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Prevention of Hepatitis B in India

An Overview

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1. HEPATITIS B IN INDIA: BURDEN OF DISEASE ANALYSIS

1.1 Introduction

Hepatitis B is a major public health problem worldwide. Approximately 30% of the world's population, or about 2 billion persons, have serological evidence of either current or past infection with hepatitis B virus. Of these, an estimated 350 million have chronic (lasting more than six months, and often for lifetime) HBV infection and at least one million chronically infected persons die each year of chronic liver disease, including cirrhosis and liver cancer.

The hepatitis B vaccine is highly safe and effective, and prevents HBV infection and its serious consequences. The World Health Organization (WHO) recommends that hepatitis B vaccine should be given routinely to children in all countries.

The purpose of this document is to review data regarding the disease burden due to hepatitis B in India, as a basis for a decision to introduce hepatitis B vaccine into the national immunization programme.

1.2. Background

(1) General features of Hepatitis B virus

HBV, the cause of hepatitis B infection, is a DNA virus. The outer surface membrane of HBV contains hepatitis B surface antigen (HBsAg). Detection of HBsAg in the serum of an individual indicates that the person is currently infected with the virus. Detection in the serum of hepatitis B e antigen (HBeAg), a soluble protein in the inner core of the virus, correlates with the presence of virus in large amounts and is associated with greater infectivity.

Another agent, called hepatitis D virus (HDV), is an incomplete virus that requires the presence of HBV infection for replication. HDV cannot multiply in the absence of hepatitis B virus. Persons with acute or chronic HBV infection are at risk of infection with HDV. HDV infection in a person with chronic HBV infection significantly increases the risk and rapidity of serious outcomes of HBV infection, including cirrhosis and liver failure.

(2) Clinical features of hepatitis B

Infection with HBV can cause both short-term (acute) disease and long-term (chronic) disease. Acute hepatitis B occurs approximately 45-160 days after exposure to the virus. Symptoms associated with acute HBV infection typically include abdominal pain, nausea, fatigue, and jaundice (yellowing of the skin and eyes), but can range from none to occasionally fulminant hepatitis and death within days or weeks of onset of symptoms. Young children with acute HBV infection generally do not have symptoms. In comparison, adults with acute HBV infection are more likely to develop symptoms; however, even among them, a large majority (75%) of HBV infections go entirely unnoticed.

Acute HBV infection can lead to one of several outcomes. Most patients with acute infection recover from the infection in a few weeks to a few months and become immune. A small minority (nearly 1% of those with symptomatic acute hepatitis) persons with acute HBV infection develop a serious illness, known as fulminant hepatitis, which is fatal in a large majority within days or weeks of onset of symptoms. Some persons with acute HBV infection develop a chronic infection. The risk of development of chronic HBV infection depends on the age at which HBV infection acquired. If the infection is acquired soon after birth, the risk of it becoming chronic is around 90%. This rate rapidly come down with increase in age at the time of infection, and by the age of six years, reaches the adult level of around 5%. Most of the serious outcomes due to HBV infection occur in persons who develop chronic HBV infection. Persons with chronic HBV infection may be asymptomatic for decades after infection; however, these persons are at high risk of eventually developing liver cirrhosis and/or primary liver cancer. The risk of death from HBV-related liver cancer or cirrhosis is approximately 25% for persons who become chronically infected during childhood and approximately 15% for persons who become chronically infected at an older age.

(3) Transmission of Hepatitis B virus

HBV is found in blood and blood-derived body fluids of infected persons. Transmission results by either percutaneous or mucosal exposure to blood or other infectious body fluids. The primary routes of HBV transmission areperinatal (from mother to baby at birth)--the risk of HBV infection among infants born to HBV-infected mothers ranges from <10% to >85%, with higher rates of transmission from mothers who are HBeAg-positive and lower rates of transmission from mothers who are HBeAg-negative; child to child, through frequent interpersonal contact of non-intact skin or mucous membranes with blood-containing secretions, or perhaps saliva from unsafe injections and transfusions, sexual contact, and tattooing and scarification.

In regions with intermediate and high endemicity of HBV infection, HBV infections can occur at any age, but tend to predominate among infants and children. This is the age period when acute infection is more likely to develop into chronic infection.

1.3 Hepatitis B Immunization

(1) Hepatitis B vaccine

Hepatitis B vaccine has been available for several decades, and is highly safe and effective in preventing HBV infection and the development of its serious consequences. By preventing HBV infection, hepatitis B vaccine also protects against HDV infection.

Two types of hepatitis B vaccine are available, plasma-derived and recombinant. Plasma-derived vaccine is prepared from purified HBsAg from the plasma of persons with chronic HBV infection. Recombinant hepatitis B vaccine is made using HBsAg synthesized by genetic engineering techniques. There are no significant differences in safety, immunogenicity, or efficacy between the two types of hepatitis B vaccines. Manufacture of plasma-derived vaccine includes several inactivation processes, each of which is adequate to kill the HBV. Plasma-derived vaccine is therefore entirely safe. The choice between the two types of vaccines should be based on cost, availability and other considerations and not efficacy.

(2) Strategies for Hepatitis B immunization

In 1991, the Global Advisory Group of the Expanded Programme on Immunization of WHO recommended that by the year 1997, hepatitis B vaccine should be introduced into national immunization programmes in all countries. This strategy was approved by the World Health Assembly in 1992. The high proportion of chronic infection that is acquired during childhood can be prevented by routine infant immunization. Numerous studies have shown that adding hepatitis B vaccine into the EPI is highly cost-effective, even in areas with low HBV endemicity.

In adding hepatitis B vaccine into EPI, an important consideration is whether a birth dose of hepatitis B vaccine should be used to prevent perinatal transmission. Issues to consider in determining the priority for preventing perinatal HBV transmission include the relative contribution of perinatal transmission to the overall hepatitis B disease burden and the feasibility of delivering the first dose of hepatitis B vaccine at birth. In countries in which a high proportion (>40%) of pregnant women are hepatitis B e antigen (HBeAg) positive (e.g., Asia), incorporating a birth dose for all infants is generally indicated. In countries in which a low proportion (<10%) of pregnant women are HBeAg-positive (e.g., Africa), use of a birth dose is encouraged, if feasible (e.g., in birthing hospitals).

When resources allow, additional strategies for hepatitis B immunization like catch-up vaccination of older children, adolescents and adults may be undertaken.

1.4 Hepatitis B in India

(1) Methods to determine disease burden due to hepatitis B

The primary methods to assess the disease burden associated with HBV infection are: surveillance for acute hepatitis B; measuring deaths from cirrhosis and hepatocellular carcinoma; and serosurveys to determine the prevalence of HBsAg (serologic marker of chronic HBV infection) among the general population or population subgroups. Data from each of these sources are available in India. However, limitations of the data for India are similar to that in other countries. Specifically, for acute disease surveillance, there is a likelihood of significant underreporting, because reporting depends on health

care workers informing higher administrative levels regarding cases they see in practice; cases, more frequently among children, are frequently asymptomatic and therefore not detected by surveillance for acute disease; and many persons with jaundice or other symptoms of viral hepatitis do not have serological testing, therefore it is not possible to determine the type of infection. Measuring deaths from cirrhosis and hepatocellular carcinoma is also subject to limitations of likely underreporting, and lack of etiological information (e.g. hepatitis B serologic status) available for deaths due to these causes. Also, primary hepatocellular carcinoma may be confused with secondary neoplasms of the liver. Issues to consider in interpreting seroprevalence data include the representativeness of the study sample, the quality (e.g. sensitivity and specificity) of testing, and inability to distinguish between acute and chronic HBV infection by HBsAg testing alone.

The following review of studies on the disease burden of hepatitis B in India is based on an active search for all available studies, including a Medline search for articles published from 1975 to early 2000, and contacting researchers and other sources for unpublished data.

(2) Acute hepatitis B

In 1994 and 1995 respectively, 110138 and 110012 cases of patients with acute jaundice (all causes) were reported to the Ministry of Health and Family Welfare, Government of India, corresponding to an annual rate of roughly 11 cases per 100,000 population. However, reporting of acute viral hepatitis is not required in India. The Ministry of Health and Family Welfare informally collects information on cases of patients with acute jaundice, but reporting is incomplete and etiological data are not collected. Because hepatitis laboratory testing is expensive and not readily available, few patients who seek clinical care for symptoms of hepatitis undergo serological testing.

While not assessing the absolute numbers of cases of acute hepatitis B, several studies have evaluated the percentage of cases of acute jaundice that are caused by various types of hepatitis viruses. These populations generally include patients attending hospitals. The results of these studies show wide variation, and range from 9% to 62% HBsAg seropositivity among acute cases, with most studies in the range of 20% to 30% (Dass Gupta et al 1981, Dharmadhikari et al 1990, Ichhpujani et al 1991, Mallaya 1989, Panda et al

1989, Sebastian et al 1990, Tandon et al 1984, and Tandon et al 1983). Many of these studies tested only for HBsAg and not for markers of acute HBV infection (e.g., IgM antibody to hepatitis B core antigen, anti-HBc IgM). In one study which used anti-HBc IgM testing, 10.4% patients presenting to Delhi hospitals with jaundice were anti-HBc IgM positive (Prakash 1998a).

Several studies have looked at the role of HBV as a cause of fulminant hepatic failure. In three series of patients with fulminant hepatic failure, the proportions positive for HBsAg were 12.7% (Irshad et al 1994b), 31% (Raju et al 1989), and 22% (Tandon et al 1991a) respectively.

Few studies of acute hepatitis B have examined risk factors among patients. One study conducted in the early 1990s among 160 cases and age and sex matched controls found that receiving injections with reusable needless in the six months prior to onset of illness was associated with development of acute hepatitis B (Narendranathan et al 1993). In India, unsafe injections may be an important source of HBV infection.

(3) Chronic liver disease and liver cancer

Few data are available regarding the incidence of chronic liver disease in India as there is no surveillance system for the purpose. Vital statistics data are not reported with a separate category for chronic liver disease (instead, such deaths are reported in the category of "diseases of the digestive system").

Population-based cancer registries have been established by the Indian Council of Medical Research in Bangalore, Mumbai, Chennai, Delhi, Bhopal and Barshi. From these data, it has been estimated that approximately 11000 to 12500 new cases of liver cancer occur each year in India (articles not available for review). This rate of 11 per 1 000 000 is low compared to other countries in Asia and other parts of the world, and may be due to under-diagnosis and underreporting.

Various studies have examined the proportion of persons with HBV infection among persons with chronic liver disease. Among patients diagnosed with chronic liver disease, the prevalence of HBsAg ranged from 33% to 75% (Acharya et al 1993, ICMR 1993, Kant et al 1995, Krishnamurthy et al 1976, Pal et al 1974, Sakhrie et al 1977, Sarin 1996, Sarin et al (in press), Sarin et al 1988, Singh et al 1976a, Sundaram et al 1990, and Sundaravalli et al 1988).

Other series of patients with cirrhosis show HBsAg positivity ranging from 56% to 70% of cases (Aikat et al 1977, Dharmadhikari et al 1990, Hill et al 1977, Kant et al 1995, Kelkar et al 1975, Kelkar et al 1973a, Saxena et al 1984, Singh et al 1976b, and Sundaram et al 1990). Histopathological studies of patients with liver cancer indicate evidence of HBV infection in 60% to 70% of cases (Kant et al 1995).

(4) Studies of HBsAg prevalence

The most complete data providing a picture of hepatitis B disease burden in India come from HBsAg seroprevalence studies. Over the last several decades, numerous researchers have conducted seroprevalence studies in India. Such studies must be evaluated carefully and interpreted with caution, because these are often not population-based. This review of seroprevalence studies focuses on those among populations that were more representative (e.g. general population, pregnant women, voluntary blood donors) rather than studies among specific risk groups (e.g. haemodialysis patients).

In interpreting the results of seroprevalence studies, sensitivity and specificity of the laboratory tests used also need to be taken into consideration. These studies are based on different techniques for detection of HBsAg in serum. These tests may differ in their sensitivity (ability to avoid false negatives) and specificity (ability to avoid false positives). Based on the characteristics of the test (like sensitivity, specificity, reproducibility, time taken for testing, and ease of performance of test), the tests may be of different generations, the more efficient tests being of a higher generation. Of the tests used in the studies under consideration, the first generation tests include immunodiffusion (ID), agar gel diffusion (AGD), and indirect haemagglutination (IHA), the second generation tests include reverse passive haemagglutination (RPHA), immunoelectrophoresis (IEOP), and countercurrent immunoelectrophoresis (CIEP) and the third generation tests include enzyme immunoassay (EIA) or enzyme-linked immunosorbent assay (ELISA), and radioimmunoassay (RIA).

The results of HBsAg seroprevalence studies in various population groups in India are shown in Annex 1. Among population-based studies, HBsAg prevalence among general population groups ranged from 0.1% to 11.7%, being between 2% to 8% in most studies, and among pregnant

women 0.6% to 11.2%. HBsAg prevalence rate among blood donors ranged from 1% to 4.7%.

In an attempt to obtain a better picture of the geographical distribution of HBV infection in India, summary prevalence rates were determined for states for which data were available. Because the studies were done in a variety of populations, only the crude measure of the midpoint of the range of HBsAg prevalence observed in each state (rather than a weighted average) was used. The results are shown in Annex 2. While no data are available for many states, there does not appear to be any substantial geographical variation, with the possible exception of higher rates in the northeast (based on two studies).

Assuming a HBsAg carrier rate of 5%, the total number of HBV carriers in the country is estimated to be about 50 million. This forms nearly 15% of the entire pool of HBV carriers in the world.

(5) HBeAg positivity among HBsAg-Positive pregnant women

Besides the overall HBsAg prevalence, the hepatitis B e antigen (HBeAg) prevalence among carriers, especially pregnant women, is an important source of information for determining potential modes of HBV transmission in a population and underscores importance of giving a dose of hepatitis B vaccine soon after birth.

Annex 3 presents results from available studies on the prevalence of HBeAg among pregnant women who are HBsAg positive. HBeAg prevalence among pregnant women who are HBsAg positive ranges between 7.8% and 47%, with most studies showing 18% or less. It appears that the HBeAg prevalence in India among HBsAg carriers is in general more similar to that in Africa (10%) than that in East Asia (30%-50%). Therefore the potential for perinatal HBV transmission in India is possibly lower than that in East Asia.

(6) Studies on hepatitis D

Hepatitis D virus (HDV) infection in HBV carriers is not infrequent in the Indian population. Several studies have examined the prevalence of hepatitis D antigen or antibodies to HDV in sera from various patient groups.

