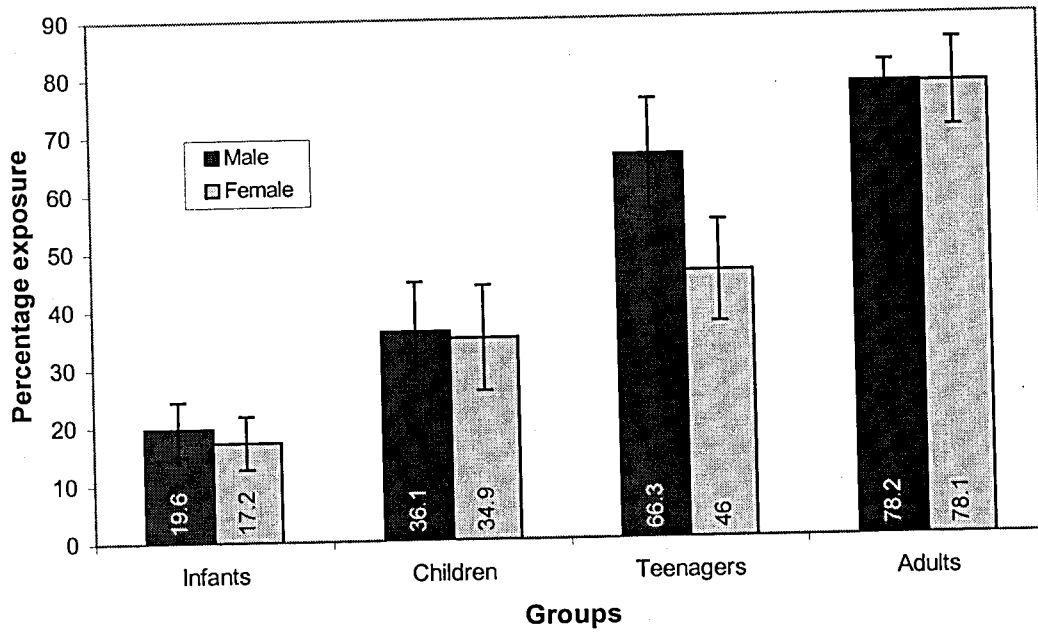


Figure 3A: Prevalence of exposure to HBV (HBsAg+ or HBsAg-negative but positive for antibody to HBV core antigen (anti-HBc+)) and 95% c.i. depicted by sex and age group

Chapter 3

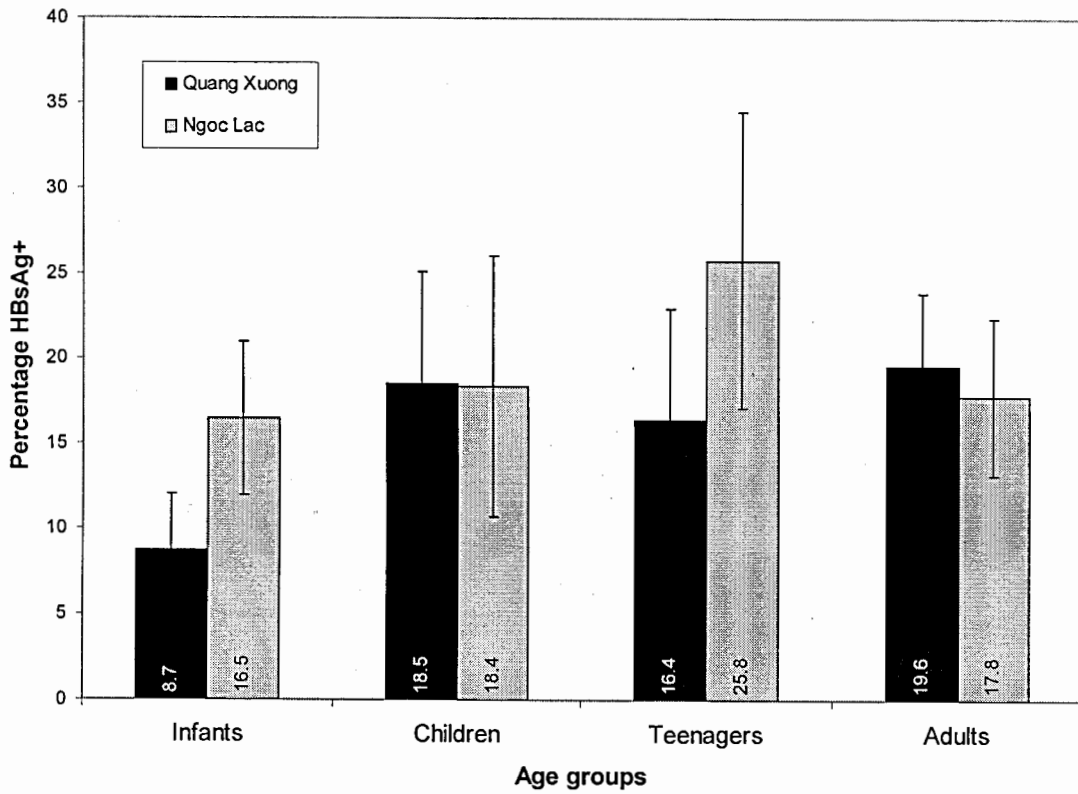


Figure 4: Prevalence of infection (HBsAg+) and 95% c.i. among groups of subjects by age and district

