

Det helsevitenskapelige fakultet



Prevention of mother to child transmission of hepatitis B: A global challenge

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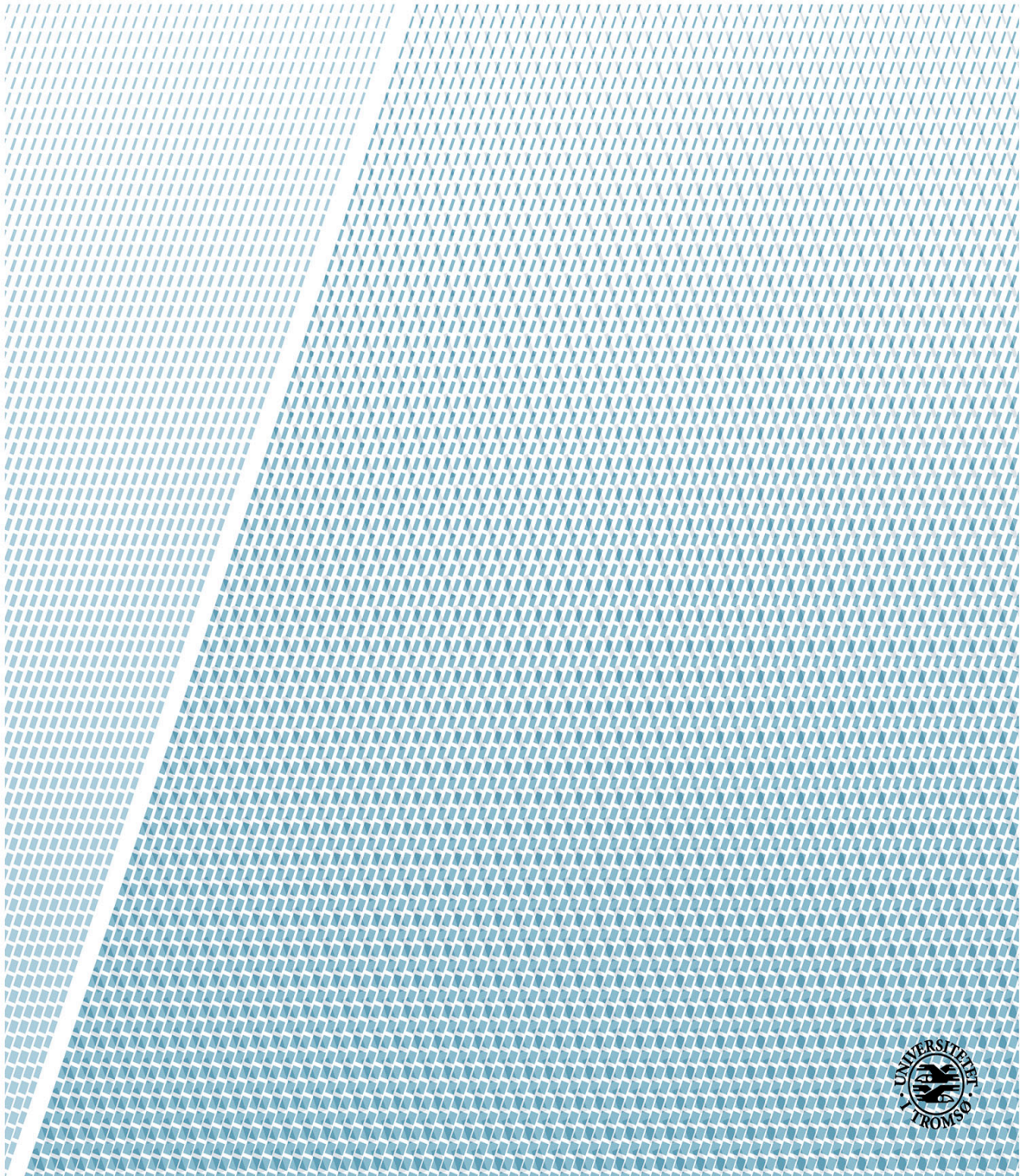


Table of Contents

FOREWORD	III
LIST OF ABBREVIATIONS	IV
SUMMARY	IX
1. INTRODUCTION	1
2. BACKGROUND	1
3. METHODOLOGY AND PROCESS	2
3.1 <i>Search strategy</i>	2
3.2 <i>Risk of bias</i>	2
3.3 <i>The process</i>	3
4. INTRODUCTION TO THE VIRUS- VIROLOGY	3
4.1 <i>Acute hepatitis B virus infection: focus on pregnant and children</i>	4
4.2 <i>Chronic hepatitis B infection: focus on pregnant and children</i>	5
4.3 <i>Immune escape in CHB- why are infected neonates more prone to develop CHB?</i>	7
5. MTCT OF HBV: MECHANISMS AND INFLUENCING FACTORS	8
5.1 <i>Intrauterine transmission</i>	9
5.2 <i>Intrapartum transmission</i>	9
5.3 <i>Puerperal transmission</i>	9
6. DIAGNOSIS AND STAGING	10
7. MONOVALENT HBV VACCINE AND HEPATITIS B IMMUNOGLOBULIN	11
7.1 <i>Follow-up after vaccination</i>	12
8. STRATEGIES FOR PREVENTING MTCT OF HBV	12
8.1 <i>Current strategy of post exposure prophylaxis (PEP). Recommendations by WHO and CDC</i>	12
8.2 <i>Current guidelines in Norway by the Norwegian Institute of Public Health</i>	14
8.3 <i>Maternal screening methods</i>	15
8.4 <i>Maternal vaccination strategies</i>	16
8.5 <i>Antiviral therapy</i>	16
8.6 <i>Postpartum strategies</i>	17
8.7 <i>Preventing MTCT of HBV at a structural level: technical strategies to update national strategies.</i> ..	18
10. PERINATAL TRANSMISSION OF HBV IN VIETNAM AND CAMBODIA: AN INTRODUCTION TO TWO HIGH-ENDEMIC COUNTRIES	19
11. DISCUSSION	21
12. CONCLUSION	23
LIST OF REFERENCES	24

Foreword

Looking back at five years as a medical student global health related topics has only been a very small part of the curriculum. Interestingly enough when looking at the situation in the world today where global health related questions are central among others due to increased globalisation and an increasing number of asylum seekers and refugees as a consequence of poverty, conflicts and accelerating climate changes. Global health, whether we realize it or not, is becoming an important part of our daily life. Throughout the past five years as a medical student I have got the chance to experience six different health authorities in Sub-Saharan countries, including hospitals and clinics. Much attention is drawn to the great infectious burden of malaria, tuberculosis and HIV. On the other hand little attention has been upon mother to child transmission of hepatitis B virus, even during a semester in Gynaecology and Obstetrics in Zimbabwe, the subject was never discussed. Knowing the epidemiology and the burden of the disease I would like to gain more knowledge about the virus and the transmission between mother and child. Moreover, I would like to better understand prevention strategies and why vaccination coverage concerning hepatitis B virus show great differences among countries and how the design of international guidelines is been developed.