Seropositivity for delta infection (delta antigen and/or delta antibody) has been reported in about 7% to 20% of patients with acute hepatitis B, 13% to 17% of HBsAg carriers, 5% to 60% of patients with chronic liver disease, and 7% to 63% of patients with fulminant hepatic failure due to HBV infection (Amrapurkar et al 1992, Bhargava et al 1990, Desai et al 1990, George 1992, Gupta et al 1993, Irshad et al 1994b, Jyotsna et al 1998, Kochhar et al 1989, Pal et al 1987, Sumathy et al 1990, and Yadav et al 1990).

(7) Estimates of numbers of HBV infections in India

The Hepatitis Branch of the US Centers for Disease Control and Prevention (CDC) has developed a computer-based model for estimating the number of HBV infections and serious disease outcomes in a population, using as input data the results of HBV prevalence studies and other data. This computer software allows the user to vary input parameters. It should be noted that the model is still being developed and evaluated.

Data collected in this review were used in this model to obtain provisional estimates of the number of HBV infections and serious outcomes due to HBV infection in India (Annex 4). The input assumptions were an HBsAg prevalence of 5% among women of childbearing age (Annex 1), HBeAg prevalence of 15% among HBsAg positive women (Annex 3), a prevalence of 15% of any marker of HBV infection among five year old children and 40% among persons 30 years of age or older (Kant et al 1995, Sobeslavsky 1980, and Tandon et al 1991b). Using these data for a single year birth cohort (surviving infants) of 22 646 467 infants, over 9 million are estimated to acquire HBV infection during their lifetime, an estimated 1507000 will develop chronic HBV infection, and nearly 200 000 will die of acute or chronic consequences of HBV infection (Annex 4).

1.5 Conclusions and Implications

Countries are classified on the basis of HBV endemicity as having high (8% or more), intermediate (2-7%), or low (less than 2%) depending on the prevalence in general population of hepatitis B carrier state. The prevalence of chronic HBV infection in different studies from India ranges from 2% to 10%, being below 8% in most studies. Therefore, India has intermediate to high

endemicity, largely the former, for HBV infection. Based on available data, there does not appear to be substantial geographical variation in HBV prevalence. Based on an average HBsAg positivity rate of 5%, the total HBV carrier pool in India is estimated at 50 million.

Reliable data on the exact burden of HBV disease in the form of number of cases of acute hepatitis B, chronic liver disease due to HBV and hepatocellular carcinoma associated with HBV are not available. It is estimated that of the nearly 22.6 million children born in India every year, over 9 million will acquire HBV infection during their lifetime, 1 507 000 will develop chronic HBV infection, and nearly 200 000 will die of acute or chronic consequences of HBV infection.

Data on frequency of different routes of transmission of HBV infection in India are scanty. However, the low frequency of HBeAg positivity among HBsAg positive persons suggests that perinatal transmission is unlikely to be a major route.

2. INCLUSION OF HEPATITIS B VACCINE IN NATIONAL IMMUNIZATION PROGRAMME IN INDIA: A REVIEW OF ECONOMIC ANALYSES

2.1 Introduction

A vaccine is available for prevention of HBV infection. This vaccine is highly effective and is entirely safe, except for minor local adverse effects. The protection provided by the vaccine is long lasting.

More than 100 countries have already incorporated this vaccine in their national immunization programme. In countries that have implemented universal childhood hepatitis B immunization, HBV carrier rates have declined markedly and incidence rates of long-term consequences like liver cancer have shown a decrease. However, India has not yet included this vaccine in its immunization programme. The reasons for this are believed to be economic.

It may be useful to carry out a cost -benefit analysis to arrive at a decision on introduction of hepatitis B vaccine in the India's national programme of immunization.

2.2 Economic Analyses in Health Care

Decision making process is a crucial element in the field of medicine, including public health. In making public health decisions, administrators and health policy- makers have to decide what to promote and what to pay for.

Any public health programmeme requires resources (input), in the form of material, money and personnel, and results in health benefits or improvement (output). These inputs and outputs, being in different units, may be difficult to compare. Decision making is even more difficult if there are several public health programmemes competing for the same scarce resources.

Economic analysis techniques allow for quantitative representation of inputs and outputs for a health care programme and thus facilitate decision making. Inputs are usually expressed in monetary terms. Output is measured either in clinical terms (improved health, duration of life, quality of life, etc) or in monetary terms. A decision can then be taken whether expected outputs justify the expected inputs (Kuo, 2000; Szucs 2000).

Economic analyses can be based on experience gained either from a pilot project or from a similar programme that is in operation in another country. However such real-life data are frequently not available and modelling techniques are used for economic assessment of health care interventions.

(1) Types of economic analysis

There are essentially three types of economic analysis for assessment of the economic impact of a health intervention like introduction of a new vaccine (Kuo, 2000; Szucs 2000). These are: cost-effectiveness, cost-utility and cost-benefit analysis. Although these three procedures are very similar in

consideration of costs, they differ in the manner in which outcomes are measures and valued.

In a *cost-effectiveness analysis*, the effect of the intervention is measured using one or more simple health parameters, viz. 'number of infections prevented', 'number of deaths prevented', or 'life years gained', etc. In a *cost-utility analysis* (sometimes considered as a special case of cost-effectiveness analysis), effects of health care intervention are expressed as improvement in health using a composite measure of morbidity (reduction in quality of life) and mortality due to a disease, e.g. quality-adjusted life-years (QALY) or disability-adjusted life years (DALY). Cost-effectiveness and cost-utility analyses allow calculation of amount spent for each life-year or QALY (or DALY) gained, and thus allow comparison of different public health interventions. In a *cost-benefit analysis*, the benefits are also, like costs, expressed in monetary terms. In cost-benefit analysis, if estimated net benefits of an intervention exceed its net costs, its introduction is justified in economic terms (Kuo, 2000).

The most appropriate type of economic analysis depends on the question to be answered. For use of a vaccine as a public health measure, e.g. universal infant hepatitis B immunization, a cost-benefit approach may be more appropriate than cost-effectiveness analysis (Szucs 2000). In comparison, for recommended vaccines, e.g. use of a vaccine for travellers' diarrhoea, cost-effectiveness analysis may be more useful. Cost-effectiveness and cost-utility approaches are better when several competing health care options are to be compared. Cost-benefit approach, on the other hand, can be useful in deciding if one health intervention under consideration should be used or not.

For performing an economic analysis, data on three major aspects are needed. These are: (a) costs of the intervention, (b) cost-savings from introducing the intervention, and (c) disease burden. The discussion here refers primarily to immunization programmes, in particular hepatitis B vaccination in developing countries with intermediate to high HBV endemicity rates.

(2) Calculation of cost of a public health intervention

Costs of a public health intervention include direct and indirect costs. Direct costs are further of two types: capital costs and recurrent costs. In relation to a vaccination programme, direct costs include the following; all these costs must be included in an economic analysis:

Capital costs	***Recurrent costs***
➢ Transport ➢ Buildings ➢ Cold chain equipment ➢ Sterilization equipment ➢ Other equipment, including spare parts	➢ Vaccine, including costs of transportation ➢ Syringes and related supplies ➢ Salaries of immunization staff and programme managers ➢ Transportation costs including costs of fuel, vehicle maintenance, etc. ➢ Maintenance of cold chain equipment ➢ Training of staff ➢ Information campaign ➢ Cost of safe disposal of material ➢ Other supplies, such as stationary

Cost of vaccine and syringes is easy to determine. Other recurrent costs are often expressed as a composite figure per contact with the child. These recurrent costs are relatively small if a new vaccine is given simultaneously with a vaccine already included in the immunization programme. Capital costs can be included in the analysis either separately or as a part of vaccine administration costs; most analyses follow the latter technique.

Indirect costs include expenditure on travel and on work time lost by the parents of the child being immunized. These costs should be included in an analysis from the societal perspective. However, since the schedule recommended by WHO for hepatitis B vaccination is similar to that for

diphtheria-pertussis-tetanus vaccine, no additional contact between the parents and immunization personnel is needed. Thus, accounting for indirect costs may not be required.

(3) Calculation of effectiveness, utility or benefits

To accurately measure the effects of introduction of a vaccine, one needs to know the burden of disease being prevented, in terms not only of its prevalence and incidence, but also the morbidity and mortality associated with it. Consequences of hepatitis B infection, in the form of cirrhosis and liver cancer, appear over several years or decades. Data on long-term sequelae of HBV infection are therefore relatively limited and are from industrialized countries with low HBV endemicity. Data from countries that are highly endemic for hepatitis B are not available. However, with epidemiologic modelling, disease burden due to HBV infection and the reduction that may be expected in it with the introduction of the immunization programme can be calculated fairly well.

Various denominators that have been used for assessing the cost-effectiveness of hepatitis B immunization programmes include: number of cases of chronic HBV infection (chronic HBV carriers) prevented, number of cases of cirrhosis or liver cancer prevented, number of deaths prevented and number of life years gained. For cost-utility analysis, number of quality-adjusted life years (QALY) or number of disease-adjusted life years (DALY) gained can be used.

For cost-benefit analysis, calculation of cost-savings is required. Such savings include direct medical costs of hospitalization and outpatient visits, e.g. for hepatoma, cirrhosis, and acute and fulminant hepatitis. The cost of treatment of these conditions can vary greatly between different countries. In industrialized countries, patients with chronic HBV infection are treated with costly interferon treatment and those with end-stage liver cirrhosis due to HBV infection may undergo liver transplantation. Economic analyses from these regions therefore include the costs saved on account of reduction in frequency of these interventions following hepatitis B immunization. In developing countries, these treatments are not easily available, or their cost is

not paid by the public exchequer. Hence, in these regions, cost savings in these forms of treatment must not be counted among the benefits of hepatitis B immunization programme. Calculation of cost savings should instead be based on the usual amount spent by patients in these countries on the treatment of the disease consequences of the infection.

(4) Calculation of cost-effectiveness

Various public health interventions differ not only in their costs but also in their effectiveness i.e. the health-gain that they provide. The ratio of cost of a public health intervention to health-gain is termed as its cost-effectiveness, cost-utility or cost-benefit, depending on the nature of the denominator (a health parameter, a composite index of morbidity and mortality, or in monetary terms, respectively). The lower this ratio, the more effective an intervention is.

A country's per capita GNP is a good measure of the order of the magnitude of economic value of a year of life or QALY, and may serve as a good benchmark for decision making.

(5) Concept of marginal costs, marginal benefits and marginal cost-effectiveness

Cost-effectiveness (or cost-utility or cost-benefit) ratio can be calculated separately for various alternatives (say immunization and no immunization). A better measure is to calculate the difference in costs and effectiveness between the different approaches, usually starting with the one that is the cheapest and least effective. These values are called marginal cost and marginal effectiveness. The ratio of marginal cost to marginal effectiveness is known as marginal (or incremental) cost-effectiveness. This ratio represents the additional cost for each additional unit of health-gain achieved with a particular intervention.

Parameter	Option A	Option B	Difference
Costs	Cost A	Cost B	[Cost B – Cost A] or Marginal cost of option B
Effectiveness	Effectiveness A	Effectiveness B	[Effectiveness A – Effectiveness B] or Marginal effectiveness of option B
Cost-effectiveness	Cost A/ Effectiveness A	Cost B/ Effectiveness B	(Marginal cost)/ (Marginal effectiveness) or Incremental cost-effectiveness of option B

(6) Other important concepts in relation to economic analysis
Perspective of economic analysis in healthcare

An economic analysis can be done from one of several viewpoints. For instance, an economic analysis could represent the way an individual, a society, a health care provider (like health maintenance organization, insurer or employer), or the government looks at the question. The *perspective* of an analysis is the point of view it represents. Analyses based on different perspectives can arrive at different conclusions, and it is important that the perspective corresponds to the type of decision to be taken.

For decisions that are to be made in public interest or whose cost will be borne by the public, a *societal perspective* should be used. Thus, for a decision on the inclusion of hepatitis B vaccine, it is imperative that the economic analysis is from a societal perspective.

Time frame of analysis

The time frame of an analysis depends on the nature of the disease condition it deals with, and the nature of the intervention. For instance, since the benefits of hepatitis B immunization occur after several years, analysis of this intervention has

to be spread over either the entire life span or at least for the duration of productive life.

Discounting

Cost of intervention and savings in health costs may extend over several years. People generally prefer to spend a given amount at a future date than spending that amount today. This preference for future costs is included in economic analysis in the form of 'discounting'. Discounting is not an adjustment for inflation. It actually represents the greater importance of money available today over that available in the future, even if there was no inflation whatsoever.

Discounting can also be done for health care benefits. Thus, a year of life gained several years later in future may be considered less important than a year of life gained at present time. Discounting for health effects is, however, not as well accepted as that for costs. (Szucs 2000)

It has been recommended that results of economic analysis should be presented both without and with discounting (usually at a rate of 3% to 5%).

Sensitivity analysis

Cost-effectiveness analyses are frequently subject to some degree of uncertainty. The parameters used in a decision model may not be known with accuracy. Errors in these assumptions may influence, at times markedly, the results of an analysis. Sensitivity analysis allows assessment of the effect of variations in the value of the variable(s) on the analysis results about which one is uncertain. These variables could relate to cost, to disease rates (e.g. incidence or prevalence of disease) or to benefits (e.g. quality of life, years of life gained, etc).

During sensitivity analysis, the model is run several times making changes in the values of the parameter(s). If different values of the parameter give similar answer to the problem, the applicability of results obtained from the model becomes more certain.

Sensitivity analysis also allows determination of a threshold, i.e. a value of the variable in question, at which two alternative public health approaches

have identical value. Below this value of the variable, one strategy is preferable and above this value, the other strategy is preferable.

Sensitivity analysis is one of the most powerful attributes of economic analysis. Such analyses must be undertaken in every economic analysis to test for robustness of the results obtained.

2.3 Relevant Economic Analysis of Hepatitis B Vaccines in other Parts of the World

Most economic analyses of hepatitis B vaccination programmes have been done in industrialized, high-income countries with low HBV-endemicity rates (Jonsson et al, 1991; Hatziandreu et al 1991; Ginsberg et al, 1992a and 1992b; Demicheli et al, 1992; Margolis et al 1995; Fenn et al, 1996; Garuz et al, 1997; Edmunds 1998; Wiewiora-Pilecka, 2000). Such analyses may not be applicable to the Indian population. Only a few analyses have been done for countries with intermediate-to-high HBV endemicity and low-income levels. The results of these studies (Hall et al, 1993; Miller and McCann, 2000) are summarized below.