Chapter 3

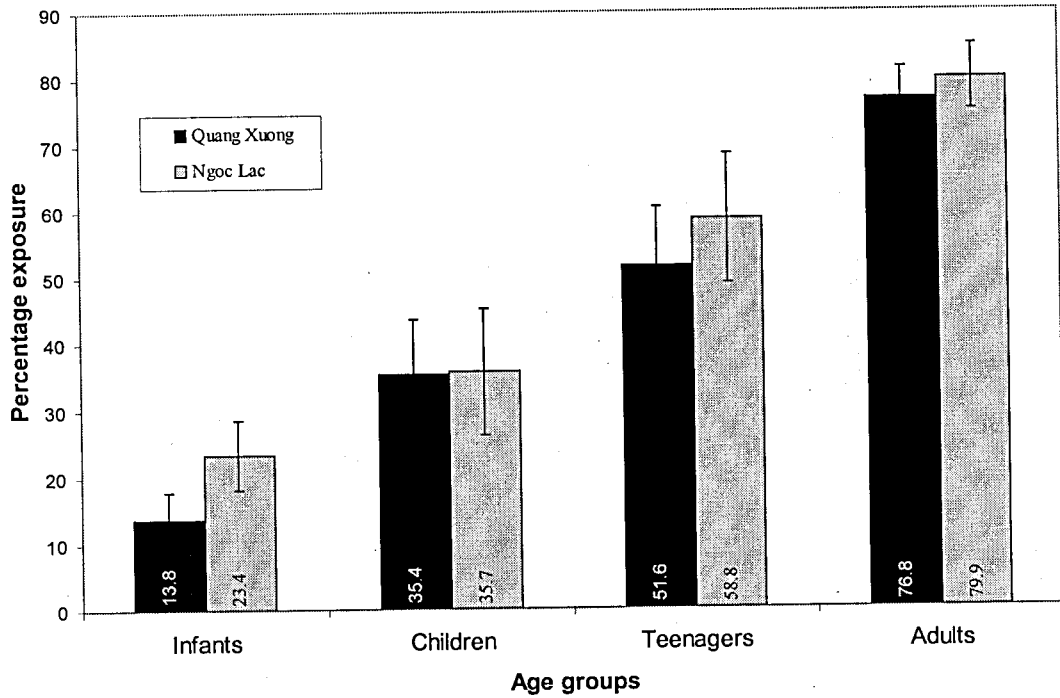


Figure 4A: Prevalence of exposure to HBV and 95% c.i. amongst groups of subjects by age and district

Chapter 3

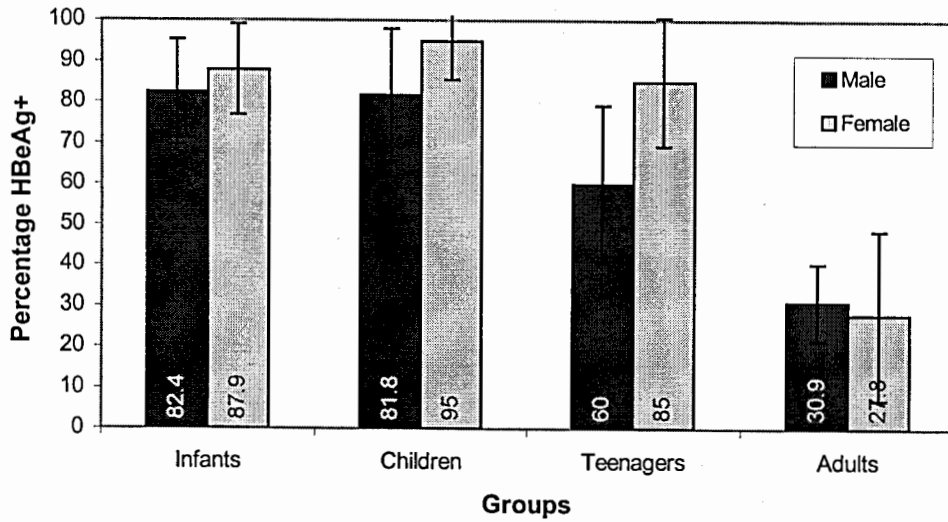


Figure 5: Prevalence of HBV “e” antigen and 95% c.i. amongst HBsAg positives, depicted by sex and age group