I would like to express my gratitude to my supervisor Tore Gutteberg, for the useful comments, remarks and for not to mention his engagement upon the topic and through the learning process of writing this assignment.

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List of abbreviations

AASLD

American Association for the Study of Liver Diseases. A non-profit organization of scientists and health care professionals committed to preventing and curing liver disease

Acute HBV infection

Initial infection, often self-limiting and characterized by acute inflammation and hepatocellular necrosis. Clinically it presents with different signs and symptoms, including nonspecific symptoms such as anorexia, nausea or malaise and clinical hepatitis with jaundice

Adaptive immune system

Also known as the acquired immune system. Characterized by highly specialized cells and processes that eliminate or prevent pathogen growth and create immunological memory. It consists of antigen-presenting cells, such as B- and T-cells. The processes of acquired immunity are the basis of vaccination

AIDS

Acquired immunodeficiency syndrome. AIDS is following an initial infection with human immunodeficiency virus. As the infection progresses, it interferes with the immune system, increasing the risk of common opportunistic infections

ALT

Alanine transferase, also called alanine aminotransferase (ALAT). An enzyme, commonly found in the liver, but also present in various body tissues. Hepatocellular injury will release ALT into the circulation system. ALT will typically fluctuate in persons with chronic hepatitis B infection and it requires several measurements to determine the trend. Norwegian reference ranges: female 10-45 IU/L, male 10-70 IU/L

Antigen

A substance/molecule capable of inducing an immune response to produce antibodies against it

Antibody

Also known as immunoglobulin (Ig). Mainly produced by plasma cells that are used by the immune system to identify and neutralize pathogens such as bacteria and viruses. The antibody recognizes the antigen

APRI

Aspartate aminotransferase-to-platelet ratio index. An index to estimate hepatic fibrosis based on a formula derived from aspartate aminotransferase (AST) and platelet concentrations

ART

Antiretroviral therapy. Medications to suppress virus replication

anti-HBc

Hepatitis B core antibody. Anti-HBc antibodies are detectable in both acute and chronic infection, thus not neutralizing antibodies

anti-HBe

Antibody to hepatitis B e antigen. Detected in persons with lower levels of HBV replication, could also be in HBeAg-negative individuals (HBV that does not express HBeAg)

anti-HBs

Antibody to hepatitis B surface antigen. Immunologic response to HBV vaccination or during a recovery phase from an acute infection. Indicating immunity booster dose

Case fatality rate

In epidemiology, a case fatality rate is the proportion of deaths within a designated population of “cases”, over the progression of the disease

cccDNA

Covalently closed circular DNA. Mini-chromosome that serves as the template for the viral transcription, during viral replication cycle of HBV

Cellular mediated immunity

Immune response involving activation of phagocytes, antigen-specific cytotoxic T-lymphocytes and the release of various cytokines in response to an antigen

CHB

Chronic hepatitis B. A chronic infection with hepatitis B virus. Defined as persistence of hepatitis B surface antigen (HBsAg) for at least six months, following an acute infection with HBV

CMIA

Chemiluminescent Microparticle Immunoassay. Serological diagnostic technique to detect antigen in blood or serum. The technique is based on the characteristics of antigens binding to commercially produced antibodies with chemiluminescent antigen

CDC

Centers for Disease Control and Prevention. Leading national public health institute of the United States. Its main goal is to protect public health and safety through the control and prevention of disease, injury, and disability

DTP

Diphtheria-tetanus-pertussis. A vaccine made of diphtheria toxoid, tetanus toxoid, and pertussis vaccine given in one dose

EASL

European Association for the Study of the Liver. Founded to promote research on the liver and its pathology and to improve therapy for liver disorders

GAVI

The Vaccine Alliance (formerly the Global Alliance for Vaccines and Immunization). A public-private global health partnership committed to increasing access to immunization in poor countries

HBcAg

Hepatitis B core antigen. HBV core protein that is coated with HBsAg, thus not detectable in free form in serum

HBeAg

Hepatitis B e antigen. Viral protein, usually a marker of a highly replicative phase of the virus

HBIG

Hepatitis B immune globulin. A solution of antibodies that are able to attach to the hepatitis B viruses and cause them to be destroyed. HBIG will prevent infection until the vaccine takes effect

HBsAg

Hepatitis B surface antigen. Glycoprotein attached to the envelope. May be detected in the blood in an acute or chronic hepatitis B infection as one of several viral proteins

HBV

Hepatitis B virus

HBV-DNA

Hepatitis B virus genom. May be detected and quantified in serum. HBV-DNA found in serum increases proportionally with circulating viral particles. Measured in IU/mL, 1 UL/mL ~ 5,3 copies/mL. Levels below 15 IU/mL are undetectable for laboratory assays

HCC

Hepatocellular carcinoma. Cancer with origin from the hepatocytes

HCV

Hepatitis C virus

HEELP

Haemolysis elevated liver enzymes and low platelet syndrome. It represents a severe form of preeclampsia. Associate with serious hepatic manifestations, including infarction, haemorrhage, and rupture

HIV

Human immunodeficiency virus. A retrovirus that causes HIV infection and over the time AIDS.

Humoral immunity

Immune response that refers to antibody production following Th2 activation

HLA

Human leukocyte antigen. A cell-surface protein responsible for the regulation of the immune system

Horizontal transmission

Here: transmission of an infectious disease from one individual to another, by either direct contact or indirect contact

IgG anti-HBc

Immunoglobulin G to hepatitis B core protein. Subclass of anti-HBc indicating/detectable in past or current infection

IgM anti-HBc

Immunoglobulin M to hepatitis B core protein. Subclass of anti-HBc indicating acute hepatitis B, but can be detected in active chronic HBV

Innate immune system

Involves of complement, phagocytes and natural killer cells. In contrast to the adaptive immune system, the innate immune system lack immunological memory and will respond in the same way with each infection

MTCT

Mother to child transmission. A vertically transmitted infection is an infection caused by bacteria, viruses, or in rare cases, parasites transmitted directly from the mother to an embryo, fetus, or baby during pregnancy or childbirth

MSIS

Norwegian Surveillance System for Communicable Diseases. Microbiological laboratories analyzing specimens from humans, all doctors in Norway are required by law to notify cases of certain diseases, included hepatitis B, to the MSIS central unit at Norwegian Institute of Public Health

NIT

Non-invasive tests.

