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SYNTHESIS OF THE EXISTING DATA ON HEPATITIS B IN ARMENIA

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EXECUTIVE SUMMARY

Hepatitis B is the world's fifth leading cause of infectious disease mortality, causing over one million deaths annually. Hepatitis B's burden is associated with both acute infection and chronic liver diseases. Fortunately, a highly effective vaccine against Hepatitis B is available. This presents national policy-makers with the responsibility of selecting and implementing a vaccination strategy appropriate to the specific epidemiologic and socio-demographic characteristics of the country.

In accordance with WHO recommendations, Armenia adopted universal vaccination of infants against Hepatitis B in 1999. The first dose is administered at birth and, if completed, can virtually eliminate the threat of perinatal transmission. This strategy, however, increases the complexity of the immunization schedule and may contribute to incomplete or late coverage. This concern may be addressed by aligning the Hepatitis B vaccination schedule with the current DPT schedule. The implication of this change would mean a delay in coverage of three months. Such a switch, unless outweighed by the increases in coverage, is only appropriate where the risk of perinatal transmission is low. Thus, knowledge of the prevalence of the infection among pregnant women, and an estimate of the risk of acquiring the infection at birth is essential. A synthesis of the available data is presented in this report.

Studies in Armenia indicate that the prevalence of Hepatitis B infection is quite low, especially in comparison to neighboring countries. Depending on the population, estimates range from 1.5% among pregnant women to 2.2% among first time voluntary blood donors. The data do suggest, however, that the prevalence of Hepatitis B infection is increasing. Nonetheless, estimates in this report indicate that from 10-50% of all infections occur during infancy, with up to half resulting from perinatal exposure. Though, this may be an artifact of the increased access children have to health services. These findings emphasize the importance of early, primary prevention through immunization. The proportion of risk attributed to perinatal versus other routes during infancy is not known for Armenia. Thus, a recommendation in support of altering the current schedule cannot be made without further study.

TABLE OF CONTENTS

LIST OF ACRONYMS

A12K	Armenia Immunization 2000
ANMF	Ani & Narod Memorial Fund
Anti-HBc	Antibodies to Hepatitis B Core Antigen
BCG	Bacilli of Calmet & Geren
CDC	Centers for Diseases Control and Prevention
DTP	Diphtheria Tetanus Pertussis
ELISA (EIA)	Enzyme Immunoassay
IgM	Immune Globulin M
HBV	Hepatitis B Virus
HBeAg	Hepatitis B e-Antigen
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
MOH	Ministry of Health
NIP	National Immunization Program
OPV	Oral Poliomyelitis Vaccine
PCR	Polymerase Chain Reaction
RA	Republic of Armenia
RCHEC	Republican Center of Hygiene and Epidemiological Control
RHID	Republican Hospital of Infectious Diseases
RIA	Radioimmunoassay
UNICEF	United Nations' Children Fund
VHPB	The Viral Hepatitis Prevention Board
WHO	World Health Organization

Chapter 1: INTRODUCTION

Immunization against Vaccine Preventable Diseases has proven to be one of the most effective and efficient forms of health care worldwide [1]. Immunization has led to a remarkable decline of infectious diseases during this past century. The successful eradication of smallpox has stimulated hopes that polio will soon follow. In 1988 a resolution was adopted by the World Health Assembly that called for global eradication of poliomyelitis by the year of 2000 [2].The reduction in the morbidity caused by other infectious diseases such as measles, Hepatitis B, mumps, and rubella in regions with universal childhood immunization makes their potential eradication also seem within reach [3].

The Armenian National Immunization Program in the 1990s

In both the Soviet era and since its independence, childhood immunization has been a priority for Armenia. In examining trend data, it should be noted that under Soviet rule, the immunization schedule and accepted list of contraindications differed significantly from the WHO recommendations. Consequently, children often were eventually fully immunized, but were rarely up-to-date [4]. Still, coverage was often better than that of many western locales [5]. Accurate assessment of coverage has been difficult due to the lack of a well-organized immunization surveillance system at the national level, but the consensus is that vaccine coverage levels in Soviet Armenia were sub-optimal [4].

Two key documents written in the past several years have provided detailed portraits of the National Immunization Program (NIP). The first is a situational analysis of women and children conducted by the Government of Armenia, UNICEF, and Save the Children in late 1998 [4]. The second is an evaluation of the NIP conducted by the Ministry of Health and UNICEF in late 1999 [6]. Both highlight the strengths, weaknesses, and accomplishments of the NIP.

Since 1994, several important changes aimed to strengthen the immunization system have been implemented in Armenia. A new immunization schedule was adopted in accordance with WHO recommendations (RCHEC) (see Appendix.1). Concurrently, the official list of contraindications

to vaccination was significantly reduced; the cold chain storage system was improved; and health care providers were trained to the new standards [6].

Despite the economic collapse that followed Armenia's independence and the ensuing near-collapse of the healthcare system, immunization services have remained strong. The few scattered outbreaks of vaccine preventable diseases that occurred were quickly addressed. According to the Ministry of Health, the population coverage levels for basic vaccines increased while other branches of health services have deteriorated [6].

During the last several years, the numbers of new cases of polio, diphtheria, and pertussis decreased in comparison with early 1990s. This trend is consistent with the reported rise in immunization coverage levels [4]. According to a recent evaluation [6], the strategies to strengthen the NIP implemented by the Ministry of Health appear to have been very effective.

The evaluation [6] also highlighted several areas for improvement. The two primary areas identified as needing improvement were late/incomplete vaccination and poor management of vaccine distribution. Coverage rates for the four core antigens by the age of 12 months (15 months for measles) ranged from 60.6% (measles) to 86.9% (BCG). These levels fall short of the NIP goals of 90%. Although the data showed that most of the children in Armenia had access to the NIP -the proportion of completely unimmunized children was very low (3.4%) - a tendency of late immunization was observed for all antigens. Crude coverage rates were 6-25% higher than timely coverage rates: only 48.5% of Armenian children received their core vaccines according to the time schedule. Common reasons for delay were contraindications (real or not) and unsatisfactory maternal knowledge/awareness. Overall, the evaluation indicated that Armenian Immunization Program provides a good level of vaccine services as compared to those in countries of the former Soviet Union [6].

Vaccine Supply in Armenia

The Armenian NIP has been capable of sustaining this level of coverage due to the generous contributions of many international agencies and organizations: the NIP is fully dependent on foreign aid to purchase its vaccines. The important donor organizations are UNICEF and, in the future, the Ani & Narod Memorial Fund, the latter of which recently signed a memorandum of understanding with the Ministry of Health to pilot the Armenia Immunization 2000 Program (AI2K). This Program was created specifically to assist Armenia in solving the problem of sustaining vaccine supplies as well as shaping the future of its immunization program. AI2K has prioritized providing WHO-recommend vaccines not currently supplied by other donors, specifically vaccines against Mumps and Hepatitis B [7]. AI2K is presently operating within the context of a comprehensive package of assessments and in concert with the national immunization services in Armenia, and as a bilateral planning/coordinating partner with the Global Alliance for Vaccines and Immunization (GAVI) on the supply of Hepatitis B vaccines.

Status of Hepatitis B Immunization in Armenia

Although the WHO called for the inclusion of Hepatitis B vaccine in childhood immunization schedules in 1991, it was not introduced in Armenia until 1999 when funds were available to acquire the vaccine. Prior to 1999, only health-care workers at high-risk were immunized for Hepatitis B. These groups were partially vaccinated in 1995 and 1999 [8]. Experience in other countries [9], indicated that this strategy alone would prove ineffective in controlling the spread of Hepatitis B. Thus, the introduction of universal vaccination of children against Hepatitis B was a significant and appropriate step forward for the NIP.

According to the newly adopted schedule (see Table 1 in Appendix 1), vaccination against Hepatitis B is provided three times during the first year of the life: at the first day of life (in the maternity hospital), at one and a half months of age and at six months of age (in the children outpatient clinic). This mode of vaccination provides protection from the virus starting at birth, virtually eliminating the threat of vertical transmission (i.e., mother-to-child transmission). In doing so, however, it increases the complexity of the immunization schedule and may exacerbate existing levels of sub-optimal/late coverage.