(1) Hall et al, 1993

This is the only published economic evaluation based on real experience of introduction of hepatitis B vaccine in a high endemicity country. Data on cost (both capital and recurrent) and coverage rate were obtained from the Gambian national immunization programme. Health effects, in the form of reduction in HBV carrier rate and incidence of liver cancer, were obtained from community surveys and national cancer register. Deaths from cirrhosis, and indirect savings by way of reduction in acute illness and loss of productivity were not taken into account.

The cost of averting a hepatitis B carrier was found to be approximately US$ 40, and that of preventing death from liver cancer US$ 150-200. Inclusion of deaths due to cirrhosis would have reduced the cost of each death prevented even further.

The authors compared the cost of averting death from liver cancer with that of averting death other vaccine-preventable diseases. This revealed

hepatitis B vaccine to be less cost-effective than measles and tetanus, but more cost-effective than polio and diphtheria.

(2) Miller and McCann, 2000

This study used a single-year birth cohort model to estimate the impact of introducing several different childhood vaccines. The effect of universal childhood hepatitis B immunization was modelled separately in countries with different HBV endemicity rates and different income levels.

Expected annual deaths from HBV were estimated from HBV carrier rate. The exact method for doing this has not been provided. Direct costs were calculated using vaccine cost of US$ 0.50 per dose and vaccine administration cost of US$ 0.18 per dose (for low income group countries). Indirect costs and treatment costs averted were not included in the model. The authors assumed that an intervention was cost-effective when the cost per life year saved was less than the per capita gross national product of the country.

For low-income countries with intermediate HBV endemicity, the cost per life year saved was calculated as US$ 14 to US$ 19, indicating that introduction of hepatitis B vaccine was cost-effective for all countries.

2.4 Economic Analyses of Hepatitis B Vaccines in India

A number of economic analyses of the inclusion of hepatitis B vaccine in the national immunization programme in India have been done (Aggarwal and Naik, 1994; Aggarwal and Naik, 1996, Prakash, 1999a, Prakash, 1999b, Miller and Kane 2000; Aggarwal et al 2002). The methods used, assumptions made and detailed results of these available cost-effectiveness studies in India have been summarized in Table 1. These studies are discussed individually in detail below.

(1) Aggarwal and Naik, 1994

This study compared the cost-effectiveness of two types of hepatitis B immunization programmes, namely universal childhood immunization against

hepatitis B and selective immunization against hepatitis B (i.e. screening of pregnant women for hepatitis B surface antigen followed by immunization only of infants born to mothers who test positive). The study found that universal immunization is a more cost-effective strategy for prevention of HBV infection in India.

This analysis based its major assumptions on a large study of hepatitis B transmission among 8/575 pregnant women in northern India to their newborns (Nayak et al, 1987). These included a HBsAg carrier rate among pregnant women of 3.7% and HBeAg positivity rate among HBsAg carriers of 7.8%. It was assumed that, 19% of the infants born to HBsAg-carrier mothers would develop HBV infection by the age of six months, and that infection would become chronic in 75% of those infected. Among the infants born to HBsAg-negative mothers, 3% were assumed to develop HBV infection and 50% of these were assumed to develop chronic infection. Based on these data, an estimate of contribution of perinatal transmission to the total HBV carrier pool was made. In addition, relative costs, effectiveness and cost-effectiveness of two vaccination strategies, universal immunization or selective immunization only of infants born to HBsAg positive mothers, was calculated. For this, hepatitis B vaccine effectiveness rates of 95% for infants born to HBsAg-negative mothers and 75% for infants born to HBsAg-positive mothers were used. In the universal immunization group, hepatitis B vaccine cost was assumed as US$ 1.00 per vaccine dose and vaccine administration costs as US$ 1.30 per child (for all 3 doses). In the selective immunization group, these costs were assumed to be twice as high as those in the universal immunization group, and the unit cost of HBsAg testing among mothers as US$ 2.0. Compliance rate was assumed as 100%. Cost of treatment of complications of chronic HBV infection was not taken into account. Cost-effectiveness was expressed as money spent for each HBV carrier prevented. Analysis in terms of years of life gained or QALY gained was not done.

Using these assumptions, it was estimated that (a) perinatal transmission was likely to be responsible for only 14% of all HBV carriers in the Indian population, (b) selective immunization only of infants born to HBsAg-positive mothers would bring about only a minor reduction in the number of new carriers (through 12%), (c) universal infant immunization beginning at birth would bring about a 7.6-fold greater reduction in the number of new carriers (through 92%), (d) the cost of universal immunization programme would be 1.85-fold higher than that of selective immunization (being US$ 4.3 and US$

2.32 per newborn child, respectively), (e) the cost per HBV carrier prevented was 3.9-fold lower for the universal immunization programme (US$ 126) than for the selective immunization programme (US$ 495).

Sensitivity analysis was not done on any of the assumptions made.

The study concluded that universal immunization was the only effective strategy for the control of the HBV infection in India, and that selective immunization was unlikely to lead to significant changes in hepatitis B disease burden.

(2) Aggarwal and Naik, 1996

This analysis was essentially a minor modification of the analysis reported by these authors earlier (Aggarwal and Naik, 1994) in that the cost estimates for vaccination were revised slightly downwards. All other assumptions remained unchanged. In the universal immunization group, hepatitis B vaccine cost was assumed as US$ 0.75 per vaccine dose and vaccine administration costs as US$ 0.33 per dose. In the selective immunization group, these costs were assumed to be twice as high as those in the universal immunization group, and the unit cost of HBsAg testing among mothers as US$ 2.0.

The conclusions reached were largely similar to those reached in these authors' previous analysis. Thus, universal immunization, as compared to selective immunization, (a) led to 7.6-fold greater reduction in the number of new carriers (92%, versus 12%), (b) cost 1.45-fold more (US$ 3.25 versus US$ 2.24 per newborn child, respectively), and (c) 5.2-fold more cost-effective (US$ 95 verus US$ 498 per carrier prevented).

The study also concluded that, in India, universal immunization was the only effective strategy for the control of HBV infection in India, and that selective immunization was unlikely to lead to significant changes in hepatitis B disease burden.

(3) Prakash, 1999a and 1999b

This study was an economic evaluation (Prakash 1999a) of universal immunization against hepatitis B as a part of the Expanded Programme on

Immunization (EPI) in India. This was done by incremental cost-effectiveness analysis, comparing this strategy with a "do-nothing" approach, that is, no immunization against hepatitis B. The study was an incidence-based cohort analysis where a decision tree (Markov Model) was constructed to estimate the expected costs and the expected effectiveness of the strategy, for the target population. Two cohorts, one with no hepatitis B immunization and the other which was immunized against hepatitis B at birth were followed up through their life time for hepatitis B infection acquired vertically at birth and the consequences thereof. The natural history of the disease was estimated from available literature. Horizontal transmission of HBV was not taken into account.

In this analysis, HBV carrier rate among pregnant mothers in India was assumed as 9.5%, and HBeAg positivity rate among HBsAg-positive mothers was assumed as 12%; these rates were based on data obtained by the author in a small study. Further, it was assumed that the risk of HBV transmission from a HBsAg-positive mother to her newborn infant was 90% if the mother was HBeAg-positive and 15% if the mother was HBeAg-positive. Further, among infants born to HBeAg-positive mothers, the risk of HBV infection would be 90%; of such infected children, 2.8% would develop acute hepatitis, 90.2% would develop HBV-carrier state and 7% would be entirely asymptomatic. Among infants born to HBeAg-negative mothers, the risk of HBV infection was assumed as 15%, with 3.2% developing acute hepatitis, 15.7% developing HBV-carrier state and 81.1% being asymptomatic. Among infants with acute hepatitis B, 25% were expected to die of fulminant hepatitis and the remaining were expected to have disease resolution. Among HBV-carriers, 90% would develop chronic hepatitis (80% chronic persistent hepatitis and 20% chronic active hepatitis). Of those with chronic active hepatitis, 12.5% would be expected to develop cirrhosis or primary hepatocellular carcinoma.

Vaccine cost was assumed to be US$ 0.75 per paediatric dose and costs of administration as US$ 0.19 per dose. Vaccine coverage rate was assumed to be 52%, vaccine wastage rate as 10% and vaccine efficacy in preventing HBV infection as 95%.

Life expectancy for the population was modelled on the standard (ideal) life table. It was assumed that chronic persistent hepatitis due to HBV would develop at the age of 40 years and such patients would live till the age of 70

years. Chronic active hepatitis was assumed to develop at age of 40 years and lead to death at the age of 55 years. Patients with cirrhosis were assumed to live for an average of 45 years.

Costs of treatment of complications of HBV infection in India was estimated on the basis of number of inpatient and outpatient care episodes available from other geographical regions and costs of each inpatient and outpatient encounter from available Indian data. Liver transplantation and costs of interferon treatment were not included.

Only direct costs of medical care were taken into account. The perspective was societal. The measure of effectiveness used in the study was Disability-Adjusted Life Years (DALYs) gained. A discount rate of three percent was used for calculation of costs. The effects were calculated with a discount rate of three percent, as well as with zero discounting.

The cost-utility ratio was computed in 1993 US$ 27.36 per DALY gained. This ratio is well within the range of commonly accepted and implemented public health interventions.

Sensitivity analysis was done for discount rate for effects (baseline 3%; alternative value = 0%). Using zero discount rate for effects, cost-effectiveness was US$ 19.08 per DALY gained. Several uncertainty analyses (using Latin hypercube sampling) were carried out to test the robustness of results to changes in variables whose values were uncertain (Prakash 1999b). The most important factors that influenced the cost-effectiveness were HBsAg positivity rate in carrier mothers and vaccination coverage. Other important variables were vaccine cost and vaccine efficacy. Vaccine wastage and HBeAg prevalence (i.e. infectivity of carriers) were less important, and treatment costs (in-patient and out-patient) had negligible influence on the result.

The results of this study have not yet been published. The study has two major limitations. First, horizontal transmission of HBV, which is estimated to play a much larger role as compared to vertical transmission in India, was not taken into account. Accounting for horizontal transmission would make the HBV vaccination even more cost-effective than the author's estimate. Second, the HBsAg carrier rate among pregnant women assumed in the model was

relatively high. A lower assumption for this parameter is likely to make the vaccination less cost-effective than the author's estimates. The two limitations may be expected to cancel out each other's effect, at least partially.

(4) Miller and Kane, 2000

This study examined the cost-effectiveness of routine infant immunization. The authors assumed a 4% hepatitis B carrier rate in the Indian population, hepatitis B vaccine cost of US$0.50 per paediatric dose, 80% vaccine coverage, 10% vaccine wastage, and 95% vaccine efficacy. Further, they assumed that 20% of carriers will die of cirrhosis or liver cancer at an average age of 45 years. The average life expectancy of the birth-cohort was assumed as 66 years (in year 2040). Morbidity and cost of treatment of complications of HBV infection were ignored. Both undiscounted and discounted analyses were done (discount rate of 3% for health benefits).

It was estimated that among a single-year birth cohort of 24 million infants, 193 000 would die of HBV- related liver disease. Hepatitis B vaccination, with the assumed coverage and efficacy rates, would save an estimated 147 000 lives for a cost between US$ 46 million dollars. The cost per death averted was US$ 312, and the marginal cost per year of life saved was US$ 12. Use of discounting increased the cost per death averted to US$ 1178 and cost per year life saved to US$ 66.

Sensitivity analysis was done on the mortality rate due to cirrhosis and liver cancer among HBV carriers. Using a higher rate of 27% (compared to baseline rate of 20%), the number of deaths due to liver cirrhosis or liver cancer in a single-year birth cohort would be expected to be 261 000. Hepatitis B vaccination would prevent 198 000 of these deaths. The undiscounted cost per death averted was US$ 231, and the marginal cost per year of life saved was US$ 9 per year. Discounting increased these to US$ 873 and US$ 49 per life year, respectively.

Sensitivity analysis on other parameters like hepatitis B carrier rate in the Indian population, cost of vaccine, vaccine coverage rate, vaccine efficacy rate, was not performed.

(5) Aggarwal et al, 2002

Cost-effectiveness/cost-utility analysis

This recent unpublished study provides the most detailed assessment of the cost-effectiveness of inclusion of hepatitis B vaccine in the India's national immunization programme. It consists of two parts: (i) a cost-effectiveness / cost-utility analysis, and (ii) a cost-benefit analysis.

This study used a decision analysis approach and Markov modelling to compare the costs and health effects in two single-year birth cohorts, one of these received hepatitis B vaccination and the other did not. These cohorts were then compared to assess the marginal cost, marginal effectiveness and incremental cost-effectiveness of the introduction of universal infant hepatitis B immunization.

The baseline analysis in this study assumed 4% hepatitis B carrier rate in the Indian population, 75% vaccine coverage, 95% vaccine efficacy and 10% vaccine wastage rate. The cost of vaccine was assumed as US$ 0.50 per dose and that of vaccine administration as US$ 0.50 per dose.

The health effects of hepatitis B carrier state were modelled using a Markov analysis. It was assumed that (i) hepatitis B carriers will progress to cirrhosis at a defined rate every year (none in the 0-9 year age-group, 0.5% annually in the 10-19 year age group, 1% every year with age $\geq$20 years), (ii) patients with cirrhosis will develop decompensated cirrhosis or liver cancer at a rate of 5% annually, and (iii) patients with decompensated cirrhosis or liver cancer would die at a rate of 20% annually. Both HBV carriers and non-carriers were subject to the age-specific death rates of the Indian population. Quality of life for patients with compensated liver cirrhosis was assumed as 0.95, and that for patients with decompensated cirrhosis of liver as 0.50.

Cost-effectiveness was calculated in terms of amount spent per life year gained or amount spent per QALY gained. Both undiscounted and discounted analyses (with 3% discount rate for life years or QALY) were done.

The cost-effectiveness/cost-utility analysis in this study showed that inclusion of hepatitis B vaccine in India's national immunization programme should lead to a reduction in HBV carrier rate from 4.0% to 1.15% (a reduction

of 71%).In a single-year birth-cohort of 25 million children, this amounted to a reduction of 712 500 carriers. The immunization programme was estimated to lead to an increase in life expectancy of 0.15 years, and a gain of 0.17 QALY per child. The cost to the programme per carrier averted was US$ 98.7; cost per life year gained was US$ 19.06 and cost per QALY gained was US$ 16.26. These values are much lower than the per capita GNP of the Indian population, and well within the range of health care interventions considered as useful and worthy of spending public money.

Several sensitivity analyses were done. These are summarized in Annex 5.

Lower HBV carrier rate was associated with increase in cost per life year or QALY saved. However, even with carrier rate as low as 1%, the cost per life year was only US$ 76.22 and cost per QALY only US$ 65.06.