NF-kB

Nuclear factor-kappaB. A protein complex that controls transcription of DNA, cytokine production and cell survival

NTCP

Sodium-taurocholate co-transporting polypeptide. A liver bile acid transporter

Occult infection

Occult HBV infection. Typically individuals who have cleared the hepatitis B surface antigen, HBsAg-negative, but can have low levels of HBV-DNA (<200 IU/mL)

PCR

Polymerase chain reaction. A method used in molecular biology to amplify a single copy or a few copies of a piece of DNA to millions of copies of that particular DNA sequence

PEP

Post exposure prophylaxis. Combination of HBIG and a monovalent HepB vaccine given within 24 hours of birth

Polymorphism

Here: genetic polymorphism. Occurrence in the same population of two or more alleles at one locus, each with different frequency

RAVN

Resistance against Antivirals in Norway. National surveillance system including following viruses: influenza virus, HIV-1, hepatitis B virus, cytomegalovirus and herpes simplex virus, with focus on the HIV and influenza

RNA

Ribonucleic acid. Polymeric molecule consisting of nucleic acids found as a single-strand. Hepatitis C virus encode its genetic information using RNA genome

Transient elastography

FibroScan. A technique to measure grade of liver fibroses through the detection of liver stiffness using ultrasound

TDF

Tenofovir disoproxil fumarate. Antiretroviral medication used to prevent and treat HIV/AIDS and to treat chronic hepatitis B

TORCH

Toxoplasmosis, other (syphilis), rubella, cytomegalovirus, herpes simplex virus. A group of perinatal infections that may have similar clinical presentations, including rash and ocular findings

UNICEF

United Nations Children's Emergency Fund. A program that provides long-term humanitarian and developmental assistance to children and mothers in developing countries

Vertical transmission

Here: Transmission of an infectious disease from parent to offspring, such as perinatal transmission

VL

Viral load. Hepatitis B viral load in serum, same as HBV DNA. Measured in IU/mL

WHO

World Health Organization. Specialized agency in United Nations that is concerned with international public health

Summary

Globally, mother to child transmission (MTCT) of hepatitis B virus (HBV) is the major route of transmission, while horizontal transmission, between adults, dominates in countries such as Norway. 2 billion people worldwide have serologic evidence of past or present infection with hepatitis, emphasizing that this infectious disease should be acknowledged as a global health problem in line with HIV, tuberculosis and malaria. MTCT of hepatitis B is the most important factor for developing a persistent infection, thus the risk of chronicity is inversely proportional with age, and most of the newborns (90%), to hepatitis B positive mothers, will get the virus without any prevention strategies. This is leading us to the focus of this assignment upon the prevention of mother to child transmission of hepatitis B. Despite an existing and effective vaccine and immunoprophylaxis regime, the implementation of immunoprophylaxis in developing countries has been challenging. The infections burden of the disease is well established in highly endemic East Asia where the prevalence is estimated to be above 5% and the virus is one of the major infectious causes of death. Vietnam and Cambodia are two high endemic countries facing great challenges concerning the combat against MTCT of the virus. The main focus on prevention strategies should be to obtain better coverage of the monovalent HBV vaccine and HBV immunoglobulin, timely after birth. Additionally, antiviral therapies to decrease the hepatitis B viral concentrations in the mother before delivery will be important in future. This assignment is a literature study and gives an introduction to the virus and the major routes of MTCT. Moreover, it looks into current guidelines by WHO and Centres for Disease Control and Prevention (CDC) and discusses prevention strategies, and also gives an overview on the situation in Norway today. It will point out research gaps and the need for policy changes, including better national plans for serosurveys. However, the question of how to prevent MTCT of HBV is more intricate than it seemingly looks like, there are many challenges and factor to take into consideration, factor that are not so evident for decision makers living in our part of the world.

Finally, without better control of the transmission between mother and child of the virus in high endemic East Asia, control at a global level will be difficult to obtain. Hopefully this assignment can contribute to put focus on the infections disease of the virus.

1. Introduction

According to the most recent estimates from the World Health Organization (WHO), about 240 million people are chronically infected with hepatitis B virus (HBV) [1, 2], 3,6% of the world's population. An estimated 686 000 people will annually die as a consequence of complications to the HBV infection, either acute or chronic [3]. It is further estimated that 2 billion people have serologic evidence of past or present infection, with East Asia as one of the regions in the world with highest prevalence (<5 %) [4]. The virus is one of the major infectious cause of death in the region, ahead of malaria, tuberculosis and Human Immunodeficiency Virus (HIV) [5].

In Asia vertical transmission of HBV, also known as mother to child transmission (MTCT), is the major route of transmission [6]. According to previous studies [7] vertical transmission, particularly during the perinatal period, is pointed out to be the most important phase for the prevention strategies against developing a chronic hepatitis B (CHB) infection. Without vaccination about 50% of the children, with Hepatitis B surface antigen (HBsAg) positive mothers, will get the virus. If the transmission occurs during the perinatal period, and with a HBsAg and hepatitis B e antigen (HBeAg) positive mother, 90% will develop a chronic HBV infection without immunoprophylaxis [6, 8, 9]. In contrast, the risk of a chronic HBV infection decreases to 30% if the transmission takes place at the age of between one and four. Furthermore, horizontal transmission to a healthy adult will in less than 5% of the infections develop into a chronic infection [4]. This gives us an inversely proportional risk of developing chronic HBV infection to the age at time of exposure, which will be discussed further below. China is a good example to emphasise the consequences of perinatal transmission. The country has a 94% coverage of a three-dose HBV vaccination, but MTCT still accounts for 40-50% of new infections [10]. Given what we know about 90% risk of developing a CHB infection if transmission occurs perinatally, it is obvious that HBV still remain a major public health problem, as newly published literature also points out [8, 11, 12]. This again emphasises the importance of preventing MTCT as well as immunization [13], which this assignment will try to cover. Looking at existing global and regional prevention strategies to battle Human Immunodeficiency virus (HIV), tuberculosis and malaria, the fight against MTCT of HBV seems to be coming in second line [12, 14]. However, WHO newly launched a plan which sets targets for 2020, it includes among others 90% childhood vaccine coverage for HBV and 50% birth dose vaccine coverage to prevent MTCT [15].