Chapter 5

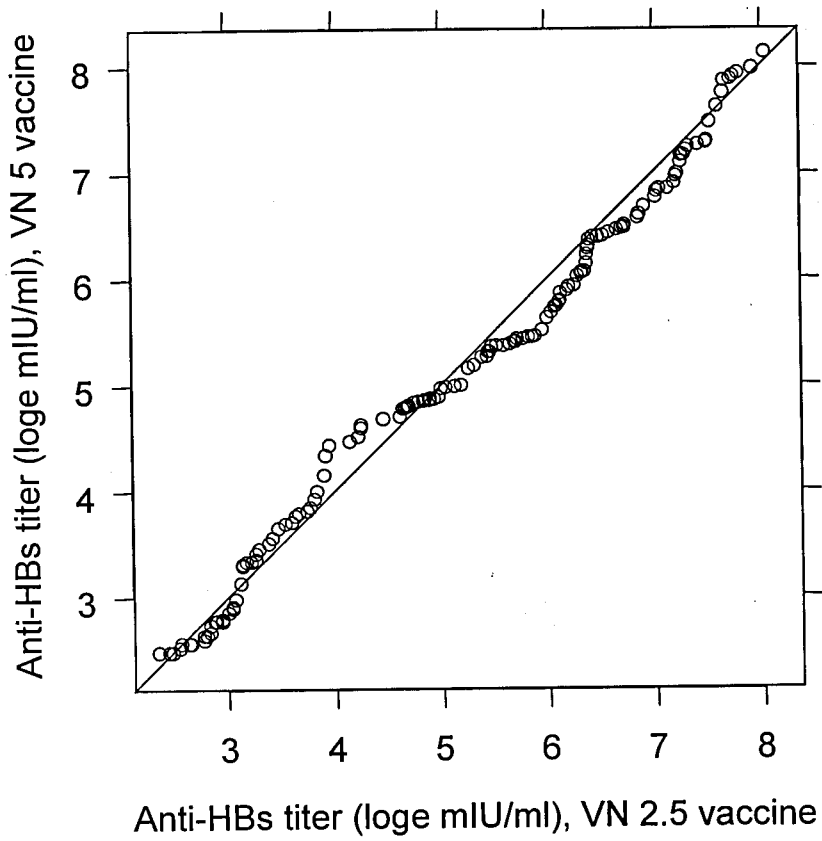


Figure 6: Centile distribution of natural log titres of antibody to HBsAg (anti-HBs) amongst infants of mothers lacking HBV markers and seroconverting after a course of the Vietnamese vaccine at 2.5µg/dose (VN 2.5) or 5µg/dose (VN 5)

Chapter 6

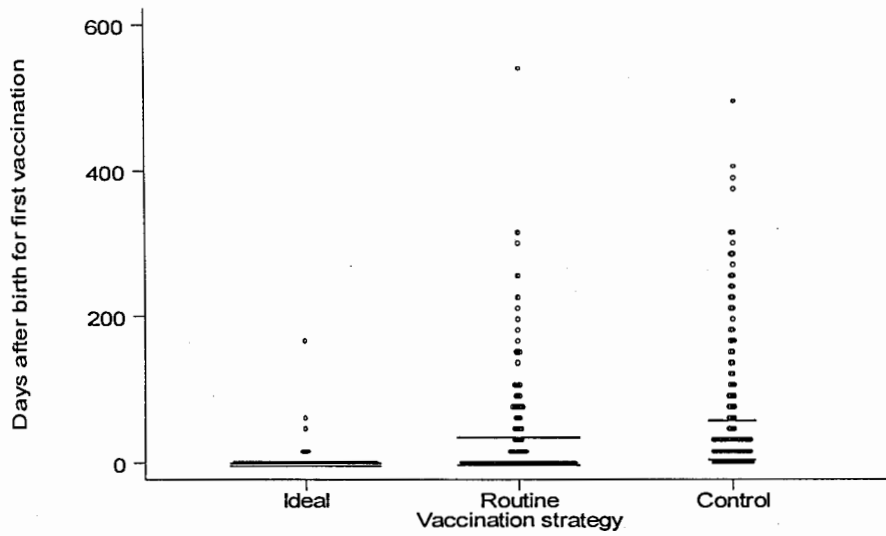


Figure 7: Dot-plot of the day after birth for the first dose of HepB vaccine (dose-1) by strategy, showing 25th and 75th percentiles for each as horizontal bars