Increase in cost of immunizing each child to two-fold (US$ 6.0 for three doses for one child) increased the cost per life year to US$ 38.10 and that per QALY to US$ 32.54; both these values are within the cost-efficacy estimates considered acceptable for public health interventions.

The baseline analysis assumed a vaccine efficacy rate of 95%. It has been calculated that perinatal transmission accounts for only a minority of hepatitis B carriers in India. Concern has been expressed that administration of first dose of hepatitis B vaccine at six weeks may not prevent perinatal transmission, leading to reduced vaccine efficacy. However, with reduction of vaccine efficacy to as low as 70% (corresponding to perinatal transmission being responsible for around 30% to 35% of carriers), the cost-effectiveness of the immunization programme did not change much. Changes in the rate of vaccine wastage did not alter its cost-effectiveness significantly.

Changes in vaccine coverage rate influenced the effectiveness of the programme but not cost-effectiveness, because reduced coverage rate also proportionately reduces the costs.

Life years after 70 years of age may not be as productive as those below this age. This study also looked at the gain in life years and QALY before the cohort reached the age of 70 years. These gains were 0.11 life-years and 0.13 QALY respectively, at a cost of US$ 25.84 per life-year and US$ 21.56 per QALY.

Discounted analysis (discount rate for benefits = 3% per year) found the cost per discounted life-year gained to be US$ 101.70 and cost per discounted QALY as US$ 82.94.

2.5 Cost-benefit Analysis

The cost-benefit analysis used the same assumptions as for the cost-effectiveness analysis, except that costs of treatment of complications of chronic HBV infection were also included in the analysis. Cost of treatment of liver cirrhosis was assumed as Indian Rupees 2 000 (US$ 1.00 = approximately INR 50) at onset and INR 2000 annually thereafter, and that of decompensated cirrhosis as INR 5 000 at onset and INR 5 000 annually thereafter. Indirect costs and money lost due to loss of work and reduction in life span were not included in the analysis. Both undiscounted and discounted (discount rate = 3% for costs) were undertaken.

In the undiscounted analysis, cost-savings in the treatment of complications of chronic HBV infection, i.e. liver cirrhosis and liver cancer, induced by hepatitis B immunization programme would more than offset the entire expenditure on the immunization programme.

Threshold analyses were done based on variations in the cost of treating complications of chronic HBV infection. Threshold for immunization to be the preferred option over 'no immunization' was found to be 0.30 times the baseline cost assumptions for treating complications of chronic HBV infection in undiscounted analysis and 1.15 times the baseline assumptions in undiscounted analysis.

2.6 Summary of Findings of Cost-effectiveness Studies in India

Annex 6 summarizes the main findings of various cost-effectiveness studies on universal childhood vaccination that have been undertaken in India. Also included is a column showing the entire range of values obtained for each cost-effectiveness parameter in various studies, and the results of studies from other parts of the world that may be applicable to Indian situation.

Despite differences in the model and methodology used, various cost-effectiveness and cost-utility studies are unanimous in that inclusion of hepatitis B vaccine in the national programme of immunization will be cost-effective.

Cost per carrier prevented

Four studies looked at the cost per HBV carrier prevented, and found this to be US$ 126, 95, 63 and 99, respectively, providing values in a relatively narrow range. The difference in the values arrived at in these studies was primarily due to differences in price estimates for hepatitis B vaccine.

Cost per death averted

This parameter was calculated in one study and was found to be US$ 231-312 (undiscounted) and US$ 873-1178 (discounted). The undiscounted cost of each death averted is expectedly somewhat larger than that recorded in a study in Gambia (US$ 150-200; Hall et al, 1993), where HBV endemicity rate is much higher than in India.

Cost per life year gained

Two studies calculated this value. Undiscounted estimates were US$ 9-12 and US$ 19, respectively, and discounted values (discount rate = 3% for health benefits in both studies) were US$ 49-66 and US$ 102, respectively. The difference in the results of these two studies is primarily related to differences in assumption about the cost of HBV vaccination (US$ 2.07 and US$ 3.00 per child, respectively).

Cost per QALY (or DALY) gained

Two studies calculated this value. In one study, undiscounted cost was US$ 16 and discounted value (discount rate = 3% for health benefits) was US$ 83. In the second study, cost per QALY gained was US$ 27. The assumptions of second study are not fully known and hence it is not possible to determine the reason for differences in estimates arrived at in the two studies.

Comparison of marginal cost effectiveness in terms of US$ per life year gained and per QALY gained with India's per capita GNP (World Bank, 2001) favored inclusion of hepatitis B vaccine in the national immunization programme.

Cost-benefit analysis

This type of analysis was done in only one study. It found that savings in health care costs for complications of HBV infection would exceed the amount spent on hepatitis B immunization. This too suggests that universal childhood hepatitis B immunization should be introduced in India.

2.7 Possible Limitations of Cost-effectiveness Studies in India

This section addresses various limitations which may exist in the available economic analyses and their impact, if any, on the conclusions drawn.

Variability in data on HBsAg carrier rate in Indian population

Various studies on hepatitis B carrier rate in India have shown widely different results. This variation is most likely related to sampling errors, and does not reflect a genuine variation in different geographical regions or in various subgroups in the population.

Various cost-effectiveness studies have used carrier rates of 3.7% to 5%. This raises a concern that the results of cost-effectiveness studies may not be applicable to subpopulations with a lower HBsAg prevalence rates. However, sensitivity analyses performed in two of the cost-effectiveness studies showed that immunization was cost-effective over a wide range of carrier rates (even as low as 1%).

Vaccine coverage rates

According to data from Ministry of Health and Family Welfare, Government of India, coverage rates for DPT and OPV were 73% (Ministry of Health and Family Welfare, 1999). A lower vaccine coverage rate, as has been reported in some other surveys, (International Institute of Population studies, 2000),

may affect the effectiveness of the immunization programme adversely. However, sensitivity analyses in two studies showed that variations in this parameter influenced the cost-effectiveness only marginally.

Vaccine efficacy

It may be argued that all the studies used vaccine efficacy rates of 95%, based on studies done elsewhere and vaccine efficacy data from India were not taken into account. However, use of data from other countries appears appropriate since (i) there are no large Indian long-term follow-up studies of vaccine recipients; (ii) efficacy rates for prevention of carrier stage have uniformly been exceeded 95%, and (iii) there is no reason to suspect a lower vaccine efficacy rate in the Indian population.

Perinatal transmission may not be prevented without a vaccine dose at birth

HBeAg positivity rates among HBV carriers in India are fairly low. Hence, perinatal transmission is likely to be responsible for only a small minority of HBV carriers. In one study, this was calculated as 14% (Aggarwal and Naik, 1994). Hence, failure to provide birth dose will not affect the effectiveness of vaccination, and hence its cost-effectiveness, much.

Failure to include indirect costs

None of the studies explicitly mentioned inclusion of indirect costs. This may have made the vaccination programme look too attractive. However, this may not be required since the recommended hepatitis B immunization schedule does not need any extra contact with children, additional indirect costs are likely to be minimal.

Failure to account for acute and fulminant hepatitis

None of the studies has taken into account morbidity and mortality due to acute and fulminant hepatitis B. This however does not alter the conclusions drawn since (a) the morbidity due to these clinical presentations is short-lasted and mortality rare, and (b) their inclusion would, if anything, make vaccination strategy even more cost-effective.

Vaccine cost used were much lower than the current market costs

Most studies used vaccine costs in the range of US$ 0.5 to 1.00 per pediatric dose. The current retail price of the vaccine in the market is higher than that. However, bulk purchases of hepatitis B vaccine lead to marked reduction in price and, in several instances, even lower prices have been offered.

Hepatitis B vaccine may be diverted to adults

Hepatitis B vaccine differs from other childhood vaccines in that it is useful in adults too, and this may increase the chances of its pilferage, thereby increasing programme costs. Two of the four analyses did consider 10% and 20% vaccine wastage rates and this should cover the excessive pilferage, if any.

Estimates of cost and QOL, and discounting rate used are arbitrary

Indian data on these aspects are not available. Though errors in assumptions may affect the results of economic analyses, the rates used appear quite reasonable. The estimates used for cost of treatment of complications of chronic HBV infection were quite low and that for quality of life for patients with cirrhosis (0.95 on a scale of 0 to 1) fairly high. Thus, these estimates were, weighed against the policy of universal childhood immunization.

All studies look at single-year birth cohort and not beyond it

All the studies have looked at the effect of hepatitis B immunization on a single-year birth cohort, i.e. all children born during a one-year period. In practice, reduction of carrier rate in a birth cohort by hepatitis B vaccine may be expected to reduce the opportunities for infection of the younger generations. Since siblings and playmates are a frequent source of horizontal transmission of hepatitis B, this effect can be expected to appear soon. A reduction in HBV transmission will also lead to an increase in age at transmission. Since the chance of HBV infection becoming chronic decreases rapidly with increase in age at the time of acquisition of infection, a further reduction in HBV carrier rate may be expected. These effects are non-linear and hence difficult to model (Medley et al, 2001). However, these effects will make HBV infection even more, and what is suggested by the available economic analyses.

2.8 Conclusions

A review of available studies on economic analysis of hepatitis B vaccine in India's national immunization programme shows that this vaccine is highly cost-effective in terms of cost per life year gained and cost per QALY gained. In all the available studies, even on excluding the cost-savings on expenditure for treatment of complications of chronic HBV infection, cost per life year gained and cost per QALY gained are much lower than the country's per capita GNP. In addition, the only available cost-benefit analysis shows that the cost of HBV immunization programme will be offset by savings in treatment costs of long-term sequelae of chronic HBV infection.

The assumptions made in these analyses appear reasonable.

Sensitivity analyses for several of the parameters confirm the robustness of the conclusions reached. The similarity of results obtained in various analyses, despite the use of different models for calculations, further confirms the validity of these conclusions.

This review of various economic analyses strongly supports inclusion of hepatitis B vaccine in India's national programme of immunization.

3. ACTION PLAN FOR INTRODUCTION OF HEPATITIS B VACCINE INTO IMMUNIZATION SERVICES IN INDIA

3.1 Introduction

Based on the prevalence of hepatitis B carrier state in the general population, countries are classified as having high (8% or more), intermediate (2-7%), or low (less than 2%) HBV endemicity. India has intermediate endemicity of hepatitis B, with hepatitis B surface antigen (HBsAg) prevalence between 2% and 10% among populations studied. The prevalence does not vary significantly by region in the country. The number of HBsAg carriers in India has been estimated to be over 40 million. It has been estimated that, of the nearly 22.6 million infants forming a single-year birth cohort in India, over 1.5 million will develop chronic HBV infection, and nearly 200 000 will die of acute or chronic consequences of this infection.

Hepatitis B e antigen (HBeAg) prevalence rate among pregnant women who are HBsAg positive ranges between 8% and 47%, being 18% or less in most studies. Therefore, perinatal transmission is unlikely to be a major route of acquisition of HBV infection in India.

Several cost-effectiveness analyses of inclusion of hepatitis B vaccine in India's national immunization programme have been conducted. These analyses indicate that with universal childhood hepatitis B immunization in India will be highly cost-effective, with cost per life year gained of US$ 9 to 19 (US$ 49-102 after discounting) and cost per quality-adjusted life year (QALY) gained of US$ 16 to 27 (US$ 83 after discounting). The cost of preventing each HBV carrier will be US$ 63 to 99. These analyses thus support the need to incorporate routine infant immunization with hepatitis B vaccine in India's national immunization programme.

National Immunization Programme in India

After successful eradication of smallpox in India, an Expanded Programme on Immunization (EPI) was started in the country with BCG, DPT and OPV in 1978. This programme was introduced in a phased manner due to financial and infrastructural constraints. In 1985, it received a major boost, with the launch of Universal Immunization Programme, in the form of increased funding, better availability of vaccines, and establishment of a cold chain. In that year, measles antigen was added to the list of childhood vaccines included in the EPI. The programme was gradually extended from 30 districts in 1985-86 to the entire country by 1989-90.

To date, the use of hepatitis B vaccine in Indian children has been fairly limited. A pilot hepatitis B vaccination programme was conducted in East Delhi beginning late 1996 using vaccine donated by the WHO. In this pilot project, between 200,000 to 300,000 doses of hepatitis B vaccine were administered to infants. The objective of this pilot project was to assess the feasibility of including hepatitis B vaccine into Universal Immunization Programme (UIP), and to assess the requirement for forms and educational material. In this pilot project, three-dose coverage rate among the target population was estimated to be around 60%. Following the pilot project, the Government of Delhi successfully introduced hepatitis B all over Delhi. Experience from this pilot project has been incorporated in the proposed plan for phased introduction of hepatitis B vaccine in India.

In addition, two states (Kerala and Haryana) began hepatitis B vaccination using a cost-recovery strategy. These programmes were, however, discontinued because of logistic difficulties. These projects were endeavours of the state governments. Unfortunately, the experience of these projects and the lessons learnt from them were not documented.

During the last few years, hepatitis B vaccine has been available in the private sector in urban areas for those who can afford it. The Indian Academy of Paediatrics, which is the highest professional body of paediatricians in the country, has advocated hepatitis B vaccine as part of routine immunization schedule. Many doctors therefore administer hepatitis B vaccine to patients and children under their care. Many schools and non-governmental voluntary organizations have been organizing hepatitis B vaccination drives on a payment basis. Though these drives possibly reflect public acceptance and demand for hepatitis B vaccine, these have not reached the rural population and the urban poor. It is important to note that over 90% of immunization in India is provided by the public sector.

Government of India is also supporting planned state programmes for introduction of new vaccines in the routine immunization. These include the Government of Andhra Pradesh's partnership project with the Gates Children's Vaccine Programme at Path. This project is expected to (i) help in development of IEC resource material and (ii) provide experience with training of staff, planning of cold chain and other vaccine logistics planning. These will prove useful when the national-level programme is launched.

Government of India is now working towards a planned phasing-in of hepatitis B vaccine, based on the capacity of the states and districts and sustainable funding. The opportunity afforded by GAVI and the Vaccine Fund is appreciated and now there is government approval for sustaining this programme through planned allocation of national resources.

3.2 Goals and Objectives of Hepatitis B Immunization

The ultimate goal of hepatitis B vaccination is to reduce morbidity and mortality associated with chronic HBV infection, including cirrhosis and liver

cancer. However, because the long-term consequences of HBV infection occur several years after infection, this goal will take a long time to attain. Therefore, the following short-term goals and objectives have been defined:

- Phased introduction of hepatitis B vaccine into Expanded Programme of Immunization (EPI) beginning in the year 2002.
- Delivery of hepatitis B and all other EPI vaccines according to safe injection practices.
- Training of health care workers, and sensitization of policy makers and the community about HBV infection and hepatitis B vaccine.
- Reduction in vaccine wastage by promoting an open vial policy.
- Reduction in prevalence of HBsAg among 3-5 year old children through 55%, compared to the prevalence in the pre-vaccine period, by 2008.