2. Background

Consider the prevention of MTCT as an important component of reducing the global burden of CHB infection leads to the focus of this assignment. The main effort will be to look at the prevention strategies of HBV infection in the perinatal period. I will look into international, as well as national guidelines in Norway. To better understand the great differences in epidemiology of the virus I will look into the situation in East Asia, particularly in Vietnam and Cambodia. As a base I have used the WHO database to

find data upon vaccination rates in these two countries. This will hopefully give the readers a better understanding of how the global situation concerning the virus can vary so greatly. A basic understanding of the hepatitis B virology, host immune response and modes of transmission will be presented and used to better understand my main focus on perinatal infection prevention. Furthermore it seems reasonable to touch upon the mechanism behind the hepatitis B vaccination and current routines for diagnosis and staging of the disease. I would like to point out that the immunology presented is simplified to avoid losing track of the essentials of this assignment. The very important topic of co-infection with HIV is deliberately not presented, although this is highly problematic and a present issue. Finally, my aim is to address the major global health problems, not the minor and put the combat against hepatitis B on the agenda in line with HIV, malaria and tuberculosis.

3. Methodology and process

3.1 Search strategy

Studies and other relevant references for the assignment were identified through searches in electronic databases and guidelines. I have used PubMed and Medline for articles mainly published from January 2014 to get the latest research in a field of constant change. However, some of the literature used has been published before 2014. The search terms used in combination with hepatitis B were: “mother-to-child transmission”, “perinatal transmission”, “pregnancy”, “vaccine”, “Vietnam”, “Cambodia”, “neonatal”, “child”. Other relevant articles were identified through searches in Google Scholar. Central articles have also been looked up using Google Scholar to see other articles that have cited that particular article of interest. Especially was this used to follow the development of research within one topic from a couple of years back up to date. Scanning of reference lists of central articles has been used. Guidelines by WHO, AASLD, EASL, APASL, CDC and FHI concerning hepatitis positive pregnant and children born to positive mothers have carefully been read, but only some of the guidelines have been used in this assignment.

3.2 Risk of bias

As I started up with the research of this assignment I had a vision of how it would look like. My way of finding literature could possibly be affected by selection bias. However I have tried to find multiple, independent, references to support the topics, especially where literature seems to not be in consensus. The same was done with the guidelines, but as the extent of this assignment is limited, I have not included them all. For most of the articles included the author declared no conflict of interest. I would like to point out one of my experiences concerning newly published literature, which could be a weakness in this assignment. It is easy to be blinded by the date of publication, but the list of references is often built up on studies from many years back, typically in reviews. This might have been the case in this assignment as I have used a few reviews throughout. Publication bias might be a problem, as in all research, but my searches have been as broad as possible and only using independent databases. The data upon vaccination rates from WHO database is based on WHO/UNICEF estimates and not on official country estimates,

neither on coverage surveys. Interestingly the official country estimates in Vietnam and Cambodia concerning the birth dose are over all overestimated compared to WHO/UNICEF estimates. Looking at the three-dose vaccine, the data are identical. However, since the database is based on estimates and not coverage surveys the risk of incorrect estimations are present.

3.3 The process

The description of the project was handed in according to guidelines given by the university, thus due to a semester in Zimbabwe the whole process was difficult to start before returning to Norway in December 2014. My plan was initially to focus on the transmission of hepatitis between mother and child in Vietnam and Cambodia using national data upon vaccination coverage and seroprevalences. A shift of focus due to difficulties with data access and the fact that these data do not exist, lead to a shift toward a global perspective. However I have chosen to use Cambodia and Vietnam, two high endemic countries, to give insight in resource limited countries to better understand mother-to-child-transmission. As a substitution to national based data, I have chosen to use WHO databases, based on WHO/UNICEF estimates. With these data I have made some basic figures demonstrating vaccination coverage the past years using Excel. Moreover, the process has mainly been dependent on searches in literature and guidelines spring 2016. My supervisor, Tore Gutteberg, has always been available either on e-mail or for meetings, which has made the progress smooth.

4. Introduction to the virus- virology

HBV virions are DNA double-stranded enveloped virus [9], build up by an outer lipoprotein envelope containing three glycoproteins (viral surface antigens). It contains a polymerase, which also serves as a reverse transcriptase. HBsAg is one out of three glycoproteins attached to the envelope. Hepatitis B core antigen (HBcAg) is among others important in regulation of replication [16], and HBeAg is described to play a role in modulating the host immune response [17]. A liver bile acid transporter, sodium-taurocholate co-transporting polypeptide (NTCP), was newly discovered as the target for HBV to bind to the hepatocyte [18]. Subsequently, HBV enters the hepatocytes through either endocytosis or fusion with the viral lipoprotein envelope to the plasma membrane [19]. Furthermore, the core particles of the virus enters the nucleus where covalently closed circular DNA (cccDNA) is formed, figure 1 [16].

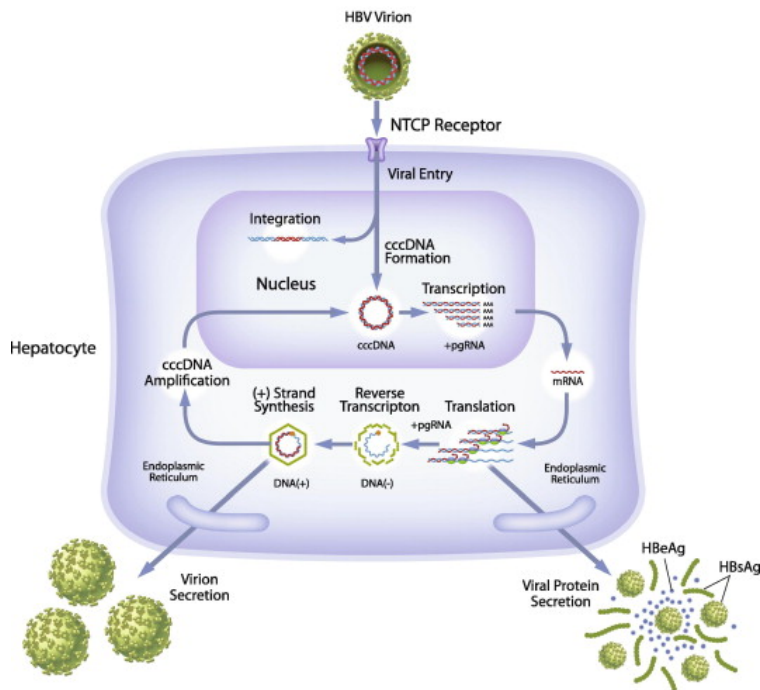


Figure 1. Lifecycle of HBV using a hepatocyte as host. The cycle includes viral entry, integration and cccDNA formation, viral transcription into mRNA and translation. Moreover the cycle is completed by virion secretion or the secretion of viral proteins, such as HBeAg and HBsAg, that can be detected in blood [16, 19].