Policy Issue

In order to streamline the vaccination schedule and thereby hopefully increase coverage and improve on-time delivery, a proposal is being considered which would align the Hepatitis B vaccination schedule with the current schedule of DPT vaccinations. A concern that must be assessed prior to implementing this proposal is the risk of infection (perinatal or otherwise) during the first 3 months of life. If the prevalence among pregnant mothers is high or moderate, vaccination at birth is appropriate; if the prevalence is low, delaying the start of the Hepatitis B vaccination series may be acceptable, particularly if the added value of increased timely coverage is considered [1, 3].

Chapter 2: GENERAL INFORMATION ON HEPATITIS B

A great body of literature exits describing the distribution and burden of Hepatitis world-wide. This chapter summarizes the key epidemiologic data that will provide a framework against which to assess the Armenia-specific data presented in Chapter 3.

2.1 Burden of Disease Associated with Hepatitis B

According to the World Health Organization [10], Hepatitis B is the fifth leading cause of infectious disease mortality in the world. It causes 1 million deaths worldwide annually; its burden is related to both acute disease and complications of chronic infection. Diagram 1 in Appendix 2 presents a conceptual framework for understanding the burden of disease associated with Hepatitis B derived from WHO data [10].

The likelihood of developing acute Hepatitis B is related to the age of infection. Infected infants develop symptoms of acute disease only in 1% of cases; 10% of infected children 1-5 years old and 40% of older children and adults who are infected are symptomatic. The case fatality rate for acute Hepatitis B is 0.5-1.0% [10].

Chronic infection with Hepatitis B is one of the leading causes of chronic liver disease, including cirrhosis and liver cancer. WHO data [10] suggests that 3 million persons worldwide have chronic viral Hepatitis B infection. The chance of developing chronic or persistent hepatitis heavily depends on the age of infection: 90% of children infected perinatally or during the first year of the life, 30% of children infected during ages 1-5, and 6% of children infected at later ages will develop chronic infection. The risk of dying from HBV-related chronic liver disease is around 25% if the disease was acquired in infancy or early childhood, and 15% if acquired later in childhood or adulthood.

According to available data, more than 60 million people suffer from liver cirrhosis because of Hepatitis B infection worldwide. This is more than the number of cases of liver cirrhosis caused by alcohol [9]. Chronic Hepatitis B infection is also a primary cause of hepatocellular carcinoma.

Hepatocellular carcinoma is the most frequently occurring cancer worldwide and is responsible for 1 million deaths annually [11]. The likelihood of progression appears to increase with other assaults to the liver such as co-infection with Hepatitis C [12]. Studies have shown that the roles of Hepatitis B and C viruses in causing progressive chronic liver disease including hepatocellular carcinoma vary considerably between different regions [11]. Thus, one should be cautious in extrapolating the burden of Hepatitis B infection from proxy measures such as chronic liver disease prevalence absent information about the prevalence of Hepatitis C.

Assessing Burden

The WHO suggests several methods for assessing the disease burden associated with HBV infection [13]:

- serosurveys for determining age-specific prevalence of HBsAg (*serologic marker of chronic infection*) and the antibody to Hepatitis B core antigen (anti-HBc) (*serologic marker of acute, chronic, or resolved infection*);
- surveillance of acute Hepatitis B; and
- measuring deaths from cirrhosis and hepatocellular carcinoma.

One of the commonly used indicators of the burden of disease is the incidence of acute clinical Hepatitis B. Another indicator is the prevalence of Hepatitis B in the population. The latter measure is often categorized into three levels: low (<2% of the population), intermediate (2-8%), and high (>8%). The prevalence rate of Hepatitis B infection is often underestimated because Hepatitis B is mainly an asymptomatic infection [9].

Indicators such as the prevalence of carriers of HBsAg as well as the incidence of acute clinical HBV infection have to be interpreted with caution, however, since they represent divergent populations. For example, data on blood donors are readily available, but this group reflects a self-selected population that may differ from the general population along socio-economic and cultural domains. Furthermore, those previously screening positive would self-select out of this population. Incidence data are even more unreliable, since data are typically based on case-finding and often derived from a number of methodologies, e.g., identification of HBsAg carriers, acute clinical Hepatitis B, and presumptive clinical diagnoses absent laboratory

analyses. The usage of a variety of laboratory tests, each with its own sensitivity and specificity, further complicates the picture [9].

2.2 Epidemiology of Hepatitis B In The World

According to the WHO [13], approximately 2 billion persons are infected with Hepatitis B virus worldwide. Due to the persistent nature of the virus, there are more than 350 million carriers, of whom 3 million have developed chronic hepatitis. Countries with high endemicity are predominantly located in East and Southeast Asia and in sub-Saharan Africa. In these countries, the disease is primarily transmitted perinatally. Western Europe and North America have low endemicity, and report parenteral manipulations or sexual contact as the primary mode of transmission.

Latin America

The prevalence of Hepatitis B infection and the dominant modes of its transmission vary widely among countries. A study on Hepatitis B sero-prevalence conducted in Latin America by Silveira and colleagues [14] indicated the highest levels of sero-positivity were found in the Dominican Republic (21.4%), followed by Brazil (7.9%), Venezuela (3.2%), Argentina (2.1%), Mexico (1.4%), and Chile (0.6%). Across these countries the highest sero-prevalence was found among persons 16 years old and older, suggesting sexual transmission as the major route of infection. In addition, comparatively high levels of sero-prevalence were seen at early age in the Dominican Republic and Brazil, implicating a vertical route of transmission.

An investigation of the prevalence of Hepatitis B and C viruses in blood donors attending a 3rd-level hospital of Mexico City [15] indicated low prevalence of Hepatitis B and C. The main risk factors of acquisition of these infections were dental procedures (11.6% for HCV and 20%, for HBV), and unsafe sexual practices (20%) for HBV.

Europe and NIS

According to data reported at a 1996 meeting organized by the Viral Hepatitis Prevention Board (VHPB), the WHO, and the CDC [9], the lowest rates of Hepatitis B infection are in

Scandinavian countries, Ireland and the UK (0.001%). The rates generally increase southwards, but differ markedly when moving east versus southeast. Eastern European and NIS countries generally experience high levels of endemicity: e.g., Albania -18% (1996), Kyrgyzstan -11.1% (1994), Tajikistan-16.5% (1994), and Turkmenistan- 15.6% (1995). Intermediate rates are found in Belarus, Bulgaria, Former Yugoslav Republic of Macedonia, Georgia, Lithuania, Romania, and parts of Russian Federation. Recently published study on hepatitis prevalence in Moldova indicated that 17.1% of the children and 52.4% of pregnant women were positive to the anti-HBc test, and 6.8% and 9.7% respectively were positive to HBsAg [16].

Armenia

Armenia differs from its neighbors: it has a reported level of Hepatitis B endemicity of less than 2%. A 1996 report [9] of blood donors identified only a 1.25% prevalence rate based on HBsAg. This finding was similar to rates reported over the previous 6 years. Given the endemic levels in Armenia's neighbors, caution must be taken in interpreting these findings without a more rigorous assessment of the disease burden and identification of factors protecting Armenia from the spread of Hepatitis B.

2.3. Assessment of Hepatitis B Prevalence

A simple approach to assessing the prevalence of Hepatitis B is a critical examination of existing data. Laboratory tests for HBV markers have improved and third-generation tests -- tests of high sensitivity and specificity -- are now available. Older data derived using less sensitive tests are not necessarily invalid, but would likely underestimate the true prevalence [13].

In order to study the prevalence of Hepatitis B, serological surveys are the best choice. It is particularly appropriate to conduct a serological survey when considering policy recommendations that would alter the vaccination schedule. For the proposed change in the timing of the Hepatitis B vaccination, a representative sample from the population of pregnant women should be selected [13].

Another approach to estimating Hepatitis B prevalence is to examine the HBsAg prevalence in the first-time voluntary blood donor population recruited from a wide geographical area. There is, however, a threat to under-estimate the true prevalence of Hepatitis B assessed via this method: voluntary blood donors are typically a biased (healthier) subset of the population. Similarly, use of data from such groups as paid blood donors, prisoners and certain types of hospitalized patients are rarely generalizeable and of little value [13]. According to FitzSimons and VanDamme [9], changes in the prevalence of chronic Hepatitis B infection over time, with data derived from serial population-based studies of children is the best measures of the effectiveness of routine infant immunization programs.