3.3 Strategies for Hepatitis B Immunization

(1) Vaccine preparation

In addition to monovalent hepatitis B vaccine, a polyvalent preparation that combines hepatitis B vaccine with diphtheria-tetanus-pertussis vaccine in a single injection has recently become available. Such combined vaccines decrease the number of injections that a child receives at each visit, make distribution of vaccine easy and reduce the requirement for storage space.

It is currently proposed to use monovalent hepatitis B vaccine in multidose vials.

Several companies manufacture hepatitis B vaccine in India. These companies have the capacity to provide adequate vaccine for routine infant immunization. Due to increased competition and with bulk purchases, the price of hepatitis B vaccine has dropped substantially to as low as US$ 0.40 per dose.

Vaccination Schedule

The proposed new schedule for childhood immunization using monovalent hepatitis B vaccine is given in Table 1 below:

***Table 1**: Proposed childhood vaccination schedule, India*

Vaccine	*Schedule*
BCG	Birth
OPV	6 weeks, 10 weeks, 14 weeks
DPT	6 weeks, 10 weeks, 14 weeks
Hepatitis B	6 weeks, 10 weeks, 14 weeks
Measles	9 months

(2) Birth dose of Hepatitis B vaccine

Because of low rate of HBeAg-positivity among persons with chronic HBV infection in India, perinatal HBV transmission probably accounts for a minor proportion of HBV transmission. Further, only about 25% of all births in India take place in hospitals. Therefore, a birth dose of hepatitis B vaccine is not being incorporated in the EPI schedule. Feasibility of providing a birth dose to neonates of women who deliver in hospital may be considered at a future date.

3.4 Approach to Vaccine Introduction: Phased Introduction

Approach paper to the Ninth Five-Year-Plan had recommended the introduction of hepatitis B vaccine into the routine immunization programme of the country. However, this was not possible because of limitation of resources and preoccupation of state governments and field health staff with activities related to polio eradication. As the country is fast approaching the stage of zero-incidence of polio, activities relating to polio eradication are being rapidly scaled down. This would lead to release of resources, both financial and human, for undertaking fresh initiatives. Concurrently, the Ministry of Health and Family Welfare (MOHFW), Government of India, has taken measures to strengthen the routine immunization programme as well as

to improve the reach of reproductive and child health services. The stage is therefore set for the introduction of hepatitis B vaccine in the routine immunization programme in India.

Given its vast size, the financial and logistical constraints, and the fact that India is currently in the middle of a five-year planning cycle, it is not possible to introduce hepatitis B vaccine to all states and districts in India simultaneously. Instead, the hepatitis B vaccine must be introduced in phases, over a period of years. Although data are limited for some states, the prevalence of HBV infection is relatively homogenous in various parts of the country (with some pockets of high prevalence). Therefore, the order of various regions of the country for phasing-in will be determined mainly by their vaccination performance and their capacity (including availability of cold chain) to incorporate a new vaccine into the immunization schedule. The benefits of this gradual phasing in vaccination include: (i) need for less funds during the initial years, and (ii) providing an opportunity to assess the operational feasibility of the programme and to take mid-term corrective measures based on experience in the regions where vaccine is initially introduced.

It is therefore proposed to introduce hepatitis B vaccine, during Phase I, in 15 metropolitan cities (Phase IA) and in 32 rural districts (located in 17 states), which have satisfactory coverage rates for other EPI vaccines (Phase IB). The planned duration for this phase is two years (part of ninth five-year plan period, and rolling into the Tenth Five-Year Plan period (2002-2007). Phase II of the introduction of hepatitis B vaccine will correspond with the Tenth Five Year Plan. The detailed plan for this phase will be incorporated in to the Tenth Five Year Plan document.

The Ministry of Health and Family Welfare intends to make the vaccine available in additional districts with the intention of covering all the districts in phases over the next Five Year Plan, 2003-2006. The India UIP also plans to introduce AD syringes for administration of all vaccines in areas where hepatitis B vaccine is introduced. As far as possible, Indian UIP wants to have a uniform system of injection for all vaccines.

3.5 Vaccine Logistics

(1) Vial size

Indian EPI currently uses 10-dose vials of DPT vaccine. To facilitate introduction of hepatitis B vaccine into the existing EPI, it is proposed to use 10-dose vials.

(2) Wastage

Vaccine wastage has been currently estimated as approximately 25%, i.e. five percent higher than that for DPT to account for expected leakages during the phasing-in period. However, prior to the introduction of hepatitis B vaccine, a study will be undertaken to determine baseline wastage rates and reasons. This will help evolve strategies to reduce vaccine wastage. Vaccine manufacturers are soon likely to start attaching vaccine vial monitors (VVMs) to all hepatitis B vaccine vials to indicate whether the vaccine has been damaged by heat. Once VVMs become commonplace, an open vial policy will be encouraged to reduce vaccine wastage. Special attention will need to be given to prevent use in non-targeted populations.

(3) Vaccine requirements

The estimated number of doses of monovalent hepatitis B vaccine that will be required over the next two years (2002-2003) is presented in Annex 7. These estimates were produced using the following assumption of 25% vaccine wastage rate in 2002 and 20% in 2003.

(4) Injection safety

Currently, reusable glass syringes and needles and sterilization equipment like autoclaves/double rack steam sterilizers are used throughout India. The quality and safety of injection techniques and sterilization is uncertain. The Government desires to improve injection safety and is planning to conduct a comprehensive injection safety assessment and use the findings for improvement. However, UIP is committed to moving from using re-sterilizable

syringes and needles to auto-disable (AD) syringes in accordance with the WHO-UNICEF-UNFPA policy statement on injection safety.

3.6 Cold Chain Logistics

Introduction of hepatitis B vaccine, whether in the form of monovalent or combination vaccine, will require an assessment of cold-chain capacity. This will be particularly important if a decision to use monovalent hepatitis B vaccine is made. In addition, as compared to other EPI vaccines, the hepatitis B vaccine is relatively heat stable but is easily destroyed by freezing. Therefore, storage and shipping procedures to prevent freezing of vaccines at all levels of the cold chain will need attention. Under the Immunization Strengthening Project (World Bank), a major effort, not only to replace but also to expand the cold chain, has been undertaken over the last two years. Several states (Andhra Pradesh 2001, Madhya Pradesh 2000, Orissa 2000 and Uttar Pradesh 1999) have conducted assessment of their cold chain requirements. In these states, it has been shown that the need for cold chain space can be addressed by moving equipment form some districts with excess refrigerators to those that are deficient. This fact was proved to be true when these districts successfully conducted national immunization days for polio immunization, without any cold chain capacity constraints. Some ongoing activities of the Government of India regarding the cold chain are:

(1) Procurement of additional cold chain equipment and vaccine vans that would be required in the next three years through the Immunization Strengthening Fund.

(2) Assistance from KfW of Germany for cold chain is already in progress and the equipment is being installed in priority districts.

(3) Solar refrigerators provided by JICA are also being installed in eastern India.

(4) Funds from the Immunization Strengthening Fund are available for maintenance of the existing cold chain equipment.

Even though the government is convinced that cold chain will not be a major problem in the target districts, the Government of India will conduct

further district-specific cold chain capacity assessment. As a first step in this process, the Government of India has approached the WHO/Regional Office cold-chain expert to conduct a brief review of the cold chain space requirement in these districts. The cold-chain expert has calculated the extra cold chain space required. District Programme Officers have been requested to review the cold chain system prior to introduction of hepatitis B vaccine in all districts, in order to ensure that refrigerators are working properly.

3.7 Administrative Aspects

All UIP forms, administrative and training materials will need to be revised/updated to include hepatitis B vaccine. These include:

- Immunization schedule
- Immunization card
- Daily tally sheet
- Vaccine register
- Vaccination register
- Monthly report forms

These materials will be created during the 6-month preparatory period from July-November, 2001.

3.8 Training

Consideration will be given to separate training of EPI staff through a National "Training of the Trainer" programme. National trainers will train mid-level managers at national and regional level, who will in turn train field workers. The training will be integrated with Universal Immunization Programme (UIP) or IMCI training programmes, as much as possible. The India UIP will use funding made available through the World Bank for these training activities. Programme for Appropriate Technology in Health / Bill And Melinda Gates Children's Vaccine Programme (PATH/CVP) has also been approach and has agreed to provide the required training materials.

3.9. Information, Education, Communication (IEC)

Success of an immunization programme lies in creating awareness about it in parents, the general public, decision-makers, community groups, and health care workers. IEC activities are, therefore, an important part of implementation of hepatitis B immunization programme.

The addition of hepatitis B vaccine to the national immunization programme can improve the coverage of other EPI vaccines. This is related to renewed motivation among health workers to deliver a new vaccine to the population. In addition, inclusion of a new vaccine in the immunization programme creates increased awareness the public and among health care staff about benefits provided by vaccination leading to an increase in participation rates.

The MOHFW acknowledges the difficulty of introducing a new vaccine in 15 metro cities and 32 districts all over the country. To strengthen the local capacity, the MOHFW will approach partner agencies to fund recruitment and hiring of a hepatitis B accine introduction advisor, to coordinate and monitor smooth introduction of the vaccine. In Phase II of the vaccine introduction, during the 10th five -year plan, the MOHFW will assign four more coordinators to monitor introduction of the vaccine in four zones of the country. Creation of a national-level advisory group, that will include leading hepatologists and paediatricians, will also be considered to assist the efforts of the MOHFW in the smooth introduction of the vaccine.

Between July and September 2002, information materials on hepatitis B and hepatitis B vaccine for parents, the general public, and key decision makers and community leaders will be prepared. Information materials appropriate for medical and nursing staff in academic and private facilities will also be developed. A national-level workshop including policymakers, nongovernmental voluntary organizations, Ministry of Health staff, and clinicians will be held to disseminate information. Consideration will also be given to incorporating this information into IMCI training, if feasible.

Important messages for these groups will include the following: (i) hepatitis B infection and its consequences, (ii) how the virus is transmitted, (iii)

benefits of hepatitis B vaccine, (iv) who should receive hepatitis B vaccine; and (v) how many doses of hepatitis B vaccine should the infants receive, and at what age. Specific materials to be revised include posters, leaflets and stickers.

3.10 Programme Evaluation

The ultimate objective of hepatitis B immunization is to prevent chronic HBV infection and its long-term consequences (cirrhosis and liver cancer). However, these outcomes are difficult to measure. Also, since most HBV infections in children are asymptomatic, disease surveillance cannot be used to evaluate the impact of hepatitis B immunization. Furthermore, cirrhosis and liver cancer caused by HBV infection generally do not occur until adulthood. Therefore, indirect measures of programme impact must be used. In addition to monitoring the introduction process, the following methods can be used to evaluate implementation of hepatitis B immunization.

(1) Monitoring introduction of hepatitis B vaccine

The experience of districts where the vaccine is introduced in the first phase would be useful to the districts where it is introduced later. Close monitoring will therefore be essential in the first phase. It should include visits of the national hepatitis B vaccine introduction advisor, joint site visits of the hepatitis B vaccine introduction advisor with the national staff to selected districts, and preparation of reports by the states describing their experience, including any problems encountered and suggestions for improvement. Aspects to be reviewed should include acceptability to the public, ease of use and acceptability to health staff, coverage of infants with each dose, and appropriate storage, distribution and use of hepatitis B vaccine.

(2) Evaluating programme effectiveness

The effectiveness of introduction of hepatitis B vaccine can be evaluated by measuring coverage through (i) routine reports, and (ii) coverage surveys. For both of these, hepatitis B vaccine indicators and targets can be the same as those for DTP3. Coverage surveys may provide more accurate information than routine reports.

Serological surveys can be used to provide serological evidence of receipt of vaccination. Such surveys can also provide data on reduction in

rates of HBV infection, compared to baseline HBsAg positivity data already available. Thus, a serological survey of 3-5 year old children conducted approximately five years after the full implementation of hepatitis B immunization programme and comparison with results from children of similar age in previous surveys can provide data on the programme's effectiveness of the programme.

References

Acharya SK, Panda SK, Duphare H, et al. *Chronic hepatitis in a large Indian hospital*. Natl Med J India 1993; 6: 202-6.

Aggarwal R, Naik SR. *Prevention of hepatitis B infection: the appropriate strategy for India*. Natl Med J India 1994; 7: 216-20.

Aggarwal R, Naik SR. *Cost-efficacy evaluation of inclusion of hepatitis B vaccine in Expanded Programme of Immunization in India*. *In:* Sarin SK, Singal AK, Eds. Hepatitis B in India: Problems & Prevention. New Delhi: CBS. 1996; pp 203-13.

Aggarwal R, et al. *Cost-effectiveness of inclusion of hepatitis B vaccine in India's national immunization programme using a decision analysis approach*. 2002. Submitted for publication.

Aikat BK, Pathania AGS, Sharwal SP. *'Shikata' cell in liver diseases*. Indian J Pathol Microbiol 1977; 20: 145-50.

Amarapurkar DN, Vishwanath N, Kumar A, et al. *Prevalence of delta virus infection in high risk population and hepatitis B virus related liver diseases*. Indian J Gastroenterol 1992; 11: 11-2.

Bhargava K, Pokharna DS, Nag BP. *Prevalence of delta hepatitis in Rajasthan (Abstract).* Indian J. Gastroenterol. 1990; 9 (suppl): A38.

Biswas SC, Gupta I, Ganguly NK, et al. *Prevalence of hepatitis B surface antigen in pregnant mothers and its perinatal transmission*. Trans Royal Soc Trop Med Hyg 1989; 83: 698-700.

Blumberg BS, Melartin L. AuAg and lepromatous leprosy: *Studies in south India and elsewhere*. Indian J Leprosy 1970; 38: 60.

Chakraborthy MS, Mukherjee KK, Mithra KK, et al. *Association between Australia antigen and leprosy In Calcutta.* Bull Cal School Trop Med 1977; 25: 19.

Chowdhury A, Santra A, Chaudhuri S, et al. *Prevalence of hepatitis B infection in the general population: a rural community based study*. Trop Gastroenterol 1999; 20: 75-7.

Dass Gupta C B, Saxena S. *Hepatitis B surface antigen in Indian childhood cirrhosis and viral hepatitis*. Indian J Pediatr 1981; 48: 777-9.