HBV causes liver injury through immune-mediated killing of the hepatocyte and is also an oncogenic virus [20]. There are multiple viral genotypes and serotypes that have been identified. Each with a different geographical prevalence [16]. In total, it is identified eight HBV genotypes (A-H) and two temporary (I, J). Although the mechanism is not fully understood, these genotypes show differences in disease severity/ outcome of infection [9, 21]. Allelic dominance in genetic polymorphism in human leukocyte antigen (HLA) class II and nuclear factor-kappaB (NF-kB) may explain why people from East Asia more easily develop a chronic infection than in the European population [13], moreover genotype C and B is endemic in East Asia while E and D are more prevalent in Europe [22]. A higher rate of hepatocellular carcinoma (HCC) has been found in persons infected with genotypes C and F [20], and HBV genotype C is more rarely cleared by antiviral immunity than genotype B [13]. HBV has a high rate of replication and is as a consequence to this prone to undergo genetic mutations [20].

An infection with the hepatitis B virus can either be acute or chronic, and has a great variety of presentations. Clinically, individuals that undergoes an infection can be asymptomatic or have mild disease to a serious, and fulminant hepatitis [20].

4.1 Acute hepatitis B virus infection: focus on pregnant and children

The acute phase of the infection is often self-limiting and characterized by acute inflammation and hepatocellular necrosis. Clinically it presents with different signs and symptoms, including nonspecific

symptoms such as anorexia, nausea or malaise and clinical hepatitis with jaundice. Of individuals undergoing an acute infection 0.5-1% is thought to die from a fulminant hepatitis (case fatality rate) [20]. Worth mentioning is that children do have less chance of an clinical acute HBV infection, they often present as asymptomatic, while adult have about 30% chance of developing symptoms [23]. Acute HBV infection is serological characterized by the presence of HBsAg and Immunglobulin M (IgM) antibody to the hepatitis B core antigen (HBcAg). In the initial phase, the individual is also HBeAg positive, figure 2 [1]. Recovery, without progression to a chronic infection, is characterized by the disappearance of HBsAg with seroconversion to antibodies to hepatitis B surface antigen (anti-HBs), commonly within 3 months [20].

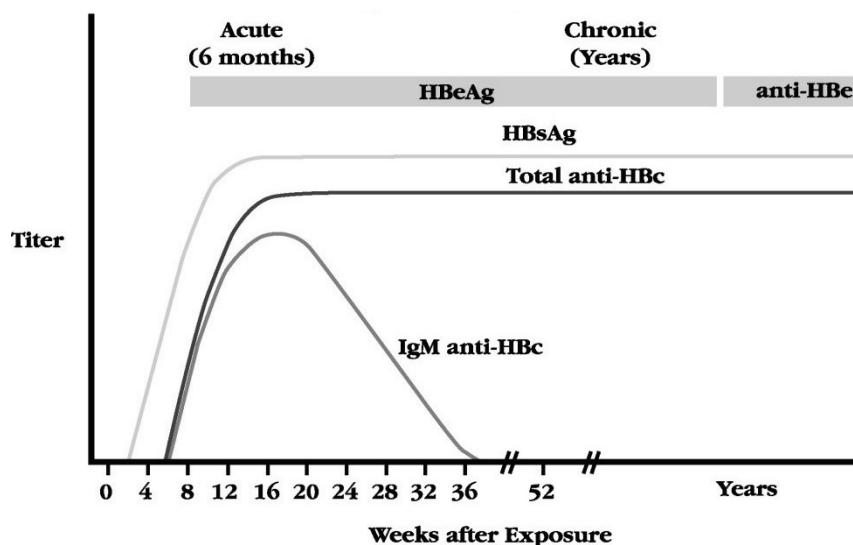


Figure 2. Typical serologic course of acute HBV infection with progression to chronic HBV infection [24].

A pregnant woman that undergoes an acute HBV infection mostly undergoes the same course as individuals in the general adult population. However, the risk of intrauterine transmission and preterm labour increases the later in gestation the infection occurs [9, 25]. Another important factor is the levels of viremia that the mother have in pregnancy. High levels of viremia increases the risk of vertical transmission, this will be discussed further below [25]. It is critical to differentiate between pregnancy associated acute liver disease and acute viral hepatitis. Pregnancy associated acute liver diseases includes preeclampsia, acute fatty liver of pregnancy and haemolysis elevated liver enzymes and low platelet syndrome (HELLP). The distinction of these states of disease and acute viral hepatitis is often difficult based on clinical signs and symptoms or nonspecific laboratory findings [26].

4.2 Chronic hepatitis B infection: focus on pregnant and children

A CHB infection is characterized and defined by the presence of detectable HBsAg (with or without coexisting HBeAg) in the blood or serum for more than six months. Regardless of associated active viral replication and proof of hepatocellular injury and inflammation, this is called a persistent HBV infection and is the principal marker of risk for developing chronic liver disease and liver cancer, see figure 2 [1,

20].

CHB includes a range of different presentations from inactive, leading to no significant liver disease, to gradually liver fibrosis and the development of liver cirrhosis [20]. HBV and hepatitis C virus (HCV) infection promote end-stage liver disease and liver cirrhosis and is found in 80-90% of patients with HCC. Replication state of the virus (HBV DNA levels), HBV genotype, duration of infection and co-infections with HCV or HIV are all factors that are reported to increase the risk of HCC. HCC is the most common form of liver cancer [27] and poses a great health problem on the individual patient as well as a socioeconomic burden, affecting less developed countries to a greater extent [11, 28].

As pointed out in the introduction, age at time of infection is a critical factor and determinant in regards to the risk of progressing to a chronic infection. The risk of obtaining CHB is inversely proportional with time of exposure, leaving neonates and children in a vulnerable group, figure 3.