2.4. Strategies to Prevent Hepatitis B Transmission

Hepatitis B virus is transmitted by artificial (parenteral) and natural (sexual, vertical and horizontal) routes. Diagram 2 in Appendix 2 presents a conceptual framework of HBV transmission routs partially derived from the information presented at the 1996 meeting report organized by the Viral Hepatitis Prevention Board (VHPB), the WHO, and the CDC [9]. According to this report [9], strategies for the control and prevention of Hepatitis B can be summarized in four categories:

- general preventive measures (*increase knowledge of HBV and methods of individual protection among the general population, health-care providers, and policy makers*);
- universal precautions (*usage of appropriate equipment according to the rules of hygiene*);
- passive immunization; and
- active immunization.

When choosing an immunization strategy one must consider its potential effectiveness, its feasibility of implementation, and its ability to address the problem [17].

Early Immunization Strategies

With the introduction of the first Hepatitis B vaccines, early strategies focused on high risk populations such as health-care workers, infants of Hepatitis B positive women, homosexuals, prostitutes, and intravenous drug users. Due to the difficulty in identifying and reaching most of these at-risk populations, only health-care workers were immunized at appreciable levels.

Health-care workers, however, are not a major component of the cases. The limited success of selective immunization for Hepatitis B highlights the need for universal immunization of infants [1, 9].

Strategy Selection Criteria

As summarized by the WHO [13], selection of a strategy to prevent Hepatitis B Virus transmission depends on the prevalence of the disease (endemicity): in regions with high prevalence, universal immunization of newborns is crucial; in the countries with low prevalence the immunization of adolescents and/or the selective vaccination of high-risk groups is often sufficient. Recent studies, however, suggest that HBV vaccination is efficient and effective even in countries with low endemicity [1].

The effectiveness of available vaccines is estimated at 95% in preventing the chronic carrier state and liver cancer. Few side effects or complications have been reported. The new combined vaccines containing HBV and DTP are also safe, sufficiently immunogenic and free of the problem of interference. [1]. Currently approximately 100 countries incorporate Hepatitis B vaccination into their routine pediatric preventive practices. Most also vaccinate adults at increased risk [18].

Chapter 3: EXISTING DATA ON HEPATITIS B IN ARMENIA

This chapter summarizes the available data from Armenia regarding Hepatitis B exposure and burden. This chapter covers information ranging from the tests available in the country to the descriptive epidemiology of the disease and its sequellae. Incidence data indicate the reported number of new cases and thus the rate of spread of disease and a sense of the effectiveness of primary prevention methods. Prevalence data indicate the burden of disease and predict demand for health services. Measures of treatment for acute care and co-morbidities such as hepatocellular cancer indicate how well the disease is being identified and managed.

3.1. Available Screening And Diagnostic Measures

Epidemiology teaches us that the positive predictive value of a diagnostic test is dependent upon three elements: sensitivity of the test, specificity of the test, and the prevalence of the characteristic in the population [19]. In terms of the former two criteria, these characteristics have been documented for the various generations of tests on the market (see table below). Tests typically focus on either detecting antigens specific to Hepatitis B or to antibodies specific to antigens of Hepatitis B.

Generation	***Test***	***Relative sensitivity***	***Detection power (ng/ml)***
First	Agar gel diffusion	1	2000
Second	Reverse passive hemagglutination	100	20
	Latex agglutination	100	20
Third	Radio immunoassay	10000	0.2
	Enzyme immunoassay	10000	0.2

Source: Center for Disease Control and Prevention as reported by Fields HA, 1996

As the above table details, each generation of assays has sensitivity 2 orders of magnitude (100 times) greater than the previous one. As such, first-generation tests are no longer in use. Due to

the high cost of third-generation tests, however, second-generation tests are still used throughout the world [9, 20].

Armenia is one of the countries where second-generation tests are still widely utilized, due both to financial constraints and to limited technical capacity. Given the superior sensitivity of third-generation tests and the availability of reasonably priced alternatives within this category, second-generation tests are no longer considered acceptable for most public health uses [21]. The WHO recommends Radio immunoassays (RIA) or Enzyme Immunoassays (EIA) as the only appropriate tests for assessing the prevalence of Hepatitis B infection in antenatal patients, since only these tests have adequate sensitivity [13]. The EIA and the Immunocomb screening tests are available in Armenia, though mostly limited to the capital, Yerevan. Despite slightly better performance, RIA is not used in Armenia because of technical considerations associated with its application [13].

One of the latest high-sensitivity, high-specificity tests is Reverse-transcriptase Polymerase Chain Reaction (PCR). This test detects the nucleic acids of Hepatitis viruses in the serum. This test, however, is both expensive and labor intensive. Currently there is only one laboratory in Yerevan which uses it. In addition, recent studies suggest that when the PCR is used in less-experienced laboratories, problems of non-specificity, primarily due to specimen contamination, might complicate the interpretation of results [22].

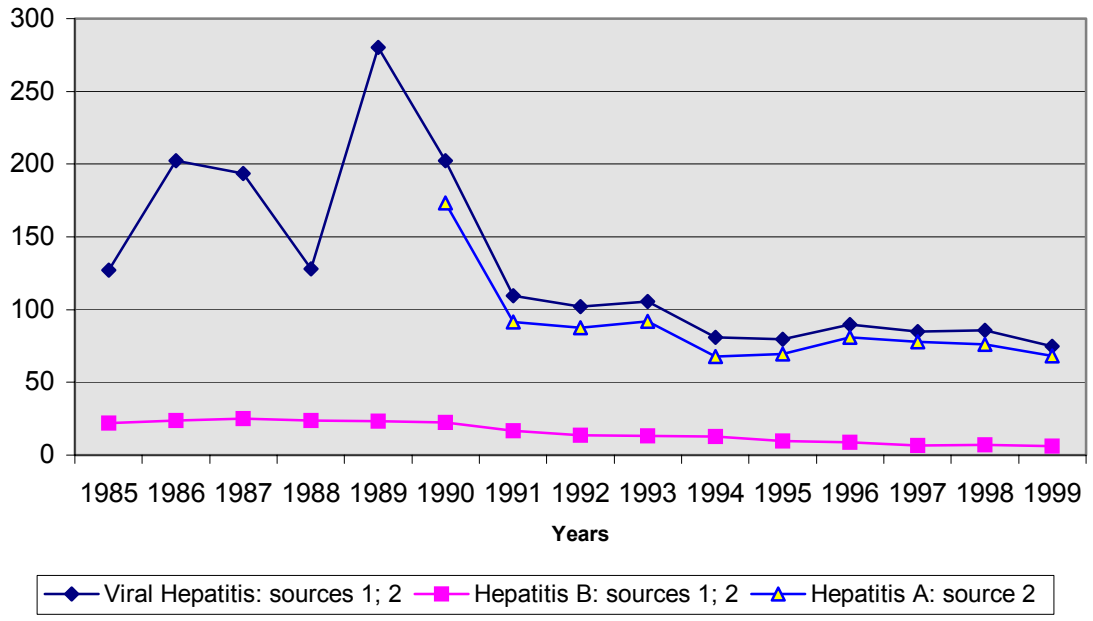
3.2. Incidence of Hepatitis B

The section describes the incidence of Hepatitis B in Armenia, its proportion among other viral hepatitis and age structure as well as provides the estimates of probability of infection acquisition through vertical transmission. The possible sources of bias in assessment of incidence are also considered.

According to data that are available from the Republican Center of Hygiene and Epidemiology Control (RCHEC) [32], the incidence of acute viral hepatitis during the last decade ranged from 75 to 280 per 100,000 population (see graph below). In 1998, hepatitis constituted almost 10%

of all infectious disease cases registered in Armenia. Hepatitis A accounted for the majority of hepatitis cases, with incidence rates ranging from 68 to 173 per 100,000 during the last several years. Due to its association with food and waterborne transmission routes, incidence of Hepatitis A fluctuates widely in response to seasonal and episodic events. Hepatitis B, meanwhile, showed a stable tendency toward small declines during the last 10 years, decreasing from 22-23 per 100,000 in the late 1980s to 6-7 per 100,000 in the late 1990s (see also Table 1 in Appendix 1).