Datta SK, Gulati AK, Pandey LK, et al. *Hepatitis B virus carriage in pregnant women*. J Commun Dis 1988; 20: 209-12.

Demicheli V, Jefferson TO. *Cost-benefit analysis of the introduction of mass vaccination against hepatitis B in Italy*. J Public Health Med 1992; 14: 367-75.

Desai P, Banker DD. *Hepatitis B and delta viruses in fulminant hepatitis*. Indian J Gastroenterol 1990; 9: 209-10.

Dharmadhikari CA, Kulkarni RD, Kulkarni VA, et al. *Incidence of hepatitis B surface antigen in liver diseases and voluntary blood donors*. J Indian Med Assoc 1990; 88: 73-5.

Dutta RN, Mohammed GS. *Incidence of AuAg in voluntary and professional blood donors and also in cases of viral hepatitis*. Indian J Med 1972; 60: 1774.

Dutta RN, Sen S. *A study of Australian antigen, cold antibodies and ABO blood group frequencies in Ladakhies*. Indian J Med Res 1975; 63: 1635-40.

Edmunds WJ. *Universal or selective immunization against hepatitis B virus in the United Kingdom? A review of recent cost-effectiveness studies*. Commun Dis Public Health 1998; 1: 221-8.

Elavia AJ, Banker DD. *Prevalence of HBsAg and its subtypes in high risk group subjects and voluntary blood donors in Bombay*. Indian J Med Res 1991; 93: 280-5.

Fenn P, Gray A, McGuire A. *An economic evaluation of universal vaccination against hepatitis B virus.* J Infect 1996; 32: 197-204.

Garuz R, Torrea JL, Arnal JM, Forcen T, Trinxet C, Anton F, Antonanzas F. *Vaccination against hepatitis B virus in Spain*: a cost-effectiveness analysis. Vaccine 1997; 15: 1652-60

George C. *Hepatitis B and delta viruses in hepatitis of varying severity*. Thesis submitted to the Punjab University. 1992.

Gill HH, Majumdar PD, Dhunjibhoy KR, et al. *Prevalence of hepatitis B e antigen in pregnant women and patients with liver disease*. J Assoc Physicians India 1995; 43: 247-8.

Ginsberg GM, Berger S, Shouval D. *Cost-benefit analysis of a nationwide inoculation programmeme against viral hepatitis B in an area of intermediate endemicity*. Bull World Health Organ 1992b; 70: 757-67.

Ginsberg GM, Shouval D. *Cost-benefit analysis of a nationwide neonatal inoculation programmeme against hepatitis B in an area of intermediate endemicity*. J Epidemiol Community Health 1992a; 46: 587-94.

Gupta I, Sehgal A, Seghal R, et al. *Vertical transmission of hepatitis B in north India*. J Hyg Epidemiol Microbiol Immunol 1992; 36: 263-7.

Gupta ML, Sharma Usha, Saxena S, et al. *Vertical transmission of hepatitis-B surface antigen from asymptomatic carrier mothers*. Indian Pediatr 1985; 22: 339-42.

Gupta P, Kar P, Chakravarty A, et al. *Delta virus infection in cirrhotics in a north Indian hospital*. J Assoc Physicians India 1993; 41: 503.

Hall AJ, Roberston RL, Crivelli PE, Lowe Y, Inskip H, Snow SK, Whittle H. *Cost-effectiveness of hepatitis B vaccine in the Gambia*. Trans Roy Soc Trop Med Hyg 1993; 87: 333-6.

Hatziandreu EJ, Hatzakis A, Hatziyannis S, Kane MA, Weinstein MC. *Cost-effectiveness of hepatitis-B vaccine in Greece. A country of intermediate HBV endemicity*. Int J Technol Assess Health Care 1991; 7: 379-402.

Hill PG, Jacob John T, Shanmugham RV, et al. *Australia antigen in blood donors in Vellore*. Indian J Med Res 1973; 61: 378-82.

Hill PG, Johnson S, Madanagopalan N. *Serum alpha-fetoprotein and hepatitis B in subjects with hepatoma in south India*. Indian J Med Res 1977; 65: 482-7.

Hill WD, Pattanayak S, Arora DD. *Detection of Australia antigen in human viral hepatitis*. Indian J Med Res 1970; 58: 1172.

Ichhpujani RL, Riley IW, Duggal L, et al. *Demographic features of sporadic acute hepatitis as determined by viral hepatitis markers*. J Commun Dis 1991; 23: 138.

ICMR collaborative study on chronic hepatitis, acute viral hepatitis and sub-acute hepatic failure; ICMR, New Delhi 1993.

International Institute for Population Sciences (IIPS), ORC Macro. 2000. *National Family Health Survey (NFHS-2), 1998-99: India.* Mumbai: International Institute for Population Studies. Pp 178-9.

Irshad M, Acharya SK. *Status of hepatitis viral markers in patients with acute and chronic liver diseases in northern India*. Intervirology 1994b; 37: 369-72.

Irshad M, Joshi YK, Acharya SK, et al. *Prevalence of hepatitis B virus infection in healthy persons in North India*. Natl Med J India 1994a; 7: 210-2.

Irshad M, Singh YN, Acharya SK. *HBV status in professional blood donors in north India*. Trop Gastroenterol 1992; 13: 112.

Jayaprakash PA, Shanmugham J, Hariprasad D. *Hepatitis B surface antigen in blood donors. An epidemiologic study*. Transfusion 1983; 23: 346-7.

Jonsson B, Horisberger B, Bruguera M, Matter L. *Cost-benefit analysis of hepatitis-B vaccination. A computerized decision model for Spain*. Int J Technol Assess Health Care 1991; 7: 379-402.

Jyotsna, Chawla Y. Hepatitis delta virus. In: *Transfusion Associated Hepatitis: Diagnosis, Treatment and Prevention*. Ed: Sarin SK, Hess G. 1998. New Delhi: CBS Publishers and Distributors. Pp 19-31.

Kant L, Hall AJ. *Epidemiology of childhood hepatitis B in India: vaccination related issues*. Indian J Pediatr 1995; 62: 635-53.

Kelkar SS, Karhade NV, Bhagwat RB. *Australia/hepatitis associated antigen in cirrhosis of liver at Aurangabad.* Indian J Med Res 1973a; 61: 1614.

Kelkar SS, Karhade NV, Kotal SE *Haemolytic complement, anti-complementary activity and hepatitis B antigen in sera of patients with cirrhosis of liver*. Indian J Med Res 1975; 63: 41-4.

Kelkar SS, Niphadkar KB, Khare PM. *Titres of AuAg in healthy carriers, leprosy, cirrhosis of liver and acute hepatitis.* Indian J Med Res 1973b; 61: 684.

Khatri JV, Kulkarni KV, Vaishnav PR, et al. *Vertical transmission of hepatitis-B*. Indian Pediatr 1980; 17: 957-62.

Kochhar R, Singh L, Bhasin DK, et al. *Delta hepatitis infection in north India. A preliminary report*. J Assoc Physicians India 1989; 37: 310-1.

Kotwal SE, Kelkar SS. *Hepatitis-B antigen In endemic hepatitis at Aurangabad*. Indian J Med Sci 1973; 27: 855-60.

Kou U. *Cost-effectiveness of hepatitis B vaccination in high endemicy countries: Review of evidence and methods*. Background document for the Expert Review of Methods for Estimating Hepatitis B Disease Burden. WHO Headquarters, Geneva, May 30-31, 2000.

Krishnamurthy L, Singh DS, Tandon HD, et al. *Chronic active hepatitis*. Indian J Med Res 1976; 64: 1376-84.

Kulkarni ML, Reddy P, Vishnuvardhan. *Prevalence of HBsAg in asymptomatic carrier mothers and vertical transmission in South India*. Am J Dis Child 1988; 142: 124-5.

Makroo RN, Hassain G, Koul A, Shah GN. *Prevalence of hepatitis B surface antigen in Kashmiri blood donors*. Indian J Med Res 1989; 89: 310-3.

Mallya PS. *Incidence of hepatitis B antigen in Mangalore*. J Commu Dis 1989; 21: 309-12.

Margolis HS, Coleman PJ, Brown RE, Mast EE, Sheingold SH, Arevalo JA. *Prevention of hepatitis B virus transmission by immunization. An economic analysis of current recommendations*. JAMA 1995 18; 274: 1201-8.

Medley GF, Lindop NA, Edmunds WJ, Nokes DJ. *Hepatitis-B virus endemicity: heterogeneity, catastrophic dynamics and control*. Nat Med 2001; 7: 619-24 .

Miller MA, Kane M. *Routine hepatitis B immunization in India: cost-effectiveness assessment*. Indian J Pediatr 2000; 67: 299-300.

Miller MA, McCann L. *Policy analysis of the use of hepatitis B, Haemophilus influenzae type b-, Streptococcus pneumoniae-conjugate and rotavirus vaccines in national immunization schedules*. Health Economics 2000; 9: 19-35.

Ministry of Health and Family Welfare (MOHFW). 1999. *Evaluation of Routine Immunization 1997-98. New Delhi*: Department of Family Welfare, MOHFW.

Mittal SK, Rao S, Rastogi A, et al. *Hepatitis B: Potential of perinatal transmission in India*. Trop Gastroenterol 1996; 17: 190-2.

Mittal VN, Gupta OP, Nigam DK, et al. *Pattern of hepatitis B antigen contact and carrier state in northern India*. J Indian Med Assoc 1980; 74: 105-7.

Mohite JB, Urhekar AD. *Prevalence of HBsAg positivity in staff and patients at MGM Medical College and Hospital, Navi-Mumbai*. Indian J Med Sci 1999; 53: 434-8.

Nanu A, Sharma SP, Chatterjee K, Jyoti P. *Markers for transfusion –transmissible infections in north Indian voluntary and replacement blood donors: prevalence and trends 1989-1996*. Vox Sang 1997; 73: 70-3.

Narendranathan M, Philip M. *Reusable needles: a major risk factor for acute virus B hepatitis*. Tropical Doctor 1993; 23: 64-6.

Nayak NC, Panda SK, Zuckerman, AJ, et al. *Dynamics and impact of perinatal transmission of hepatitis b virus in north India.* J Med Virol 1987; 21: 137-45.

Pal SR Prasad SR. *Delta virus infection in and around Chandigarh, northern India: evidence for endemicity*. Trop Geograph Med 1987; 39: 123-5.

Pal SR, Chitkara NL, Choudhury S, et al. *Hepatitis B virus infection in northern India*. Bull WHO 1974; 51: 13-7.

Pal SR, Dutta DV, Choudhry S, et al. *HBsAg among patients with liver diseases and voluntary blood donors: a prospective study.* Indian J Med Res 1973; 61: 1784.

Panda SK, Datta R, Gupta A, et al. *Etiological spectrum of acute sporadic viral hepatitis in children in India.* Trop Gastroenterol 1989; 10: 106-10.

Panda SK, Ramesh R, Rao KV, et al. *Comparative evaluation of the immunogenicity of yeast derived (recombinant) and plasma-derived hepatitis B vaccine in infants*. J Med Virol 1991; 35: 297-302.

Patnaik SK, Biswas S, Lal S, et al. *Community studies on prevalence of HBsAg in two urban populations of southern India*. Indian Pediatr 2000; 37: 149-52.

Prakash C, Sharma RS, Bhatia R, et al. *Prevalence in north India of hepatitis B carrier state amongst pregnant women*. Southeast Asian J Trop Med Public Hlth 1998b; 29: 80-4.

Prakash C. *Hepatitis C and hepatitis E in acute sporadic non-A, non-B hepatitis in hospital patients of Delhi (India).* Southeast Asian J Trop Med Public Hlth 1998a; 29: 475-9.

Prakash C. *Universal hepatitis B immunization in India: cost-effectiveness analysis*. Takemi Programme Research Paper, Takemi Programme in International Health, Harvard School of Public Health, USA. 1999a; Paper No.147.

Prakash C. *Crucial factors that influence cost-effectiveness of universal hepatitis B immunization in India.* Takemi Programme Research Paper, Takemi Programme in International Health, Harvard School of Public Health, USA. 1999b; Paper No.152.

Prasad SR, Rodrigues FM, *Dhorje SP, et al. Prevalence and subtypes of hepatitis B surface antigen in the tribal population of Arunachal Pradesh*, India. Indian J Med Res 1983; 78: 300-6.

Raju GS, Broor SL, Singh V, et al. *Fulminant viral hepatitis: Indian experience*. J Gastroenterol Hepatol 1989; 4: 161.

Roychoudhary A, Bhattacharyya DK. *Incidence of hepatitis B carriers in Calcutta, West Bengal*. J Assoc Physicians India 1989; 37: 160-1.

Sakhrie HV, Shrivastava PN, Chuttani HK, et al. *Australia antigen in persistent hepatitis in northern India.* J Indian Med Assoc 1977; 69: 170-2.

Sama SK, Anand S, Malaviya AN, et al. *Australia/SH Antigen in normal population and patients of viral hepatitis in Delhi*. Indian J Med Res 1971; 59: 64-8.

Sarin SK, Chari S, Sundaram KR, et al. *Young vs adult cirrhotics: a prospective, comparative analysis of the clinical profile, natural course and survival*. Gut 1988; 29: 101.

Sarin SK, Guptan RC, Banerjee K, et al. *Low prevalence of hepatitis C viral infection in patients with non-alcoholic chronic liver disease in India*. J Assoc Physicians India (in press).

Sarin SK. Clinical spectrum of hepatitis B in India. In: *Hepatitis B in India: Problems and Prevention*. Eds: Sarin SK, Singal AK. 1996. New Delhi: CBS Publishers and Distributors. Pp 51-63.

Satoskar A, Ray V. *Prevalence of hepatitis B surface antigen (HBsAg) in blood donors from Bombay.* Trop Geogr Med 1992; 44 : 119-21.

Saxena S, Nigam DK, *Gupta SC, et al. Hepatitis surface antigen in hepatic disorders with reference to its sub-types*. J Assoc Physicians India 1984; 32: 547-9.

Sebastian M, Ichhpujani RL, Kumari S. *Incidence of different types of viral hepatitis in Delhi, Uttar Pradesh and Rajasthan areas*. J Commun Dis 1990; 22: 129.

Sehgal A, Gupta I, Sehgal R, et al. *Hepatitis B vaccine alone or in combination with anti-HBs immunoglobulin in the perinatal prophylaxis of babies born to HBsAg carrier mothers*. Acta Virol 1992; 39: 359-66.

Shanmugam J, Nair SR. *A three and half year follow-up study of HBsAg carrier state in asymptomatic mothers*. Indian J Pathol Microbiol 1982; 25: 273-8.