Chapter 6

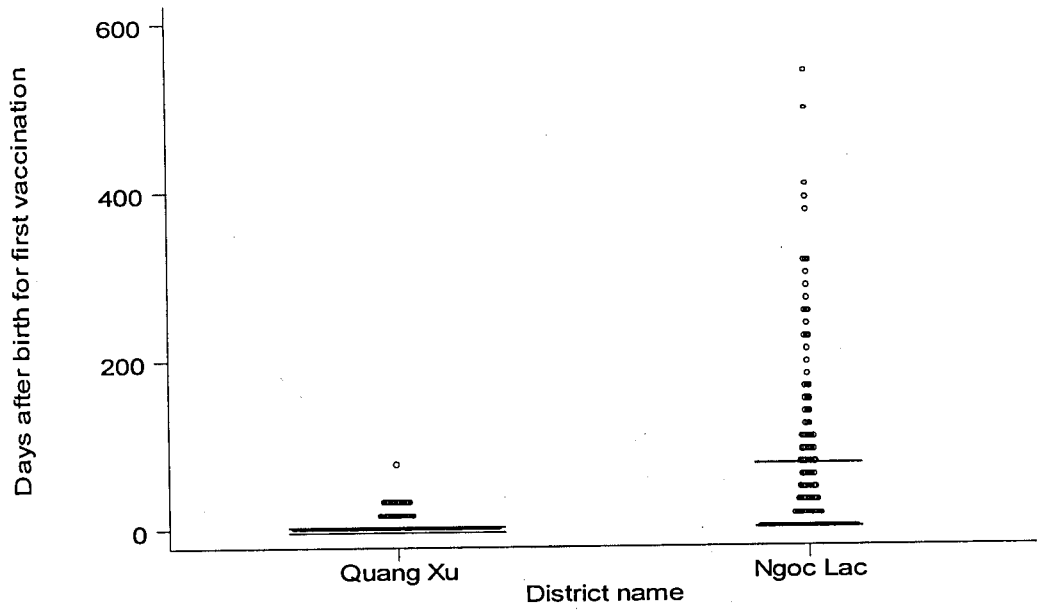


Figure 8: Dot-plot of dose-1 of HepB vaccine by district, showing 25th and 75th percentiles for each

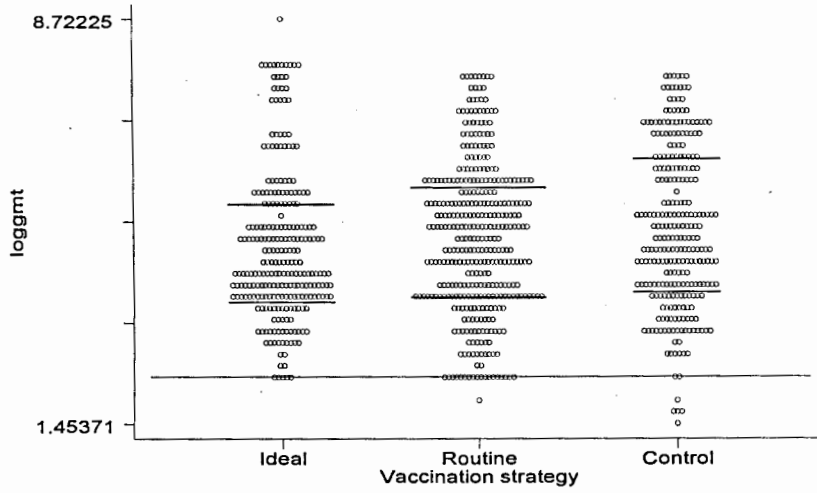


Figure 9: Dot-plot of natural logarithm of anti-HBs titre by strategy, showing 25th and 75th percentiles for each, and a continuous horizontal line for the logarithm of a protective titre of 10mIU/ml