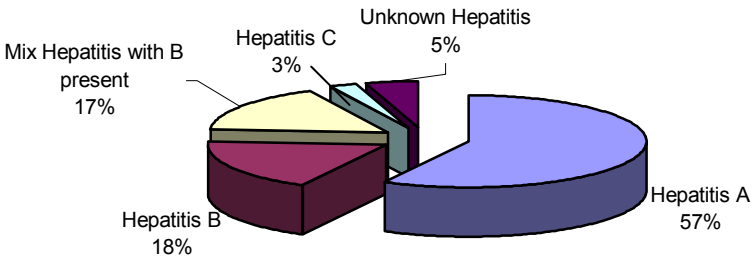
Incidence of Acute Viral Hepatitis, Hepatitis A, and Hepatitis B per 100,000 population in Armenia (1985-1999)
Sources: MOH, 1998 [1]; RCHEC, 2000 [2]



Etiology

A recent study by Asratyan and colleagues [23] sought to identify the etiological structure of acute viral hepatitis in Yerevan by use of EIA and PCR. Among a sample of 109 cases of adults with acute viral hepatitis that were taken from the Hospital of Infectious Diseases in Yerevan, Hepatitis A was identified in 57.8% of cases; Hepatitis B in 18.4%; both Hepatitis A and B in 5.5%; Hepatitis A with HBsAg (without IgM anti-HBc) in 7.3%; Hepatitis B and D in 3.7%; Hepatitis C in 2.7%; Hepatitis E in 0%; and Hepatitis non A-E in 4.6%. Hence, Hepatitis B accounted for roughly one-third of all Hepatitis Cases in this study. [see graph below]

Etiological Structure of Acute Virus Hepatitis in Yerevan
(Asratyan et al, 1998)



Age distribution

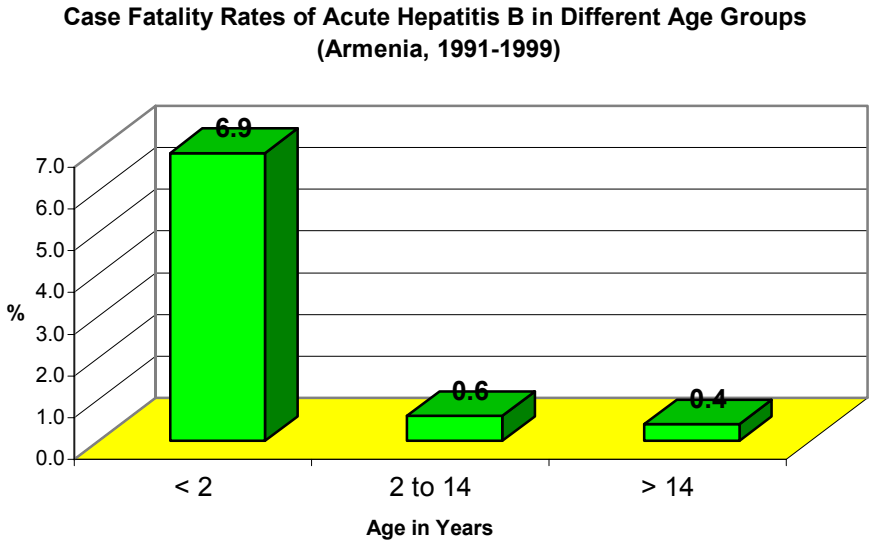
Data from RCHEC [32] on the age structure of the Hepatitis B cases in Armenia during the last decade indicate that almost one-third (28%) of the registered cases consist of children under 14 years old (see table 3 in Appendix). In 1999 this proportion increased to 39.3%. Children under 2 years old have represented 4.5% of all cases registered during 1990-1999. But when taking into consideration that most Hepatitis B infections in infants and young children are asymptomatic (only 5-10% are symptomatic) [9], one can speculate that perinatal (vertical) and/or early childhood transmission play a major role in the Hepatitis B infection in Armenia.

According to a conservative estimation based on the age structure of acute HBV cases and WHO data on the likelihood of symptomatic disease in different age groups [10], one may conclude that up to 50% of all HBV infections in the Armenian population may be acquired in infancy (see Table 6 in Appendix 1). Another method to estimate the probability of being infected through vertical transmission is to consider the prevalence of HBV carriers among pregnant women (estimated at 1.5% in Armenia) [24] and the risk of transmission in delivery estimated as 40% [16]. The approximate annual number of live births in Armenia is 40, 000 [31]. Thus, according to the aforementioned risk estimates, anywhere from 240 to 600 infections occurred during delivery, a similar though lower estimate. While these 2 estimates are convergent, the difference between them may be jointly explained by errors of the approximation and/or differences between perinatal and other modes of transmission during infancy. One must also

consider that the large fraction attributed to children may merely be an artifact of the higher level of access to and use of health services by children in Armenia, especially since the independence.

Case Fatality

Examination of the RCHEC official data on the case fatality rate of acute Hepatitis B [31] indicates that out of 3 498 cases of the disease registered since 1991, 27 cases (0.77%) died. This rate varied between 0.2% and 1.6% (See table 3 in the Appendix). Of these 27 deaths, 12 (44%) occurred in children under 14 years old, including 7 children (26% of all cases) under age 2. Case fatality rates are much higher in young children as compared to older children and adults: 6.9% versus 0.6% versus 0.4% respectively. This underscores the need for vaccination of infants.



Limitations of Data

While these data may suggest that the problem of Hepatitis B is diminishing, a critical assessment of the factors surrounding the generation of these data needs to be examined. Several explanations other than a true decline in the incidence rate need to be examined:

- Incomplete identification/testing of potential hepatitis patients (*under- reporting of numerator*);
- Use of second-generation tests with inadequate sensitivity to detect markers (HBsAg) (*under-reporting of numerator*);

- Decreased use of health services by adults (*under-reporting of numerator*); and
- Over-estimation of population due to poor adjustments for migration (*over-estimating denominator*).

The combined effects of these factors could lead to substantial under-estimation of the magnitude of the problem. A more detailed discussion of these factors follows.

Costs/financing: Economic and financial constraints arising from Armenia's independence underlie most of these factors. Although the government is responsible for the hospital costs of treating hepatitis, the reality is that most patients are expected to pay at least a portion of their treatment costs. According to calculations of the Republican Hospital of Infectious Diseases, the treatment cost for one Hepatitis B case is $230 while, according to the MOH data, the government only provides $122 for each case [8]. As a result, the health system does not have the resources to identify and treat all cases. According to official data of RCHEC only 82.6% of all registered cases with acute viral hepatitis were tested for HBsAg in 1998. In 1999 this number was even less – 79.3% (see table # 2 in the Appendix). This downward trend highlights the compounding of problems attributed to decreasing access to and utilization of diagnostic and health care services.

Tests: More often than not, the low-sensitivity second-generation tests are commonly used to detect HBsAg. Due to cost constraints, even the laboratory of the Republican Hospital of Infectious Diseases where the majority of Hepatitis B patients are hospitalized relies on second-generation tests.

Under-treatment/identification: Another limitation of the hepatitis data is that patients with acute hepatitis often avoid seeking treatment, much less hospitalization, and may never be registered. According to policy, district outpatient clinics and infectious departments/ hospitals, as the primary identifiers of new cases, are responsible for informing the Regional Hygiene and Epidemiological Stations about each new case. These data are processed and sent to the Republican Center of Hygiene and Epidemiological Control where the data are summarized and the official statistics prepared. According to the official data from the RCHEC, in previous years all the patients with acute Hepatitis B were hospitalized. In 1999, however, only 83.4% of all

registered Hepatitis B cases were hospitalized. Anecdotal reports such as patients in financial difficulties seeking the 'unofficial' care of a family doctor abound. Obviously, many of these cases that receive treatment at home will remain unregistered. To date, there is no data assessing or speculating on the magnitude of unregistered cases.