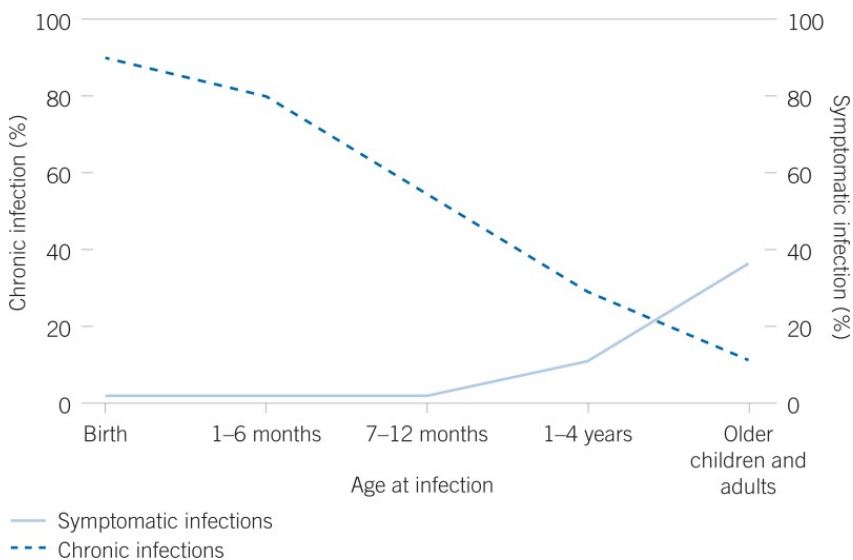


Figure 3. The risk of developing a CHB infection is inversely proportional with age of exposure, giving transmission at birth the greatest risk. As described in the figure, this group also have the fewest symptoms of an infection [20].

It was previous consensus that neonates established CHB because of the immaturity of their immune system. However, new research indicates that the immune system of neonates is efficient enough to respond immunologically. An individual that is infected perinatally will typically have a normal serum alanine aminotransferase (ALT) level, positive HBeAg, high HBV DNA levels and little liver inflammation [16]. This phase is now called “high replicative, low inflammatory” phase (first out of five phases) and can sustain many years without development [29], see figure 4. Mechanisms of transmission of HBV will be discussed below and the major route of transmission varies between continents. In more developed countries, where the prevalence is low, HBV infection typically occurs in adults and rather through sexual exposure or injection drug use, which leads to an immediate entry into the “immune clearance phase” (2nd

phase). Figure 4 includes all the five phases of CHB infection with an acute HBV infection as a starting point. However, it is pointed out in literature that these stages are not static, not always sequential, and not all patients go through all five phases [16, 30]. Table 1 summarizes all five phases of a chronic hepatitis B virus infection [16].

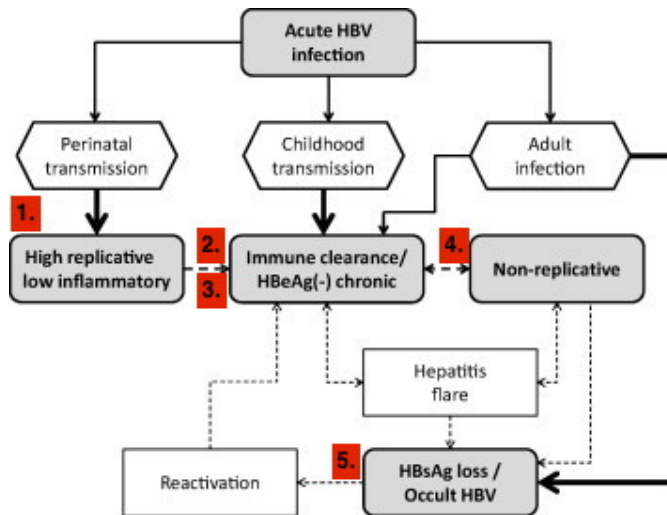


Figure 4. Five major phases of chronic hepatitis B virus infection. Perinatal transmission often results in “high-replicative, low-inflammatory” infection, phase 1 (previously called “immune tolerant”).

Transmission in childhood commonly leads to HBeAg negative (-) chronic hepatitis, characterized by persistent necroinflammation (phase 3), while adult infection commonly leads to immune clearance (phase 2) or “HBsAg loss/”occult HBV” (phase 5), also called resolution phase. Phase 4, non-replicative, was previously called “inactive carrier” with low/undetectable serum HBV DNA, very low HBsAg levels, HBeAg(-) status, and normal ALT [16].

Table 1. The division of chronic hepatitis B infection into five major phases.

Phase 1: High Replicative, Low inflammatory	Phase 2: Immune Clearance	Phase 3: HBeAg(-) Chronic	Phase 4: Non-Replicative	Phase 5: HBsAg Loss/Occult Hepatitis B
-High HBV DNA -Normal or low ALT -HBeAg(+) -Mild/no necroinflammation -No/slow fibrosis progression	-High levels of HBV DNA to low/undetectable -High ALT to normal -Declining HBeAg and HBsAg, eventual loss of HBeAg -Acute or intermittent hepatitis	-Moderate/high HBV-DNA -High ALT -Low HBsAg levels -Necroinflammation -Persistent hepatitis -Progressive liver disease -Immune clearance attempts ineffective	-Low/undetectable HBV DNA -HBeAg(-) -Very low HBsAg levels -Normal ALT	-Very low/undetectable serum HBV DNA -Detectable HBV DNA in the liver -Integrated HBV DNA

4.3 Immune escape in CHB- why are infected neonates more prone to develop CHB?

As mention previously, HBV still exists in a large part of the human population. The virus is efficient in coexisting with its host. Before going further into the topic it is worth mentioning that the consequences

of a vertical transmission of HBV is still not fully understood. Literature also points out that the difficulties and limitations in studies, of the establishment of a chronic HBV infection, are among others due to the guidelines of vaccination of neonates within 24 hours after birth. Looking at the general picture in the combat of infections, infants are more vulnerable to severe infections as a consequence of functional differences in their immune system. The development into a persistent HBV infection has previously been recognized as a consequence of this immaturity. However there is an increased recognition that the neonatal immune system is not defective. The term “trained immunity” in newborns has been used as an example to support this theory. Trained immunity is the induction of the innate (complement, phagocytes, natural killer cells) immune system, which has been successfully achieved *in vivo*, but also seen *in utero* [29].