Shanmugham J, Balakrishnan V, Venugopalan P, et al. *Prevalence of hepatitis B surface antigen in blood donors and pregnant women from southern Kerala*. Indian J Med Res 1978; 68: 91-6.

Shapiro C, Prakash C. Hepatitis B in India: *Burden of disease analysis. A report submitted to WHO*, SEARO. July 2000.

Sharma R, Malik A, Rattan A, et al. *Hepatitis B virus infection in pregnant women and its transmission to infants*. J Trop Pediatr 1996; 42: 352-4.

Singh DS, Sama SK, Singh G. *A study of chronic hepatitis in northern India*. Indian J Med Res 1976a; 64: 1728-34.

Singh DS, Sama SK, Tandon BN, et al. *Hepatitis B antigen and hepatic cirrhosis in tropics. J Assoc Physicians India* 1976b; 24: 593-7.

Singh J, Bhatia R, Khare, S, et al. *Community studies on prevalence of HBsAg in two urban populations of southern India*. Indian Pediatr 2000; 37: 149-52.

Singhvi A. Pulimood RB. John TJ, et al. *The prevalence of markers for hepatitis B and human immunodeficiency viruses, malarial parasites and microfilaria in blood donors in a large hospital in south India*. J Trop Med Hyg 1990; 93: 178-82.

Sobeslavsky O. *Prevalence of markers of hepatitis B virus infection in various countries: a WHO collaborative study*. Bull WHO 1980; 58: 621-8.

Sumathy S, Thyagarajan SP, Rajasabdam P, et al. *Prevalence pattern of marker of delta virus in blood of patients with acute and chronic liver disease (abstract).* Indian J Gastroenterol 1990; 9 (suppl): A48.

Sundaram C, Reddy CR, Ramana GV, et al. *Hepatitis B surface antigen, hepatocellular carcinoma and cirrhosis in south India: an autopsy study*. Indian J Pathol Microbiol 1990; 33: 334-8.

Sundaravalli N, Nedunchezian VSS, Sriramachari S, et al. *HBs antigenemia in chronic liver disorders in infancy and childhood*. Trop Gastroenterol 1988; 9: 80-2.

Szucs T. *Cost-benefits of vaccination programmemes*. Vaccine 2000; 18 (Suppl): S49-51.

Tandon BN, Gandhi BM, Joshi YK, et al. *Etiological spectrum of viral hepatitis and prevalence of markers of hepatitis A and B virus infection in north India*. Bull WHO 1984; 62: 67.

Tandon BN, Irshad M, Acharya SK, et al.*Hepatitis C virus infection is the major cause of severe liver disease in India*. Gastroenterol Jpn 1991a; 26 (suppl. 3): 1460.

Tandon BN, Irshad M, Raju M, Mathur GP, Rao MN. *Prevalence of HBsAg and anti-HBs in children and strategy suggested for immunization in India*. Indian J Med Res 1991b; 93: 337-9.

Tandon BN, Joshi YK, Gandhi BM, et al. *Epidemiology of HBsAg carriers In India. A holistic approach to control of hepatitis B reservoir*. J Gastroenterol Hepatol 1986; 1: 39-43.

Tandon BN, Nayak NC, Tandon HD, et al. *Acute viral hepatitis with bridging necrosis. Collaborative study on chronic hepatitis*. Liver 1983; 3: 140.

Thakur TS, Goyal A, Sharma V, et al. *Incidence of Australia antigen (HBsAg) in Himachal Pradesh*. J Commun Dis 1990; 22: 173-7.

Thyagarajan SP, Subramanian S, Sundaravelu T, et al. *HBsAg carriers among hospital personnel.* J Assoc Physicians India. 1981; 29: 941.

Vyas KK, Mathur AK, Vyas RK. *A study of prevalence of hepatitis b surface antigen among pregnant women*. J Obstetr Gynaecolov India 1983; 33: 778-81.

Wiewiora-Pilecka D. *Cost-benefit analysis of the Polish hepatitis B prevention programmeme. Vaccine 2000*; 18 (Suppl 1): S52-4

World Bank. *The World Bank Group. Development data: Country data.* Cited December 20, 2001. Available from: URL: http://www.worldbank.org/data/countrydata/countrydata.html.

Yadav SK, Jain AK Gupta S, et al. *Delta infection in HBV related liver diseases*. Indian J Gastroenterol 1990; 9 (Suppl): A61.

Annex 1

STUDIES OF HBSAG PREVALENCE IN INDIA

Population studied State/UT	Type of test	No. of subjects	% HbsAg positive	Reference
Voluntary blood donors				
Kerala	CIEP	8085	1.0	Jayaprakash et al 1983
Maharashtra	ELISA	3104	4.7	Satoskar et al 1992
Maharashtra	ELISA	3095	3.7	Elavia et al 1991
Maharashtra	ELISA	3883	2.0	Elavia et al 1991
Maharashtra	ELISA	3455	2.0	Elavia et al 1991
Maharashtra	ELISA	1042	2.1	Mohite et al 1999
Tamil Nadu	IEOP	1321	2.3	Hill et al 1973
Tamil Nadu		35 395	2.2	Singhvi et al 1990
West Bengal			2.0	Roychoudhury et al 1989
Delhi	ID, IEOP	680	2.7	Dutta et al 1972
Delhi	EIA	132093	2.5	Nanu et al 1997
Delhi		20435	2.6	Irshad et al 1994a
Jammu & Kashmir	RPHA	7900	1.1	Makroo et al 1989
Chandigarh	IEOP, ID	1470	1.5	Pal et al 1973
General population				
Andhra Pradesh	ELISA	737	3.3	Singh et al 2000
Karnataka	ELISA	816	4.0	Singh et al 2000
Kerala	IEO, AGD	475	2.0	Shanmugham et al 1978
Maharashtra	AGD	420	1.4	Kelkar et al 1973b
Maharashtra	IEOP	625	4.0	Kotwal et al 1973
Tamil Nadu	CIEP	123	1.6	Thyagarajan et al 1981
Tamil Nadu	ID	127	2.3	Blumberg et al 1970
Tamil Nadu	IEOP	531	0.8	Hill et al 1973
Uttar Pradesh		846	1.2	Mittal et al 1980
West Bengal	ID	199	0	Hill et al 1970
West Bengal	CIEP	NA	3.0	Chakraborthy et al 1977
West Bengal	ELISA	960	5.0	Chowdhury et al 1999
Arunachal Pradesh	CIEP	755	5.8	Prasad et al 1983
Arunachal Pradesh	RPHA	296	8.5	Prasad et al 1983
Delhi	ID	952	0.1	Sama et al 1971
Delhi	ELISA	1,800	11.7	Irshad et al 1992
Delhi	ELISA	1,982	2.2	Tandon et al 1991b
Himachal Pradesh	RPHA	500	3.6	Thakur et al 1990

Population studied State/UT	Type of test	No. of subjects	% HbsAg positive	Reference
Jammu & Kashmir		144	9.7	Dutta et al 1975
Pregnant women				
Karnataka	RPHA	400	5.0	Kulkarni et al 1988
Kerala	IEOP, AGD	400	3.0	Shanmugham et al 1982
Kerala	CIEP	1475	3.0	Shanmugham et al 1978
Maharashtra	CIEP, RIA	1276	0.6	Khatri et al 1980
Maharashtra	IHA	2000	5.0	Gill et al 1995
Maharashtra	RIA	1276	0.6	Panda et al 1991
Rajasthan	AGD, CIEP	500	1.0	Vyas et al 1983
Rajasthan	CIEP	1,000	2.2	Gupta et al 1985
Rajasthan	ELISA	295	6.8	Prakash et al 1998b
Rajasthan	CIEP	500	1.0	Vyas et al 1983
Uttar Pradesh	RPHA,CIEP, AGD	400	4.8	Datta et al 1988
Uttar Pradesh	ELISA	206	8.7	Prakash et al 1998b
Uttar Pradesh	RPHA	400	4.8	Khatri et al 1980
Uttar Pradesh	RPHA, ELISA	157	10.0	Sharma et al 1996
Delhi	ELISA	8575	3.7	Nayak et al 1987
Delhi	ELISA	598	11.2	Prakash et al 1998b
Delhi	ELISA	837	3.6	Tandon et al 1986
Delhi	ELISA	8431	2.6	Panda et al 1991
Delhi	ELISA	850	6.3	Mittal et al 1996
Manipur	ELISA	13	7.7	Prakash et al 1998b
Chandigarh	RPHA, ELISA	1000	2.3	Biswas et al 1989
Chandigarh	ELISA	4137	2.6	Sehgal et al 1992
Chandigarh	ELISA	2337	2.5	Gupta et al 1992
Children <5 yrs of age				
Karnataka	ELISA	1553	4.0	Patnaik et al 2000
Delhi		982	2.5	Tandon et al 1991
Students				
Kerala	IEOP, AGD		0.6	Shanmugam et al 1978

Type of diagnostic assay used (information not available unless otherwise stated): ID = immunodiffusion; AGD = agar gel diffusion; IHA = indirect haemagglutination; RPHA = reverse passive haemagglutination; IEOP = immunoelectrophoresis; CIEP = countercurrent immunoelectrophoresis; EIA = enzyme immunoassay; ELISA = enzyme linked immuno sorbent assay; RIA = radio immunoassay.

Annex 2

ESTIMATE HBsAg PREVALENCE BY STATE, INDIA

Region, State	No. of studies	HBsAg Prevalence Midpoint (Range)
North		
Chandigarh	4	2.0 (1.5-2.6)
Delhi	12	5.9 (0.1-11.7)
Himachal Pradesh	1	3.6
Jammu & Kashmir	2	5.4 (1.1-9.7)
Uttar Pradesh	5	5.6 (1.2-10.0)
South		
Andhra Pradesh	1	3.3
Karnataka	3	4.5 (4-5)
Kerala	5	1.8 (0.6-3.0)
Tamil Nadu	5	1.5 (0.8-2.3)
Northeast		
Arunachal Pradesh	2	7.1 (5.8-8.5)
Manipur	1	7.7
East		
West Bengal	4	2.5 (0.0-5.0)
West		
Rajasthan	4	3.9 (1.0-6.8)
Maharashtra	10	2.8 (0.6-5.0)

No data available: Andaman & Nicobar Islands, Assam, Bihar, Dadra & Nagar Haveli, Daman & Diu, Goa, Gujarat, Haryana, Lakshadweep, Madhya Pradesh, Meghalaya, Mizoram, Nagaland, Orissa, Pondicherry, Punjab, Sikkim, Tripura

Annex 3

STUDIES ON HEPATITIS B E ANTIGEN (HBeAg) PREVALENCE AMONG PREGNANT WOMEN, INDIA

Area	No. women tested	HBsAg positive %	HBeAg positive %	Reference
North India	1,112	9.5	12	Prakash 1998b
New Delhi	850	6.3	18	Mittal et al 1996
Mumbai	2,000	5.0	12	Gill et al 1995
Chandigarh	2,337	2.5	26	Gupta et al 1992
North India	8,575	3.7	8	Nayak et al 1987
Chandigarh	1,000	2.3	47	Biswas et al 1989

Annex 4

ESTIMATES (PROVISIONAL) OF HEPATITIS DISEASE BURDEN IN A SINGLE YEAR BIRTH COHORT, INDIA

EPIDEMIOLOGICAL SUMMARY	
(A) Disease Events	
Disease Events	**Number**
Total HBV infections	9,058,587
Acute symptomatic hepatitis B cases	2,581,924
Chronic HBV infections	1,507,286
HBV-related deaths:	
Fulminant acute hepatitis B	10,835
Cirrhosis	46,239
Hepatocellular carcinoma	145,913
Total	205,286
(B) Number of Infections by Age at Acquisition of Infection	
Age of Acquisition	**Number of Infections**
Perinatal Infection	249,111
Early Childhood Infection	3,147,859
Late Infection	5,661,617
Total Infections	9,058,587
(C) Number of Chronic Infections by Age of Acquisition of Infection	
Age of Acquisition	**Number of Chronic Infections**
Perinatal Infection	224,198
Early Childhood Infection	943,961
Late Infection	339,126
Total Infections	1,507,286

(D) Number of Deaths by Age at Acquisition of Infection	
	Number of Deaths
Perinatal Infection	36,472
Early Childhood Infection	137,427
Late Infection	31,487
Total Deaths	205,386

(E) Number of Infections by Serostatus of Mother			
Serostatus of Mother	**Number of Infections**		
	Perinatal	**Early Childhood**	**Late**
HBsAg-negative	0	2,964,423	5,455,800
HBsAg-positive, HBeAg-negative	96,247	173,245	203,818
HBsAg-positive, HBeAg-positive	152,864	10,191	1,998
Total	249,111	3,147,859	5,661,617

Appendix. Input values and assumptions

Prevalence HBsAg among women of child bearing age:	5
Prevalence HBeAg among HBsAg-positive women of childbearing age	15
Prevalence of any marker of HBV infection among 5 year olds:	15
Prevalence of any marker of HBV infection among 30+ year olds:	40

Annex 5

SUMMARY OF AVAILABLE STUDIES ON COST EFFECTIVENESS OF HEPATITIS B VACCINATION IN THE INDIAN POPULATION

Sr. No.	Study	Methods used	Assumptions	Results	Sensitivity analysis/Additional analysis/Limitations
1.	Aggarwal and Naik, 1994	Comparison of universal infant immunization versus selective immunization (screening of pregnant women with HBsAg test, and immunization only of infants born to HBsAg positive mothers) with hepatitis B vaccine	Hepatitis B carrier rate = 3.7% HBeAg positivity rate among carrier mothers = 7.8% **HBV infection rates among infants during the first six months of life** ***Mother HBsAg-positive*** Infection rate = 19% Chronicity rate = 75% ***Mother HBsAg-negative*** Infection rate = 3% Chronicity rate = 50% ***Vaccine efficacy rates*** With HBsAg-positive mother = 75% With HBsAg-negative mother: = 95%	Perinatal transmission likely to be responsible for only 14% of all HBV carriers. **Effectiveness of two approaches** ***Resultant HBV carrier rates*** Selective = 3.25% Universal = 0.29% ***Proportion of carriers prevented*** Selective = 12% Universal = 92% Universal immunization = 7.6-times more effective **Cost** Selective immunization US$ 4.30 per child Universal immunization US$ 2.32 per child Universal immunization programme 1.85-fold higher	**Limitations** Sensitivity analysis not done. Compliance assumed as 100%. Did not include 'no vaccine' option.