3.3. Prevalence of Hepatitis B Infection

Relying on acute case data to assess the prevalence of Hepatitis B infection in the population is insufficient. The proportion of Hepatitis B carriers (prevalent cases) in the population is a useful indicator for anticipating demand for services and identifying those at risk for chronic infection and sequellae such as cirrhosis and primary liver cancer [9]. Practice guidelines in Armenia recommend routine screening of two presumed healthy populations for Hepatitis B - blood donors and pregnant women. Due to financial constraints, however, this latter group is incompletely screened: the test is not currently covered under the government's basic benefits package and most families cannot afford the roughly $4 cost for one tests. According to official data of RCHEC [32], only 19.3% of the pregnant women registered in 1999 (n= 33 396) were screened for Hepatitis B. This figure is down from 27% in 1998. Of those screened, 0.2% in 1998 and 0.5% in 1999 were found to be sero-positive. While these low figures are quite encouraging and consistent with the overall prevalence data, they may misrepresent the true prevalence:

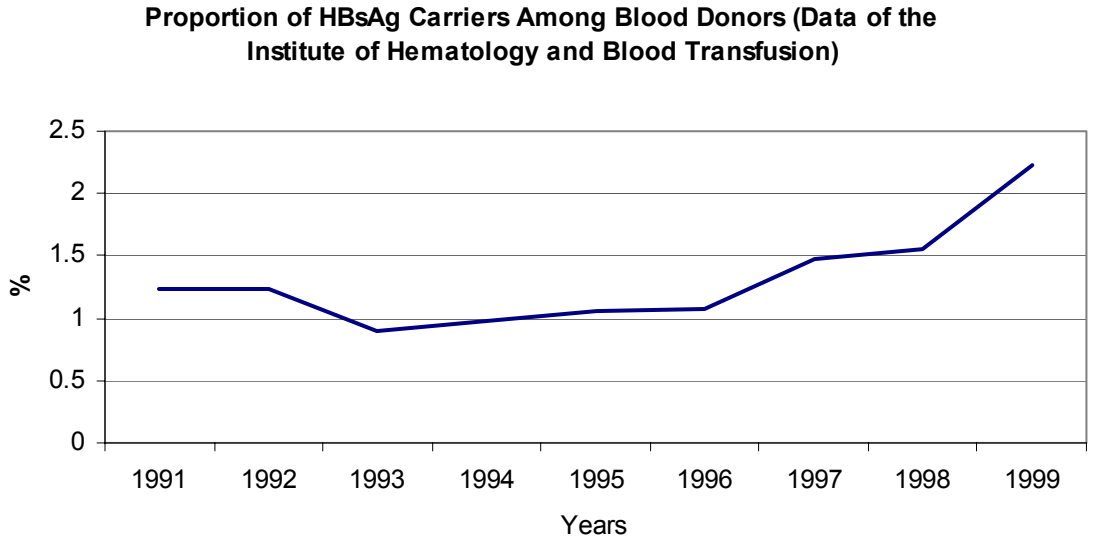
- The reliance on second-generation tests, especially in a population of presumed/known low prevalence, can lead to a disproportionate number of false-positive and of false negative results (*unknown impact on estimates*); and
- Selection bias is likely. The women opting for testing are more likely to include those affluent enough to afford the test and/or those suspecting a high degree of risk, and/or those with access to free sources of testing such as the blood bank (*underestimating true risk*).

Practice guidelines also call for the routine screening of several risk groups, among them health care providers, drug users, and patients with acute hepatitis and other acute and chronic diseases [8]. Again, screening of these groups has declined significantly during the last several years due to financial constraints. Data summarizing the proportion of HBsAg carriers among these groups

are provided in Table 3 (see Appendix 1). As indicated in this table, patients with acute hepatitis and chronic liver diseases; patients and health workers of hemodialysis departments; health workers of ambulance services; and drug users are the groups with the highest prevalence. The proportion of HBsAg positive cases among these groups ranged from 3.3% to 16.3% in 1999. While the data suffers the same limitations discussed above for the testing of pregnant women, the findings are consistent with the other data sources.

Blood Donor Data

The most reliable Hepatitis B prevalence data in Armenia comes from the Institute of Hematology and Blood Transfusion (Blood Bank) that routinely uses third-generation tests on all donated blood. According to the head of the laboratory, Dr. M. Garaseferyan, the overwhelming majority of donors are first-time donors who are giving blood specifically for their sick relatives and friends. Dr. M. Garaseferyan also indicated that their screening protocol requires confirmatory tests in the case of positive results; thus the specificity of the testing is high. It should be noted that the test results from this laboratory may include a number (< 1%) of samples from hepatitis patients (not blood donors), which can result in slight overestimation of the real prevalence. The reported prevalence of HBsAg among blood donors is provided below in graphical and tabular form.



Data of the Institute of Hematology and Blood Transfusion on HBsAg positive cases among blood donors during the period of 1991-1999, Yerevan

Year	*Number Tested*	*Percentage Positive*
1991	21 685	1.24
1992	19 418	1.24
1993	14 722	0.90
1994	14 201	0.97
1995	11 692	1.05
1996	11 623	1.07
1997	9 186	1.47
1998	9 576	1.56
1999	7 995	2.23

The prevalence of carriers has been increasing, climbing from 0.9% in 1993 to its current level of 2.23% in 1999. This trend may be due to improved sensitivity from the transition to third-generation tests over this interval, but is more likely reflective of a growing problem.

Population Research Data

The Scientific-Research Institute of Epidemiology, Virology and Medical Parasitology has undertaken several small-scale studies of hepatitis infection among presumed healthy populations. In a study by Melik-Andreasyan and colleagues in 1998 [24], 1 340 healthy persons from 16 to 65 years old, including 550 pregnant women, were tested for HBsAg and antibodies to Hepatitis C. The prevalence of Hepatitis B in this population was estimated at 1.4% and the prevalence of Hepatitis C at 1.6%. The study employed a convenience sampling methodology utilizing frozen serum collected over the past several years for other purposes. As such, its findings, although consistent with other data sources, may not be generalizeable.

Melik-Andreasyan also studied transmission of Hepatitis B virus among family members of patients suffering from acute Hepatitis B [25] and chronic Hepatitis B [26]. As expected, household members with an infected member were at substantially increased risk of hepatitis

than the general population (10.2% of family members of acute Hepatitis B cases and 24.8% of family members of chronic Hepatitis B cases were found to be infected with HBV). Implicated transmission routes included mechanical (parenteral manipulations) and natural (sexual and household contact). There is no information, however, whether the family members were healthy at the start.

Summary

While limited, the prevalence data paint a clear and consistent picture of low, but increasing, prevalence of Hepatitis B in the population of Armenia.

3.4. Proxy Measures: Chronic Liver Diseases

The burden of diseases associated with hepatitis provides another means of assessing its impact on a society. Such co-morbid diseases include cirrhosis, chronic hepatitis, and hepatocellular carcinoma. [10] When utilizing these diseases as proxies for the burden of Hepatitis B, one must account for the contribution of Hepatitis C to these diseases as well [11]. Several studies [27, 28, 29] indicate that the level of Hepatitis C infection is similar to, if not slightly higher than, that of Hepatitis B, but its presence in chronic liver disease patients may be considerably higher than that of Hepatitis B, making attributions of the role of Hepatitis B in these diseases difficult [30].