Looking at adults, they are in most cases able to spontaneously “clear” the virus from the blood after an acute infection, as described above in phase 5. However they often maintain a low level of infection throughout their lives, so called an occult infection. It was previously thought that these people was free from the virus, this is however not entirely true as the virus persists in the hepatocytes [31]. For the virus to become chronic and prevent clearance, it is dependent on modifying the host immune response. The virus has developed mechanisms to counteract and escape different host response [30]. The host innate and adaptive (antigenpresenting cells, B- and T-cells) immune response itself is also thought to be contributors to the formation of fibrosis, and risk of developing HCC [16, 31]. As literature points out, much has been learned about the HBV-specific adaptive immunity, but early innate host immune response during an acute infection is still in general unknown [30, 32]. Some literature speculate that HBeAg might establish chronic HBV infection through induction of T-cell tolerance to HBV in utero [33]. Various factors influence on the timing of HBeAg seroconversion, including age, genotype and age at acquisition of virus. In perinatally infected Asians, it is seen a prolonged period of immune tolerance and low rate of clearance of HBeAg until later life [13, 34]. A study published in 2015 upon trained immunity poses two possible theories, either is the development into CHB in neonates associated with a strong Th1-cell response, or it may be related to defects in priming of adaptive immunity, as seen in studies with animals [29].

5. MTCT of HBV: Mechanisms and influencing factors

As briefly described in previous sections, modes of transmission vary depending on the endemicity of the virus. In highly endemic areas, such as South-East Asia, the major route of transmission is perinatally or in early childhood [12]. Even in areas with low endemicity one third of the cases of chronic infection happens as a consequence of transmission during the perinatal period or early childhood [14]. This assignment will not look further into horizontal transmission, but it is worth mentioning that the HBV is transmitted through percutaneous and mucosal contact, with blood or body fluids, and can persist viable for several days in the environment [1, 9]. However understanding the mechanisms of MTCT

transmission is essential when trying to understand the different prevention strategies that will be described below. Literature divides MTCT into three possible routes [12].

5.1 Intrauterine transmission

Intrauterine transmission occurs while the foetus is still in the uterus. There is not yet fully consensus about the mechanisms, but there are several hypotheses. Transmission of serum/body fluid, as a consequence of placenta damage, is one of the most frequently mentioned. Other routes described are due to invasive procedures into uterus, such as amniocentesis. Specific infections with Toxoplasmosis, Rubella, Cytomegalovirus and Herpes Simplex (TORCH) are also pointed out as possible co-factors [7, 12]. Genetic transmission [7, 12] and transmission at the level of sperm cell and oocytes that can be infected and transfer the HBV to the embryo, has also been suggested [35].

Intrauterine transmission is considered to be the main route of the three possible MTCT as a consequence of treatment failure, which will be discussed below [12, 36]. The risk of intrauterine transmission increases with higher levels of HBV DNA in serum and HBeAg positive status in the mother [37, 38].

5.2 Intrapartum transmission

Intrapartum transmission includes natal transmission during delivery [7, 12]. This route of transmission is said to be the major route responsible for perinatal transmission [12]. During childbirth the newborns pass through the genital tract and may be exposed to maternal body fluids or blood [33]. Strong uterine contractions during birth can also lead to damage of the placenta villi vessels and leakage of maternal blood into the foetal circulation. Factors such as mode of delivery and length of labour could in theory influence the transmission, but is controversial [7]. Most studies find no significant difference in MTCT between children born with elective caesarean section and vaginal deliveries, thus caesarean delivery is not recommended in HBsAg-positive mothers. However, procedures such as foetal scalp electrode insertion, or instrumental delivery should be avoided in HBV-carrying mothers [9].

An indirect cause of MTCT is described in literature as compliance of birth dose of HBV vaccine as a consequence of out-of-hospital births, these factors will be discussed below [39].

5.3 Puerperal transmission

This route is more commonly called postpartum transmission. The transmission occurs during care with exposure to maternal body fluid or blood, or through breast milk and represents a less common way of MTCT [7, 12]. It is more or less consensus in literature that breastfeeding after injection of hepatitis B immunoglobulin (HBIG) does not contribute to MTCT of HBV. However some of these studies do not include maternal HBV DNA levels [9, 40].

6. Diagnosis and staging

HBsAg is the standard diagnostic marker used to screen for in pregnant women. A positive test indicates an acute or chronic infection. HBeAg indicates that the virus is actively replicating and typically correlates with higher levels of HBV DNA. IgG and IgM to HBcAg indicates either that the individual has previously been infected or has an ongoing infection. IgG anti hepatitis B core (IgG anti-HBc) will typically persists for life. Detection of anti-HBs indicates that the individual has obtained immunity either from infection or vaccination. Table 2 summarizes the diagnostic testes for HBV antigens and antibodies [31, 41], table 3 gives an overview of serological markers for hepatitis B and possible status of the individual [31].

Table 2. Diagnostic tests for hepatitis B virus antigens and antibodies including field of use.

Factors to be tested	HBV antigen or antibody	Use
HBsAg	Hepatitis B surface antigen	Detection of acutely or chronically infected people; antigen used in hepatitis B vaccine; can be detected for up to a month after a dose of hepatitis B vaccine
HBeAg	Hepatitis B e antigen	Identification of infected people at increased risk (active replication of virus) of transmitting HBV
Anti-HBs	Antibody to HBsAg	Identification of people who have resolved infections with HBV; determination of immunity after immunization
Anti-HBe	Antibody to HBeAg	Identification of infected people with lower risk of transmitting HBV
Anti-HBc (total)	Antibody to HBcAg	Identification of people with acute, resolved, or chronic HBV infection (not present after immunization); passively transferred maternal anti-HBc is detectable for as long as 24 months among infants born to HBsAg-positive women
IgM anti-HBc	IgM antibody to HBcAg	Identification of people with acute or recent HBV infections (including HBsAg-negative people during the "window" phase of infection; unreliable for detecting perinatal HBV infection)
HBV DNA		HBV DNA correlates with levels of circulating viral particles in blood and is an important marker to evaluate the clinical progression, e.g. evaluate the effect of antiviral treatment. HBV DNA is measured as IU/mL

Table 3. Overview of serological markers for hepatitis B and possible hepatitis B-status.

	HBsAg	Anti-HBs	Anti-HBc IgM	Anti-HBc
Susceptible to infection	Negative	Negative	Negative	Negative
Acute infection	Positive	Negative	Positive	Positive
Chronic infection (carrier)	Positive	Negative	Negative	Positive
Chronic active infection	Positive	Negative	Positive/ Negative	Positive
Immunity after infection	Negative	Positive	Negative	Positive
Immunity after vaccine	Negative	Positive	Negative	Negative
Uncertain status*	Negative	Negative	Negative	Positive

*Could indicate previous infection and immunity, low grade of CHB infection or a late phase in an acute infection.