Chapter 6

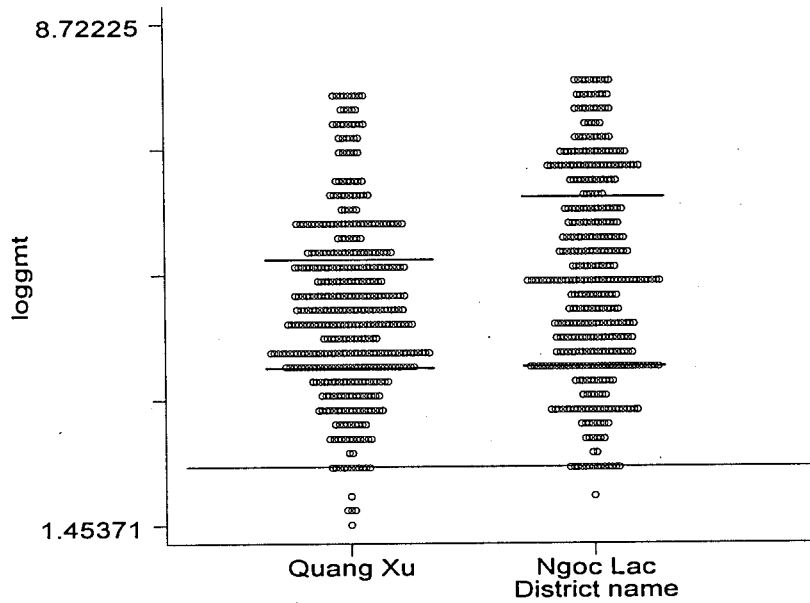
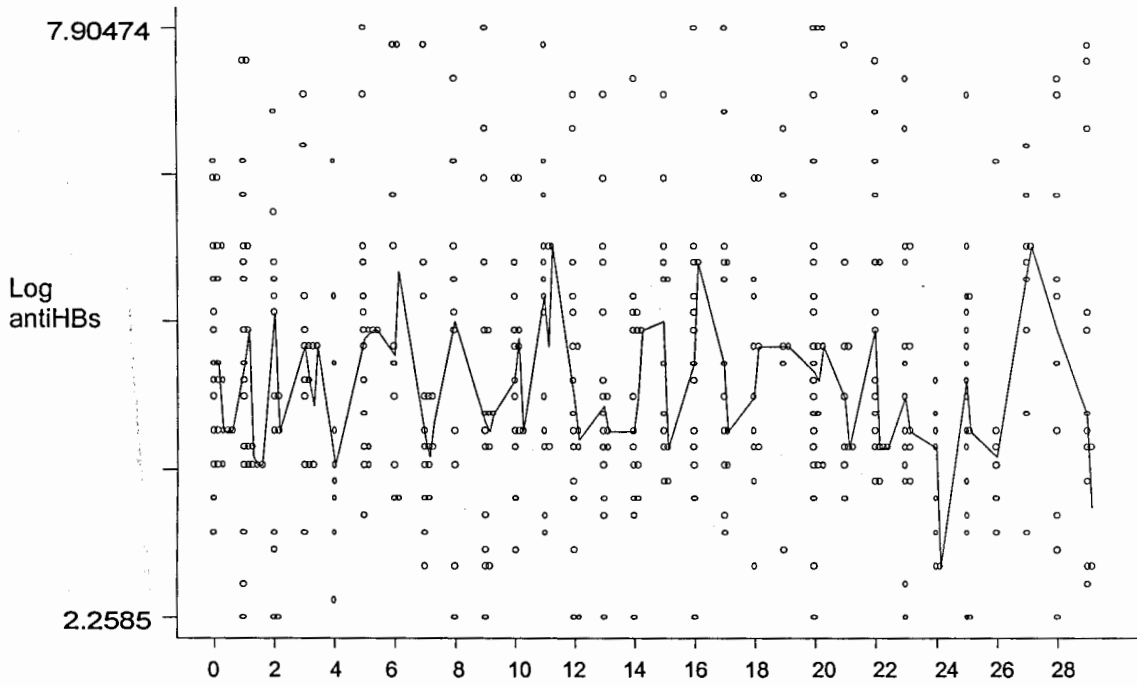


Figure 10: Dot-plot of natural logarithm of anti-HBs titre by district, showing 25th and 75th percentiles for each, and a continuous horizontal line for the logarithm of a protective titre of 10mIU/ml



Days of storage of vaccine outside the cold chain
(line represents median anti-HBs titres of infants receiving vaccine on each day)

Figure 11: Dot-plot of the natural logarithm of anti-HBs amongst infants born in ideal and routine communes according to duration of heat-exposure of dose-1 in days (represented by date of receipt of dose-1) showing median titre for each day