General

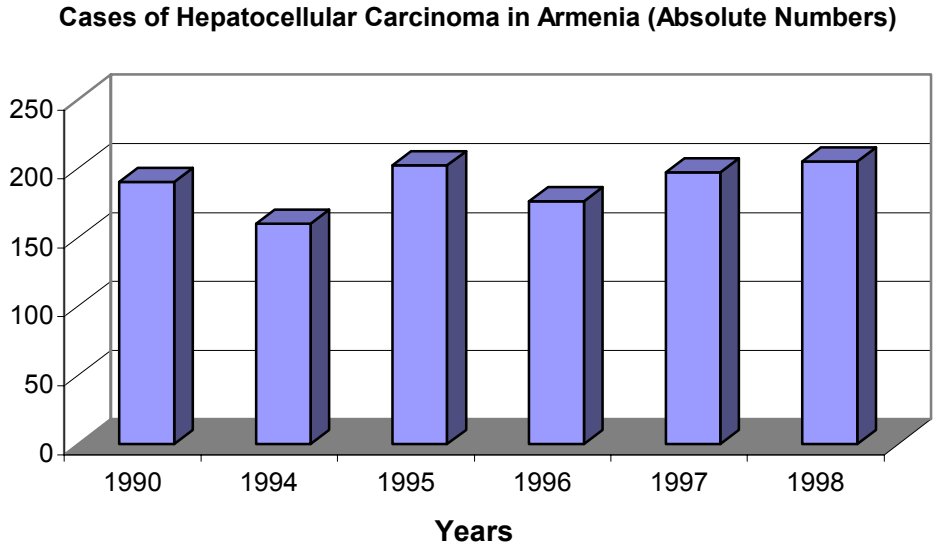
According to the existing data from the MOH, the incidence rate of chronic liver diseases and cirrhosis was 32 per 100 000 in 1998. The prevalence rate was 198 per 100 000. As data of this type are only available for 1997 and 1998 (see table below), interpretations of trend are impossible. Furthermore, the numbers and rates provided in this table may significantly underestimate the real prevalence of these diseases due to the combined effects of reduced access to/utilization of health services, poor registration procedures, and difficulties in estimating the true population size. The data are, however, consistent with a gradually increasing burden of hepatitis.

Data On Chronic Liver Diseases And Cirrhosis During 1997-1998 According To The MOH

	Incident Cases	Incidence Rate (per 100 000)	Prevalent Cases (registered)	Prevalence Rate (per 100 000)
1997	1 073	28.4	6 211	164.3
1998	1 213	32.0	7 508	198.0

Hepatocellular Carcinoma

Available data [31] on hepatocellular carcinoma suggest that its prevalence has remained uniform throughout the 1990s. (see also Table 5 in Appendix 1). MOH data show that cancer is the cause of 16.5% of all deaths in Armenia, of which liver cancer accounts for 5.4%. The data presented include cases reported through Oncological Dispensary, hospitals, and death certificates. However, people who died from hepatocellular carcinoma without ever having sought treatment for it will likely be overlooked as autopsies are seldom performed. Such biases could distort perceptions of the magnitude of the problem and the groups most at risk. Conversely, the lack of confirmatory histological examinations for identified cases raises the possibility that persons are inappropriately classified as cases.



Chapter 4: SYNTHESIS OF DATA

While the available data are limited and often derived from only a few sources, a number of patterns and observations emerge. This section will organize and distill these observations in a framework that lends itself to straightforward interpretation and the formulation of policy options. The following are the main conclusions that can be derived from the presented data:

Epidemiological findings

- Hepatitis B accounts for roughly one-third of all reported hepatitis cases.
- Children account for roughly one-third of all reported Hepatitis B cases; this proportion may be growing; suggesting a change in transmission patterns or a change in access to care.
- The case fatality rate for Hepatitis B is low, but children, especially those under 2, have higher case fatality rates than older individuals.
- Given the declining morbidity of acute Hepatitis B during the last decade and the increasing prevalence of Hepatitis B carriers in the population of Armenia, it can be concluded that the transmission patterns are shifting from artificial to natural modes.
- Estimates from a variety of sources, limited as they may be, all support a general population estimate of roughly 2% prevalence and also indicate the rate is beginning to rise.
- As a group, pregnant women appear to be slightly below the population risk (approximately 1.5%).
- The burden of hepatitis-related complications such as liver disease and hepatocellular cancer appear quite low, especially in comparison with other parts of the world. This lends credence to the long-term observations of low prevalence of hepatitis infection in the population. Additionally, these diseases represent long-term and poorly managed outcomes of hepatitis infection. As such, one would expect these indicators to lag behind changes in incidence/prevalence.

Systemic findings

- Systemic and societal factors are contributing to decreased access to and utilization of diagnostic and health services. Available technology is at the trailing edge of current practice and generally accessible only to the affluent and the acutely ill.
- The reliance on older testing methodology and the tendency of hepatitis infection to be asymptomatic compound the difficulties in early diagnosis and treatment of hepatitis infection.
- The increasingly complicated vaccination schedule/well child visits may contribute to the poor timeliness of vaccine coverage.
- The crude coverage rates suggest that vaccination is still one of the highly functioning components of the health care system and its strength should be drawn upon for attacking the growing problem of Hepatitis B infection. Efforts should focus on enhancing the timeliness of vaccination as well as assuring the comprehensiveness of coverage.

For reasons that are not readily apparent, Armenia seems to have delayed the epidemic of Hepatitis B infection present in the surrounding countries. While the current estimates of infection still place Armenia in the low-prevalence category, there are indications that an upward trend has begun. There are insufficient data to speculate at this time whether the recently implemented program to vaccinate children will stem this trend or not.

Chapter 5: CONCLUSION & RECOMMENDATIONS

- Given the high long-term costs of treatment and lost productivity, the relatively low endemicity of the disease, and the availability of cost-effective vaccinations, strategies to combat Hepatitis B should focus on primary prevention through universal immunization. Given the data presented in this report, the decision to implement universal vaccination of infants was indeed timely.

- Efforts to strengthen the NIP as recommended in the recent evaluation (6) should be implemented as soon as possible, specifically prioritizing efforts to improve the timely delivery of vaccines. {*Diagram 3 in Appendix 2 presents a conceptual model for the failure to immunize by Guyer B. and colleagues [33] that may be useful in examining practices and systems for opportunities to improve timely vaccination. Further research would be needed to verify whether this model is appropriate to the Armenian context}*.

- The available data strongly suggest an important role of perinatal transmission of Hepatitis B. The proportion of new cases of HBV transmitted vertically may be quite low or as high as 50% according to the conservative estimation presented in Table 6 in Appendix 1. Given inherent limitations of the available data and the importance of the decision, a sero-prevalence survey of pregnant women should be used as a basis for assessing the risks and benefits of adjusting the immunization schedule for Hepatitis B to coincide with the DTP schedule. **In the absence of such data and without compelling evidence that a synchronized schedule would result in improved vaccine coverage, the safer course may be to retain the current schedule.**

- A long-term sustainable surveillance system should be established in order to address the information gaps regarding the incidence and prevalence of Hepatitis B in Armenia.

- Measures should be undertaken to increase perception of parents of the importance of timely vaccination of their children.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the contributions of Dr. Margarita Balasanyan, Dr. Gayane Melik-Andreassyan, and Dr. Robert McPherson who provided information and technical assistance during the preparation of this report.

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Appendix 1: Tables

TABLE 1

Routine Immunization Schedule (Republic of Armenia, 2000)

Age / Vaccine	During 24 hours after birth	1.5 mo.	3 mo.	4.5 mo.	6 mo.	12 mo.	15 mo.	18-24 mo.	3.5-4 yrs	6-7 yrs	16 yrs	Every 10 years
BCG	X									X[3]		
HBV	X	X			X							
DTP			X	X	X			X				
DT-M										X		X
OPV			X	X	X			X[1]		X		
Measles						X			X[2]			
Mumps							X					

Source: Republican Center of Hygiene and Epidemiological Control of the Republic of Armenia

[1] Two-fold OPV revaccination
[2] Administrated not earlier than two years after vaccination
[3] Administrated to those who do not have a scar

TABLE 2

Absolute Numbers and Incidence Rate of Acute Hepatitis in Armenia, 1988-1999

	YEAR	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999
Viral Hepatitis (Total)	Abs. number	4425	9224	7196	3963	3767	3946	3033	2986	3389	3207	3255	2761
	Per 100000	127.9	280.4	202.2	109.6	102.2	105.7	80.8	79.5	89.8	84.7	85.8	74.6
Viral Hepatitis A	Abs. number			6163	3314	3225	3415	2540	2608	3058	2954	2885	2527
	Per 100000			173.2	91.6	87.5	91.8	67.7	69.4	81.0	78.0	76.0	68.3
Viral Hepatitis B	Abs. number	824	774	793	602	501	484	473	360	333	253	263	229
	Per 100000	23.8	23.5	22.3	16.7	13.6	13.0	12.6	9.6	8.8	6.7	6.9	6.2

Sources: MOH; Republican Center of Hygiene and Epidemiological Control of the Republic of Armenia; MOH publication: Health and Care of Public Health, Statistical Collection, Armenia, 1998

TABLE 3

Percentage of HBsAg carriers among Different Populations in Republic of Armenia, 1998-1999