Sr. No.	Study	Methods used	Assumptions	Results	Sensitivity analysis/Additional analysis/Limitations
			Costs ***For universal immunization*** Vaccine = US$ 1.00/dose Administration cost = US$ 0.43/dose ***For selective immunization*** Vaccine = US$ 2.00/dose Administration cost = US$ 0.87/dose HBsAg testing = US$ 2.00/test	**Cost-effectiveness (Cost per HBV carrier prevented)** Selective immunization = US$ 126 Universal immunization = US$ 495 Universal immunization 3.9 times more cost-effective	
2.	Aggarwal and Naik, 1996	Comparison of universal infant immunization versus selective immunization (screening of pregnant women with HBsAg test, and immunization only of infants born to HBsAg positive mothers) with hepatitis B vaccine	**Most estimates were similar to those in the preceding row, except for costs** (Aggarwal and Naik, 1994) except the following: **Costs** ***For universal immunization*** Vaccine = US$ 0.75/dose Administration cost = US$ 0.33/dose ***For selective immunization*** Vaccine = US$ 1.50/dose Administration cost = US$ 0.67/dose HBsAg testing = US$ 2.00/test	Perinatal transmission likely to be responsible for only 14% of all HBV carriers. **Effectiveness of two approaches** ***Resultant HBV carrier rates*** Selective =3.25% Universal =0.29% ***Proportion of carriers prevented*** Selective: =12% Universal: =92% Universal immunization =7.6-times more effective	**Limitations** Sensitivity analysis not done. Compliance assumed as 100%. Did not include 'no vaccine' option.

Sr. No.	Study	Methods used	Assumptions	Results	Sensitivity analysis/Additional analysis/Limitations
				Cost Selective immunization = US$ 3.25 per child Universal immunization = US$ 2.24 per child Universal immunization programme = 1.45-fold higher **Cost-effectiveness (Cost per HBV carrier prevented)** Selective immunization = US$ 95 Universal immunization = US$ 498 Universal immunization = 5.6 times more cost-effective	
3.	Prakash, 1999a; Prakash, 1999b	Incremental cost-effectiveness comparison of hepatitis B as part of Expanded Programme of Immunization versus 'do-nothing' using decision tree (Markov model)	Societal perspective. Only direct costs. Only vertical transmission included; horizontal transmission not considered. HBV carrier rate = 9.5% HBeAg-positive rate among carriers = 12% *Disease transmission rate* From HBeAg-positive mothers = 90% From HBeAg-negative mothers = 15%	US $ 23.76 per DALY gained	Sensitivity analysis showed that if effects were not discounted, cost-effectiveness was US$ 19.08 per DALY gained. Uncertainty analysis showed that the most important factors that influenced cost-effectiveness were: (a) HBsAg positivity in carrier mothers, and (b) vaccination coverage.

Sr. No.	Study	Methods used	Assumptions	Results	Sensitivity analysis/Additional analysis/Limitations
			Disease rates in infected neonates (%) Neonatal disease / Mother's HBeAg status: Positive / Negative Acute hepatitis: 2.8% / 3.2% HBV carrier: 90.2% / 15.7% No symptoms: 81.1% / 7.0% *Disease progression among HBV carriers:* 90% develop chronic hepatitis, of which 80% have chronic persistent hepatitis and 20% chronic active hepatitis. Of chronic active hepatitis, 12.5% develop cirrhosis or liver cancer. *Survival* Chronic persistent hepatitis = 70 y age Chronic active hepatitis = 55 y age Cirrhosis/liver cancer = 45 y age *Healthy persons: ideal life table (US$ / per dose)* Vaccine cost = 0.75 Administration cost = 0.19 *Costs of treatment of complications based on Indian data* Discount rate for costs: = 3% Discount rate for benefits = 0%, 3%		Factors which had negligible effect on result were: (a) vaccine wastage, (b) HBeAg prevalence among carriers, and (c) treatment costs of hepatitis B. **Limitations** • HBsAg positivity rate assumption (9.5%) may be too high. • Horizontal transmission of HBV was ignored. • Has not been published yet.

Sr. No.	Study	Methods used	Assumptions	Results	Sensitivity analysis/Additional analysis/Limitations
				US $ 23.76 per DALY gained	Sensitivity analysis showed that if effects were not discounted, cost-effectiveness was US$ 19.08 per DALY gained. Uncertainty analysis showed that the most important factors that influenced cost-effectiveness were: (a) HBsAg positivity in carrier mothers, and (b) vaccination coverage. Factors which had negligible effect on result were: (a) vaccine wastage, (b) HBeAg prevalence among carriers, and (c) treatment costs of hepatitis B. **Limitations** • HBsAg positivity rate assumption (9.5%) may be too high. • Horizontal transmission of HBV was ignored. • Has not been published yet.

Sr. No.	Study	Methods used	Assumptions	Results	Sensitivity analysis/Additional analysis/Limitations
4.	Miller and Kane, 2000	Cost-effectiveness of routine infant immunization against hepatitis B	• Vaccine cost = US$ 0.50 per dose; • Additional administration cost = US$ 0.19 per dose • Coverage rate = 80% • Vaccine efficacy = 95% • Average life expectancy = 66 years (in year 2040) • Lifetime mortality due to cirrhosis or HCC = 20%; • Average age at death due to HBV = 45 years • Discount rate = 0%, 3% • No treatment costs	Cost per year of life saved Undiscounted = US$ 12 Discounted = US$ 66 Cost per death averted: Undiscounted = US$ 312 Discounted = US$ 1178 Total cost per year = US$ 46 million for a single-year birth-cohort (for vaccine, does not include cost of administration) Should save 147000 to 198000 lives in a single-year birth-cohort	Sensitivity analysis only on one parameter (life-time risk of mortality due to HBV) With a life-time risk of mortality due to HBV of 27%, Cost per year of life saved Undiscounted = US$ 9 Discounted = US$ 49 Cost per death averted: Undiscounted = US$ 231 Discounted = US$ 873 **Limitations** Limited sensitivity analysis. Treatment costs were not considered.
5a.	Aggarwal et al, 2002	Incremental **cost-effectiveness** comparison of hepatitis B as part of Expanded Programme of Immunization versus 'do-nothing' using decision tree (Markov model)	Societal perspective HBsAg carrier rate = 4%; Coverage rate = 80%; Vaccine efficacy = 95%; Vaccine cost per dose; = US$ 0.50 Vaccine administration cost = US$ 0.50 per dose; Discount rate for benefits = 0%, 3%	**Undiscounted** Reduction in carrier rate from 4% to 1.15% Increase in life expectancy of the entire birth-cohort = 0.15 years Increase in QALY lived for entire birth-cohort = 0.17 years Cost per carrier prevented = US$ 98.7 Cost per year of life saved = US$ 19.06 Cost per QALY of life saved = US$ 16.26	**On hepatitis B carrier rate** Carrier rate % / Cost per life year US$ / Cost per QALY US$ 1 — 76.22 — 65.06 2 — 38.10 — 32.54 3 — 25.40 — 21.68 *4 — 19.06 — 16.26* 5 — 15.24 — 13.02 6 — 12.70 — 10.84 8 — 9.52 — 8.14

Sr. No.	Study	Methods used	Assumptions	Results	Sensitivity analysis/Additional analysis/Limitations
			Disease progression rates Chronic hepatitis B to cirrhosis Age 0-9: Nil Age 10-19: 0.5% per year Age ≥ 20: 1.0% per year Cirrhosis to decompensated cirrhosis: 5% per year Decompensated cirrhosis to death: 20% per year *Quality of life* Healthy person or HBsAg carrier: 1.0 Cirrhosis of liver: 0.95 Decompensated cirrhosis: 0.50 Mid-year correction applied in Markov analysis	**Discounted (discount rate for benefits = 3%)** Cost per year of life saved = US$ 101.70 Cost per QALY of life saved = US$ 82.94	**On cost of immunization** Cost of 3 doses (Total) / Cost per life year US$ / Cost per QALY US$ US$6: 38.10 / 32.54 US$5: 31.76 / 27.12 US$4: 25.40 / 21.68 *US$3.0: 19.06 / 16.26* US$2: 12.70 / 10.84 **On vaccine efficacy rate** Efficacy rate / Cost per life year US$ / Cost per QALY US$ 70: 25.86 / 22.04 75: 24.14 / 20.60 80: 22.63 / 19.32 85: 21.30 / 18.18 90: 20.11 / 17.18 *95: 19.06 / 16.26* 100: 18.10 / 15.46

Sr. No.	Study	Methods used	Assumptions	Results	Sensitivity analysis/Additional analysis/Limitations
					On vaccine wastage rate Wastage Efficacy rate / Cost per life year US$ / Cost per QALY US$ 30% 21.78 18.58 *20% 19.06 16.26* 10% 16.94 14.46 0% 15.24 13.02 **On vaccine coverage rate** Coverage rate / New carrier rate % US$ / % fall rate % US$ 4.00 Nil 40 2.48 38 50 2.10 48 60 1.72 57 70 1.34 67 *75 1.15 71* 80 0.96 76 90 0.58 86 100 0.20 95 **Benefits limited to age of 70 years** Life years gained = 0.11/child QALY gained = 0.13/child Cost per life year gained = US$25.84 Cost per QALY gained = US$21.56

Sr. No.	Study	Methods used	Assumptions	Results	Sensitivity analysis/Additional analysis/Limitations
5b.	Aggarwal et al, 2002	Incremental **cost-benefit** comparison of hepatitis B as part of Expanded Programme of Immunization versus 'do-nothing' using decision tree (Markov model). Similar to 4 above but including the costs of care of complications of chronic HBV infection.	Same as 4 above. **Additional assumptions:** Treatment of liver disease Cirrhosis (compensated) At onset: INR 2000 Thereafter INR 2000 per year Decompensated cirrhosis At onset: INR 5000 Thereafter INR 5000 per year	**Undiscounted** Immunization is cheaper than 'no immunization'. **Discounted for cost (@ 3%)** Per life year gained = US$ 2.18 Per QALY gained = US$ 2.56	Sensitivity analysis including threshold analysis based on variations in cost of treating complications of chronic HBV infection In *undiscounted* analysis, threshold for immunization to be the preferred option over 'no immunization' was 0.30 times the baseline cost assumptions for treatment of complications of chronic hepatitis B virus infection In *discounted* analysis, threshold for immunization to be the preferred option over 'no immunization' was 1.15 times the baseline cost assumptions for treatment of complications of chronic hepatitis B virus infection

DALY = Disability-adjusted life year
HBV = hepatitis B virus
HBsAg = Hepatitis B virus surface antigen
HBeAg = Hepatitis B virus e antigen
QALY = Quality-adjusted life year
INR = Indian Rupee
US$ = US Dollar

Annex 6

SUMMARY OF MAIN BASELINE FINDINGS OF VARIOUS STUDIES

Parameter		Indian studies					Studies from other regions for comparison	
		Aggarwal and Naik, 1994 and 1996	Prakash, 1999a and 1999b	Miller and Kane, 2000	Aggarwal et al, 2002	Range	Hall et al, 1993 (Gambia)	Miller and McCann, 2000 (For intermediate
Cost per carrier prevented		95-126		63	99	63-126	40	
Cost per life year gained	Undiscounted			9 – 12	19	9-19		14-19
	Discounted			49-66	102	49-102		
Cost per DALY or QALY	Undiscounted		27		16	16-27		
	Discounted				83	83		
Cost per death prevented	Undiscounted			231-312		231-312	150-200	
	Discounted			873-1178		873-1178		

Missing data indicate that the value was not calculated in the particular study.

QALY = Quality-adjusted life-year

DALY = Disability-adjusted life-year

Annex 7

VACCINE LOGISTICS FOR IMPLEMENTATION OF MONOVALENT HEPATITIS B VACCINE (2001-2002)

	2002	2003	By 2008 (Annual requirement)
Surviving infants in millions	727 806	189 9324	25
Target children	549 321	1 709 391	
Number of doses	3 doses	3 doses	3 doses
Estimated vaccination coverage rate	85%	90%	90-93%
Estimated wastage rate	25%	20%	20-15%
Buffer stock of 25% additional	25%*	25%*	0
Total vaccine doses required in millions	2.06	7.72	112.22
AD syringe for hepatitis B vaccine in millions	2.05	5.58	88.59
AD syringe for other vaccines	9.36	25.46	324.85
Total AD syringes (including 5% wastage)	11.91	32.41	413.44
Safety boxes required (millions)	0.12	0.32	4.13
Total cost in US Dollars			

- * In different group of population. The buffer stock rate is not expected to decline in the first year.
- Based on 28 million surviving infants during 1999, with increase each year of 1%.
- Vaccination coverage for three doses of vaccine is based on attaining higher coverage than that of DPT3 measured in 1999 survey (50%) due to plans for training and education about benefits of new vaccine, minimal expected side effects compared with DPT; increased coverage estimated each year.
- Target number = surviving infants x estimated vaccination coverage rate. Vaccination programme to begin in July 2002.
- Based on maximum wastage rate of 25% for first year using 10 dose vials, with reductions each year to minimum of 10%;
- Total doses calculated during first year = target number of children x 3 doses x 1.25 x 1.25 (25% buffer); subsequent years calculated without buffer and with estimated increasing coverage estimates and decreasing wastage factors.
- Total syringes = target number of children x 3 doses x wastage factor (5% wastage gives factor of 100/100-95 = 1.0526).

Annex 8

ESTIMATED EXPENSES FOR IEC (INFORMATION, EDUCATION AND COMMUNICATION ACTIVITIES), TRAINING AND EVALUATION OF INTRODUCTION OF HEPATITIS B VACCINE

	Phase I A 2001	Phase I B 2002	Phases II 2003-2006
Training	50,000	80,000	320,000
IEC	30,000	70,000	150,000
Evaluation	20,000	30,000	100,000
Total	100,000	180,000	570,000

- Activities from regular budget
- All figures are in USD

Annex 9

TIME TABLE FOR ACTIVITIES RELATED TO INTRODUCTION OF HEPATITIS B VACCINE

	Aug-Oct 2001	Jan-Feb 2002	2002	2003-2006
Recruit hepatitis B vaccine introduction advisor[2]	X			
Procurement of hepatitis B vaccine	X			
Assessment of cold chain[1]	X			
Revision of training materials	X			
Revision of all immunization forms (schedule, immunization card, reporting, etc.)	X			
Training of EPI staff in all districts	X			
IEC[2] campaign for hepatitis B vaccine introduction	X	X		
Introduction of hepatitis B vaccine at all sites		X		
Monitoring of introduction and feedback		X	X	
Ongoing training			X	X
Review of reported hepatitis coverage data			X	X
National coverage survey				X

[1] Formal cold chain assessment will begin in October 2001

[2] Information, Education, communication