Chapter 7B

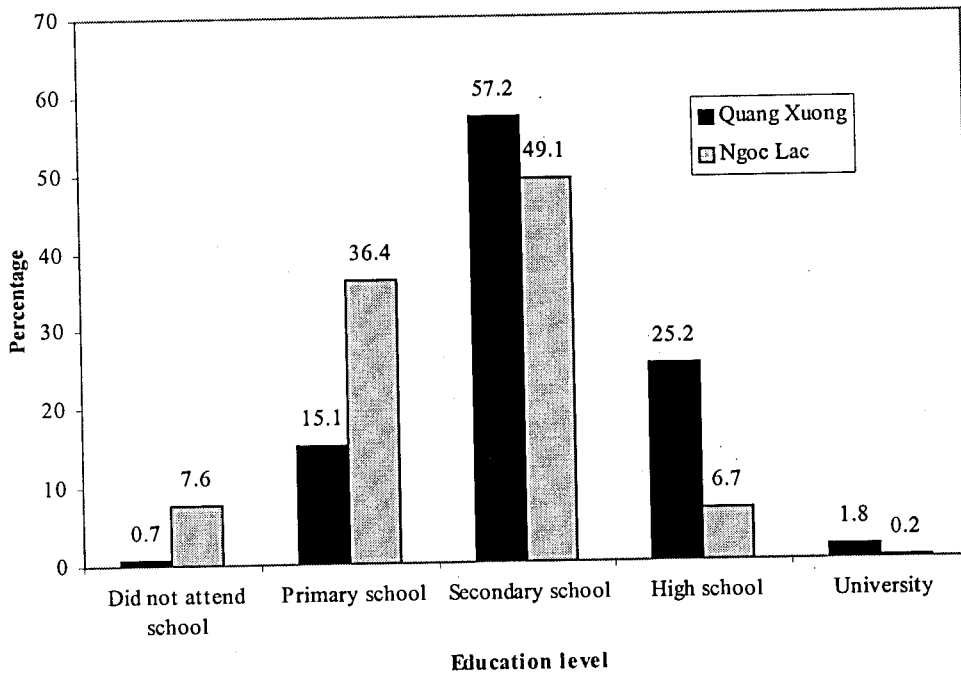


Figure 12: Highest education level of all interviewees at follow up, depicted by district

Chapter 7B

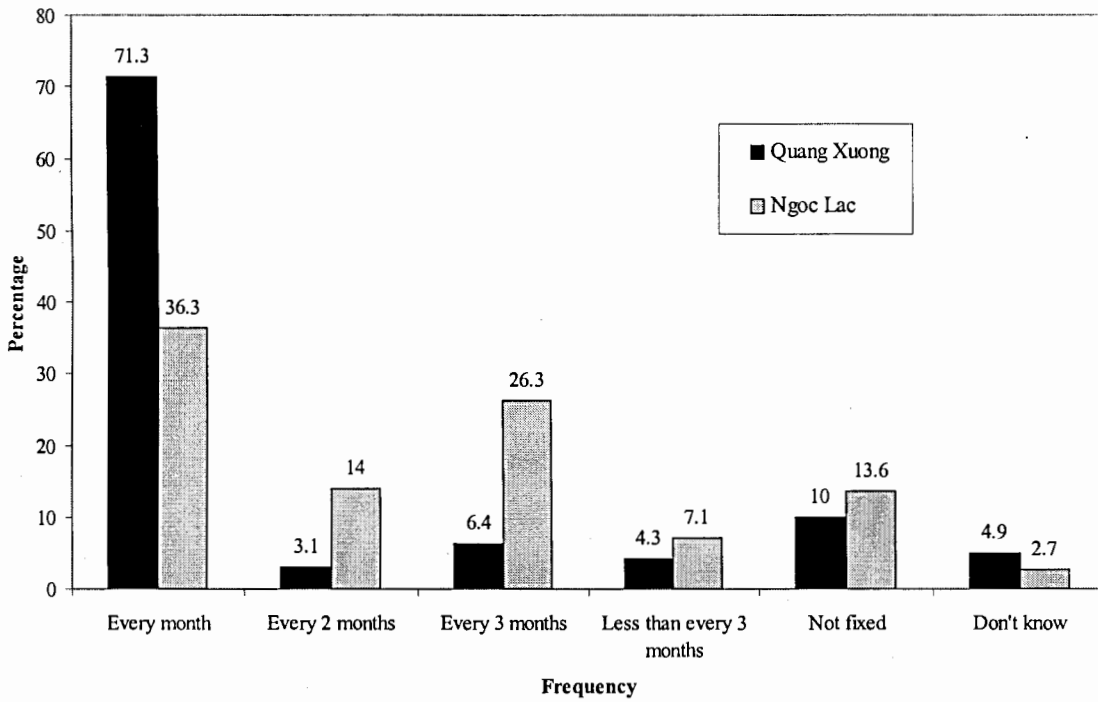


Figure 13: Visiting frequency of EPI staff at follow up

Appendix 9: Village-level Birth Registration and EPI Record Form - front side

Commune name: _____

Village name: _____

Month and year: _____

Mother's name and household number	Baby's name	No. of doses of TT mother has ever received ¹	Date of birth		Place of birth ²	Attendant at birth ³	Birthwt.	Outcome and risk factors for this infant ⁴	Date received vaccines below ⁵										
			Male	Female					First EPI contact ⁶		2nd	3rd	4th	5th	Measles	Other			
									HBV-1	BCG							OPV-0 if given	DPT-1 OPV-1 HBV-2	DPT-2 OPV-2 HBV-3

1. Include doses received during this and previous pregnancies or at other times. Total should not exceed five.

2. Home, elsewhere in the village, commune health station, polyclinic, district hospital or provincial hospital

3. No one, relative, traditional healthworker, other healthworker (state type) or doctor.

4. Statement re infant's health status at each of 5 EPI contacts, risk factors (e.g. prematurity, low birth weight, multiple birth, maternal death, recurrent illness etc).

5. Refer to schedule for appropriate dates of EPI contact, sites of injection, advice to give mothers etc. Give BCG at first opportunity, even if with DPT-1 and HBV2.