Category	1998 year			1999 year		
	Total	% tested	% positive	Total	% tested	% positive
Groups at Particular Risk						
Patients with Acute Hepatitis	3401	82.6	8.5	3165	79.3	9.1
Patients with Chronic Hepatitis	1023	5.6	5.3	1130	12.9	3.4
Drug users	516	5.8	0.0	437	8.2	2.8
Healthy Populations						
Blood donors	16392	99.3	1.5	15880	99.8	1.9
Pregnant women	32676	26.9	0.2	33396	19.3	0.5
Health Care Providers						
Blood service workers	213	91.1	0.0	230	82.2	0.0
Hemodialysis workers	64	64.1	0.0	75	81.3	3.3
Surgical service workers	1890	58.8	3.7	2323	50.8	0.6
Urological service workers	156	57.1	0.0	212	35.4	0.0
Anesthesiologists	460	62.2	0.0	312	55.1	0.0
Rehabilitation service workers	243	55.1	0.0	362	46.4	0.0
Hematological service workers	134	100.0	35.1	125	41.6	0.0
Dental service workers	1289	44.4	0.0	1186	45.1	0.0
Gynecological service workers	2470	67.9	0.1	2443	57.1	0.2
Gastroenterologists	255	60.8	0.0	260	36.5	0.0
Emergency Services' Workers	736	18.8	0.7	749	12.3	3.3
Workers of Clinical and Biochemical Laboratories	1124	54.8	0.2	1177	47.7	0.2

(Continuation of the Table 3)

Category	1998 year			1999 year		
	Total	**% tested**	**% positive**	**Total**	**% tested**	**% positive**
Patients						
Hemodialysis patients	196	93.4	16.4	120	66.7	16.3
Cardiovascular surgery Patients	49	91.8	2.2	526	0.0	
Pulmonary Surgery Patients	18	22.2	0.0	0		
Hemotological Patients	0		0.0	0		
Tuberculosis patients	1105	8.1	0.0	976	12.9	0.8
Oncological patients	936	9.1	0.0	1255	2.9	0.0
Psychiatric patients	473	15.6	0.0	878	4.3	0.0
Neurological patients	845	10.2	0.0	851	1.8	0.0
STD patients	728	59.6	0.7	401	35.4	2.1
Children						
Newborns from HBsAg positive mothers	3	33.3	0.0	2	100.0	0.0
Children under 1 year received hemotransfusion	22	77.3	5.9	39	0.0	
Children of orphanages	204	0.0	0.0	123	0.8	0.0
Children of special institutions	12	0.0	0.0	0		
Total	***64232***	***48.8***	***1.0***	***65468***	***42.0***	***1.0***

Source: Republican Center of Hygiene and Epidemiological Control of the Republic of Armenia

TABLE 4

Incident Cases and Deaths from Acute Hepatitis B in Armenia, 1991-1999

Year	Total # of Incident Cases	Total < 14 year	Including			Total # of Deaths	Total Deaths ≤ 14 year	Including		
			0-2 years	3-6 years	7-14 years			0-2 years	3-6 years	7-14 years
1991	602	151	35	66	50	5	3	3	-	-
1992	501	113	24	39	50	8	1	1	-	-
1993	484	123	12	42	69	6	4	1	-	3
1994	473	95	6	27	62	1	-	-	-	-
1995	360	85	4	20	61	1	1	-	-	1
1996	333	113	4	20	89	1	1	-	1	-
1997	253	66	5	13	48	1	1	-	-	1
1998	263	78	5	19	54	2	-	-	-	-
1999	229	90	6	17	67	2	1	1	-	-
TOTAL	3498	914	101	263	550	27	12	6	1	5

Source: Republican Center of Hygiene and Epidemiological Control of the Republic of Armenia

TABLE 5

Age and Gender Distribution of Cases of Primary Liver Cancer in Armenia (1990, 1994-1998)

Year / Age	1990		1994				1995				1996				1997				1998			
			Yerevan		Marzes		Yerevan		Marzes		Yerevan		Marzes		Yerevan		Marzes		Yerevan		Marzes	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
≤ 39			1	0	2	2	1	1	2	6	0	2	3	3	0	1	1	4	0	1	4	3
40-49			2	3	13	2	4	0	6	4	7	2	4	4	4	5	4	4	1	2	2	6
50-59			6	3	7	11	12	10	13	10	5	5	11	6	8	4	14	6	13	2	4	8
60-69			12	10	27	15	15	12	34	24	19	8	28	21	14	17	22	23	19	10	30	32
≥ 70			8	10	15	11	10	8	12	18	9	7	20	12	12	16	16	22	13	17	20	18
Total 1	105	85	29	26	64	41	42	31	67	62	40	24	66	46	38	43	57	59	46	32	60	67
Total 2			55		105		73		129		64		112		81		116		78		127	
Total 3	190		160				202				176				197				205			

Sources: MOH; Republican Oncological Dispensary

TABLE 6

Armenia: Extrapolated Age at Time of Hepatitis B Infection
(derived from average data for 1991-1999)

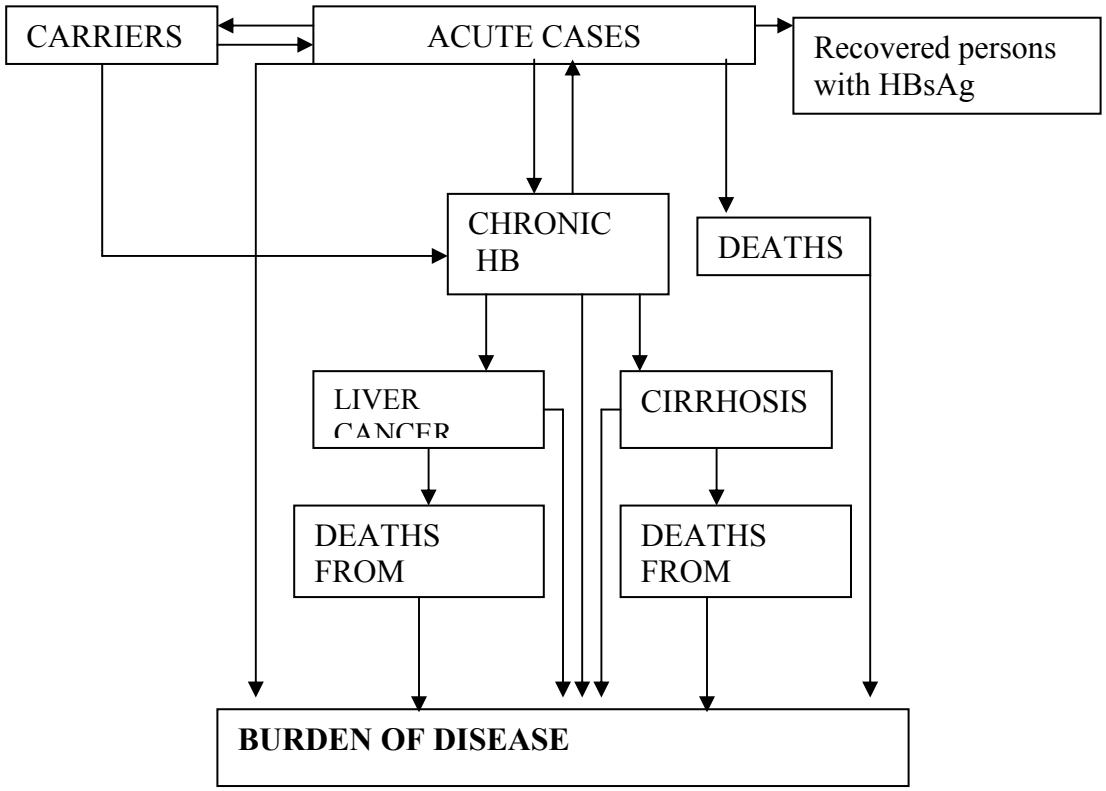
Age	Estimated % of Reported to Total Infections[1]	Interpolated Age Distribution 'A' (conservative) [2]			Interpolated Age Distribution 'B' ('best guess') [2]		
		Mean Annual Incident Cases (Registered)	Number Infected	Proportion of All Infected	Mean Annual Incident Cases (Registered)	Number Infected	Proportion of All Infected
<1	1%	11.2	1120	49.1	4.44	444	26.5
1-5	10%	29.2	292	12.8	36	360	21.5
>5	40%	348.2	870.5	38.1	348.2	870.5	52
Total		388.7	2285.5	100	388.7	1674.5	100

Note: The age distribution of the data provided by RCHEC (Table 4) did not correspond to the WHO intervals. Distributions A and B represent two different approaches to apportioning the RCHEC data into the WHO intervals.