6. Note that because they cannot be stored outside the cold chain, BCG and OPV-0 may be unavailable at the time HBV-1 is given.

In this case, BCG should be given at the next possible EPI contact, ideally when the infant is less than 4 weeks old, or with DPT1 and HBV2 at the latest.

If the infant is more than 4 weeks old, OPV0 is dropped and the infants start with OPV1.

- | | |
|----------------------|--|
| 1. At birth: | BCG
HBV – 1 |
| 2. At 1 month: | HBV – 2 (OR give with DPT-1 at 2 months) |
| 3. At 2 months: | DPT – 1
OPV – 1
HBV – 3 (or HBV – 2, if not yet given) |
| 4. At 3 months: | DPT – 2
OPV – 2
HBV – 3 (if not yet given) |
| 5. At 4 months: | DPT – 3
OPV – 3 |
| 6. At 9 - 11 months: | Measles vaccine |

Important points:

1. NEVER, NEVER re-use needles and syringes without adequate sterilisation. There is a high risk of transmitting HBV, HCV or HIV
2. HBV-1 must be given in the first week of life to protect against possible exposure to infection at birth.
3. It is possible, safe and effective, to give BCG, DPT and HBV all on the same day, provided DPT and HBV are given in separate sites.
4. HBV must be given by deep intramuscular injection, preferably in the thigh, for best effect.
5. Warn mothers that DPT will often cause fever for 24 hours.
6. Do not delay vaccination because infant has a minor illness. Remember the “herd” effect!

❖ Check the form and give comment:

.....
.....
.....

"Routine" communes:

❖ Did CHW update HBV in the EPI register:

❖ Check the EPI register and give comments:

.....
.....
.....

6. Requests of CHWs/VHWs:

.....
.....
.....

7. Supervisor's comments:

.....
.....
.....

Signature of supervisor

Signature of CHW

Date:

Appendix 11

Thanh hoa province, 2000

KAP Questionnaire on Liver Disease and the EPI – For Householders

Date: day:.....month:..... year:.....

Time of interview (tick one): Morning: [] Afternoon: [] Evening: []

Name of surveyor:.....

Number of cluster:

Number of household:

Name of interviewee:..... Age:..... Sex: Male: [] Female: []

Number of children of interviewee:Age of these children in years:

Address of interviewee: - Village:.....

- Commune:

- District:

Duration from village to CHC by foot, in hours:

- Dry season: <2: [] 1 2 - 4: [] 2 4 - 8: [] 3 >8: [] 4

- Wet season: <2: [] 1 2 - 4: [] 2 4 - 8: [] 3 >8: [] 4

Ethnicity of household (tick one): Kinh: [] 1 Muong: [] 2 Other:.....

Able to understand language spoken by CHW? Yes: [] 1 No: [] 2

Able to read Vietnamese? Yes [] 1 No [] 2

Qualification/Title (if any):

- Did not go to school: [] 1

- Primary school (First degree): [] 2

- Primary school (Second degree): [] 3

- Secondary school: [] 4

- Tertiary or higher: [] 5

TV in house? Yes: [] 1 No: [] 2 Radio in house? Yes: [] 1 No: [] 2

Is there a VHW in this village (tick one)? Yes: [] 1 No: [] 2

Does this village have a loudspeaker? Yes: [] 1 No: [] 2

Q1. Which of the following social organizations do you belong to? (tick if answers yes)

- Communist Youth member: [] 1

- Communist Party: [] 2

- Women's union: [] 3

- Farmer's union: [] 4

- None: [] 5

- Others (specify):

Q2. Do you know people in your community who have ever had liver disease?

- Yes: [] 1

- No: [] 2

- Unsure: [] 9

Q3. Does liver disease ever cause long term illness in your locality?

- Yes: [] 1

- No: [] 2

- Unsure: [] 9

Q4. Does liver disease ever cause death?

- Yes: [] 1
- No: [] 2
- Unsure: [] 9

Q5. Do many people have long term illness or die of liver disease?

- Yes: [] 1
- No: [] 2
- Unsure: [] 9

Q6. Can any causes of liver disease be transmitted from person to person?

- Yes: [] 1
- No: [] 2
- Unsure: [] 9

Q7. Can a person who does not look sick transmit any causes of liver disease to another person?

- Yes: [] 1
- No: [] 2
- Unsure: [] 9

Q8. Can causes of liver disease be transmitted from mother to baby?

- Yes: [] 1
- No: [] 2
- Unsure: [] 9

Q9. What causes of liver disease do you know?

Q9A. Have you heard of liver disease caused by the hepatitis B virus?

- Yes: [] 1
- No: [] 2 If no, go to Q10.

Q9B. By what means does this virus pass from person to person? (do not list – tick only if mentioned)

- Blood transfusion: [] 1
- Food or water: [] 2
- Sex: [] 3
- Needle: [] 4
- Razors: [] 5
- Toothbrushes: [] 6
- Casual contact: [] 7
- Don't know [] 9
- Other (specify)

Q9C. Is there a vaccine against the hepatitis B virus?

- Yes: [] 1
- No: [] 2
- Unsure: [] 9

Q10. Does an immunisation team visit your area?

- Yes: 1
- No: 2
- Unsure: 9

Q10A. *If yes*, how often does the team reach your village, or a place convenient for you? (do not list, tick one only. If variable, tick option 5)

- Monthly: 1
- 2 monthly: 2
- 3 monthly: 3
- Less often: 4
- No fixed schedule 5
- Don't know 9

Q11. Which of the following people have told you about the EPI? (list each and tick if interviewee agrees)

- Health worker: 1
- Women's union representative: 2
- Family planning worker: 3
- At a public meeting: 4
- Friend/family 5
- Other (specify):

Q11A. By which of the following methods did you learn about the EPI? (list each and tick if interviewee agrees)

- Radio/television/video: 1
- Loudspeaker 2
- Posters: 3
- Newspaper: 4
- Other (specify):

Q12. Do you keep a record of your baby's immunisations at your home?

- Yes: 1
- No: 2

Q13. Who tells you, or how do you know when your baby needs to go for immunisation?

.....
.....

Q13A. How many days before the EPI team arrives do you know they are coming?

Q13B. If your baby missed a dose of vaccine, would someone come to remind you that the baby needs vaccination?

- Yes: 1
- No: 2
- Unsure: 9

Q14. Do you know about the under 5 card? - Yes: 1
- No: 2
- Unsure: 9

Q14A. *If yes*, which of the following people keep it? (list, then tick only one)

- You [] 1
- The village health worker [] 2
- The village headman [] 3
- You, but it is lost [] 4
- Don't know [] 5
- Other (specify).....

Q15. What is the most important use of vaccination? (list, then tick only one)

- Treat diseases: [] 1
- Prevent diseases: [] 2
- Improve baby's health: [] 3
- Don't know: [] 4
- Other/don't know (specify).....

Q15A. Do you believe healthy infants need vaccination?

- Yes: [] 1
- No: [] 2
- Unsure: [] 9

Q15B. Do you always take your babies for vaccination?

- Yes: [] 1
- No: [] 2

Q16. Which of the following do you think are common reasons for mothers not bringing their babies for vaccination? (list each, tick if interviewee agrees)

- Vaccine side effects: [] 1
- Baby is too sick at the time: [] 2
- They forget: [] 3
- They are too busy: [] 4
- They are too far away: [] 5
- They dislike the waiting: [] 6

Remember, I am asking about common reasons mothers don't take a baby for vaccination

- They dislike the EPI team: [] 7
- The explanations are poor: [] 8
- The EPI team ask for money: [] 9
- They don't know the team are coming [] 10
- They think the team will not arrive: [] 11
- They think there may not be enough vaccine: [] 12
- They do not know about vaccination: [] 13
- They do not know the schedule of doses: [] 14
- They do not believe in vaccination: [] 15
- There are bad rumors about vaccination: [] 16
- Other (specify).....

Q16A. Which are the most important? (show interviewee and write numbers)

Q17. Is there an active village health worker in your village?

- Yes: [] 1
- No: [] 2
- Unsure: [] 9

- Q17A. *If yes, do they help on EPI day?* - Yes: 1
 - No: 2
 - Unsure: 9

Q18. In your village, where do the majority of women deliver their babies? (tick one)

- At home without help: 1
 - At home with help: 2
 - At the commune health station: 3
 - Somewhere else (specify):

Q18A. If at home with help, who usually helps women to deliver their baby? (List the following choices: relative, TBA, CHW, other)

Q18B. Do you think that women in your village attend the CHS for antenatal care?

- Yes, most women go: 1
 - Yes, but only some women go: 2
 - No, rarely do women go: 3
 - No, never: 5
 - Unsure: 9

Q18C. In your village, do all women of childbearing age get TT vaccine, or only pregnant women?

- All women of childbearing age: 1
 - Only pregnant women: 2
 - Unsure: 9

Q18D. Have you received TT vaccine yet? (read, and tick one alternative)

- Yes, during pregnancy
 Yes, when not pregnant
 Yes, both when pregnant and before or after this
 No, not yet

Q18E. If yes, how many doses have you received in total?

Q19. If a new vaccine required infant vaccination on the first or second day after birth, do you think mothers would agree to their new baby receiving the vaccine at this time?

- Yes: 1
 - No: 2
 - Unsure: 9

Q19A. If not, why not?

Q20. Are you aware of any cases of tetanus amongst newborns or women of child bearing age in your village in the last 2 years?

- Yes: 1
 - No: 2
 - Unsure: 9

Thank you very much for your help!

Signature of surveyor:



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