[1] Data source is WHO, 1999 [10]
[2] Data source is RCHEC [31]

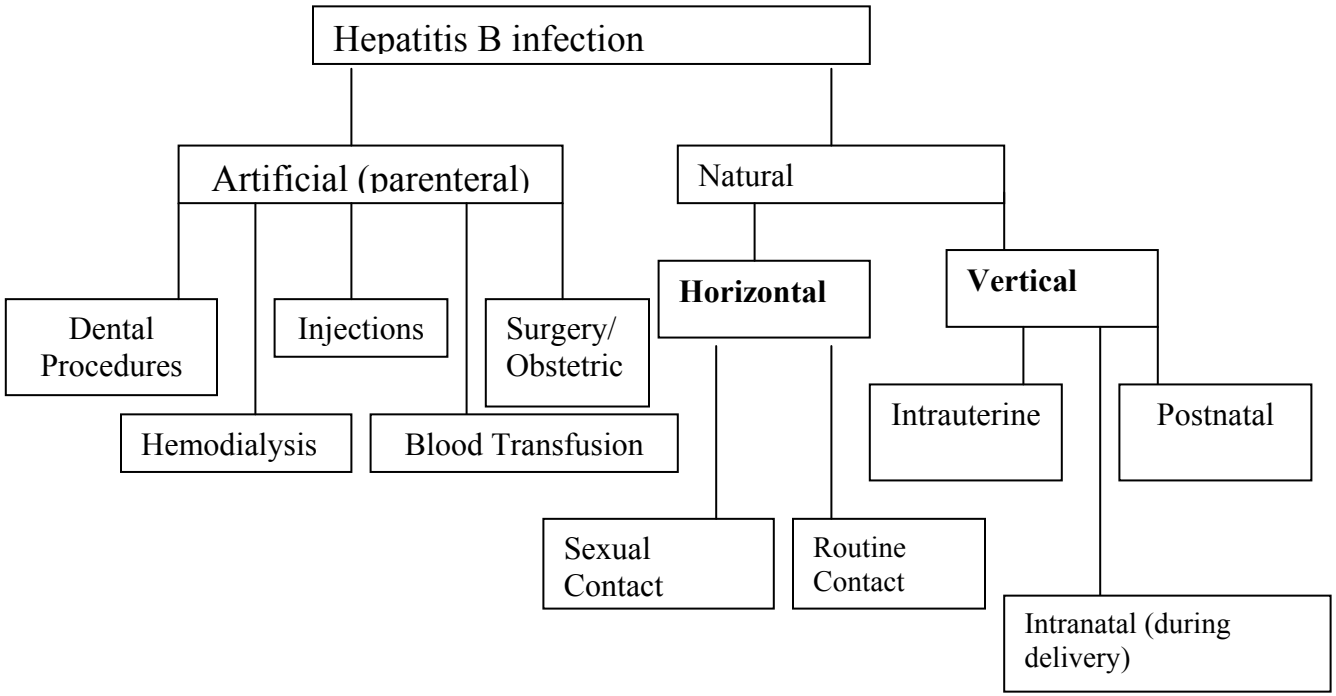
Appendix 2: Diagrams

Diagram 1. Conceptual Framework of Burden of Disease Associated with Hepatitis B Infection



Derived from information reported by WHO, 1999

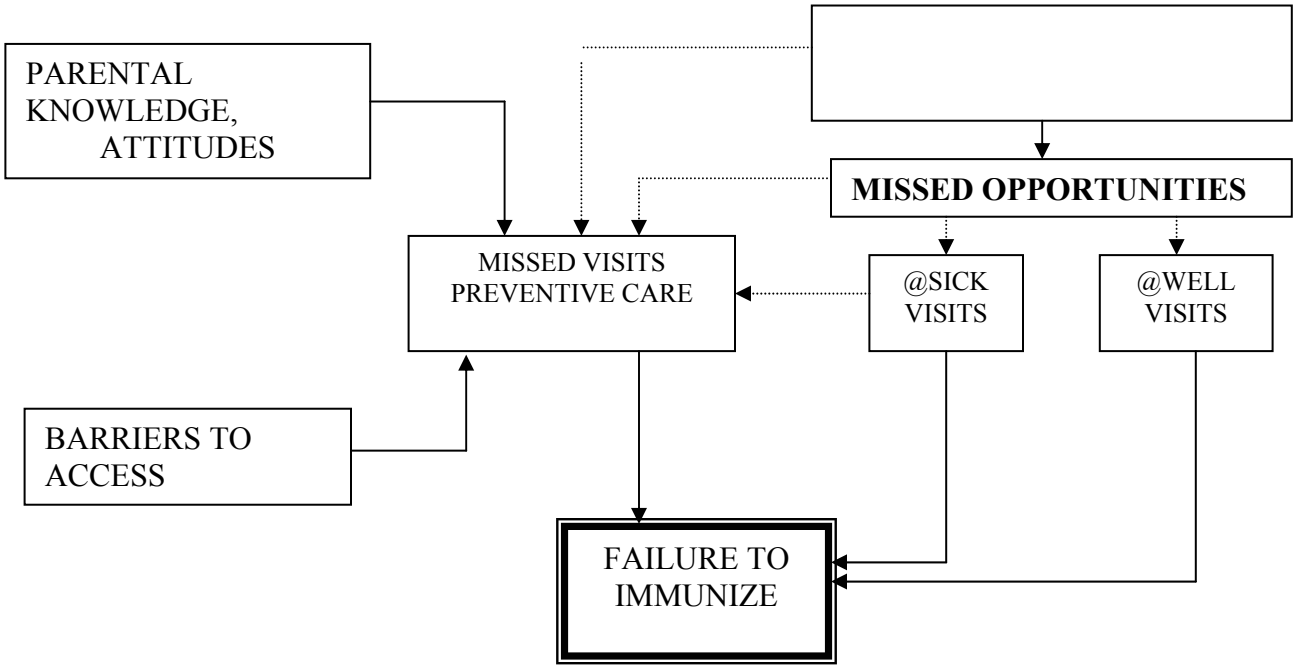
Diagram 2. Conceptual Framework of Hepatitis B Transmission



Partially derived from the information presented by FitzSimons D. & Van Damm P.

Diagram 3. Conceptual Framework for Failure to Immunize

(Guyer B. [33])



Appendix 3: List of Persons Contacted

List of Persons Contacted

Name	***Title***
Margarita Balasanyan	*Manager of the National Immunization Program*
Gayane Melik-Andreasyan	*Head, Virology Laboratory in the Scientific-Research Institute of Epidemiology, Virology & Parasitology*
Laura Danielyan	*Head of the MOH Statistical Department*
Romella Asatyan	*Chief Specialist of the MOH Mother & Child Health Department*
Poghos Poghossyan	*Statistician of the Oncology Dispensary*
Melkon Garaseferyan	*Head of Serological Laboratory, Blood Bank*
Arthur Melkonyan	*Director of "Promtest" (PCR) laboratory*
Karen Nahapetyan	*Head of "Promtest" (PCR) laboratory*
Larisa Karabekova	*"ArmMedTechnica", Chief of Deparment*
Hamayak Avagyan	*Head of Diagnostic Laboratory at the National Institute of Health*
Ada Sasunyan	*Head of Women Consultation # 6*
Ephrosia Nahapetyan	*Head of Women Consultation # 8*
Janibek Gevorgyan	*Chief children pathologist, MOH*
Ara Asoyan	*Director of the Republican Hospital of Infectious Diseases*
Svetlana Manukyan	*Pathologist, Republican Hospital of Infectious Diseases*
Robert Ambarjanyan	*Pathologist, Republican Hospital*
Paytsar Dilbaryan	*Epidemiologist, MOH*
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