Touching upon the technical procedures behind the tests, HBV serological markers are detected by different techniques, dependent on available resources. In a setting with few economic limitations, as in Norway, Chemiluminescent Microparticle Immunoassay (CMIA) is used to qualitatively prove hepatitis

antigen in blood or serum. The technique has a high specificity and sensitivity and is based on the characteristics of antigens (e.g. HBsAg or HBeAg) binding to commercially produced antibodies (anti-HB) with chemiluminescents [42, 43]. The light produced in a chemiluminescent reaction is measured. This technique is more sensitive than the former used enzyme Linked Immunosorbent Assay (ELISA) [43]. HBV cccDNA are detected by real-time polymerase chain reaction (PCR) [20]. PCR can in short be described as a nucleic acid amplification technique that binds to the HBV DNA and greatly increase the amount of DNA. This technique can qualitatively or quantitatively detect the amount of HBV DNA in the sample, which reflects the replicative state of the virus. For monitoring a HBV infection, the quantitative detection is very important, as described further below [43]. ALT levels are measured to help determine liver inflammation. ALT is an enzyme, commonly found in the liver, but also present in various body tissue, that is released into the circulation system as a consequence to hepatocellular injury [44]. Together with HBV DNA, ALT is important to characterize the phase of infection [45]. Several non-invasive tests such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI) and transient elastography (FibroScan) exist. APRI is an index to estimate hepatic fibrosis based on a formula derived from AST and platelet concentrations. FibroScan is a technique to measure grade of liver fibroses through the detection of liver stiffness. Both techniques are recommended by WHO to assess for the presence of cirrhosis, but while FibroScan is preferred in a context where availability and cost is not an issue, APRI is used in resource-limited settings. Liver biopsy has been used to determine the degree of fibrosis and necroinflammation, however the technique has multiple disadvantages and limitations, and will not be discussed further in this assignment [20].

Looking at the diagnostic part from a global health perspective the need for reliable, cost effective, rapid tests to detect HBsAg, HBeAg and antibodies is obviously present [8]. Not all current tests on the market are quality checked, and there are several problems that are pointed out to hinder the implementation of screening programs. Among some, the need for sophisticated laboratory facilities, amount of blood sample and the limitations in screening a general population, rather than detection of subgroups, such as individuals in the immune-tolerant phase [46].

7. Monovalent HBV vaccine and hepatitis B immunoglobulin

A prophylactic hepatitis B vaccine from serum was introduced in 1983. It is estimated to give protection in 90-95% of the cases [31]. In contrast, there are no current prophylactic vaccine against the HCV, a RNA virus, mainly due to the high viral replication and mutation rate [47]. The HBV vaccine contains parts of the hepatitis B virus produced in yeast cells with the aid of DNA technology. There are few reported side effect concerning the vaccine. The most common reported are tenderness, redness and swelling at the injection site. Fever, rash, weakness and aching joints and muscles in the following days are less common, but reported [48]. The vaccine comes as monovalent, meaning production of one virus type, and pentavalent preparation, together with diphtheria, pertussis, tetanus and haemophilus influenza. This is cost-effective compared to the monovalent preparation and is frequently used in Africa and East Asia.

However, the pentavalent is obviously not for use in newborn babies, thus can not be given as a birth dose. The Vaccine Alliance (GAVI) no longer supports the monovalent vaccine with the consequences following that [8].

Passive immunization with HBIG gives a temporary immunity administered as post-exposure prophylaxis through a short-term increase in anti-HBs. The combination of a vaccine and HBIG should be giving right after birth, within 24 hours [20], although the benefits of HBIG is less clear among full-term neonates of HBsAg-positive, but HBeAg-negative mothers [9]. Literature even declare no significantly improved protection by the addition of HBIG [20]. Due to HBIG storage criteria's and complex production it is an expensive procedure [8].

7.1 Follow-up after vaccination

According to the Norwegian Institute of Public Health it's among researchers an agreement that routine testing of immunological healthy individuals, that have completed vaccination according to guidelines, is not recommended. This is as a consequence of an expected 96% protection with antibodies after fulfilling the vaccination guidelines [31]. Looking at the newly published "Alaska study", a 30 years follow-up study, >94% had evidence of protection [49]. However, Norwegian authorities recommended to control the levels of anti-HBs 1-3 month after last dose is given to some specific groups, such as newborns to HBsAg-positive mothers. Testing for anti-HBs after 3 months is regarded as inadequate, as the levels of anti-HBs level will decline over time, and will not indicate whether the individual has effect of the vaccination or has accomplished long-term protection. According to Norwegian guidelines from 2015, a booster dose is recommended in those with an antibody response < 100 IU/l after 1-3 months [31]. CDC guidelines are more or less similar to Norwegians, but recommends post-vaccination testing 1-2 months after completion of the final dose [50].

8. Strategies for preventing MTCT of HBV

Currently there is no curative treatment against a HBV infection. Oral treatment with antiviral drugs suppresses the replication of the virus and slows the progression of liver complications. In the absence of a cure, prevention strategies are highly prioritized [20]. Preventive strategies of MTCT of HBV reach over different levels, from medication during pregnancy and delivery, to postpartum strategies. It involves among others screening of pregnant women, providing antiviral therapy to women with high HBV DNA levels and administering passive-active immunization to newborns of mothers who are HBsAg-positive. The integration of new findings in trials into national and international guidelines is a constant process.

8.1 Current strategy of post exposure prophylaxis (PEP). Recommendations by WHO and CDC

The hepatitis B vaccine coverage has in a global setting increased rapidly. Data from 2015 show a global coverage with 3 doses of the hepatitis B vaccine at 82%, and 92% in Western Pacific. This is a result of including hepatitis B vaccine into children immunization programs in 184 countries [51]. The combination of HBIG and a monovalent hepatitis B vaccine given within 24 hours of birth has reduced the rate of MTCT from >90% to <10% [4, 20]. Literature points out that the dose should be given as soon as possible after birth and some guidelines operate with 12 hours postpartum [40]. It is important to notice that HBIG is not an effective prevention strategy after 48 hours [48]. WHO recommend both a monovalent HBV vaccination within 24 h of birth, followed by two or three series, see table 4 [20].

Table 4. Recommended routine immunization for HBV for children

	Age of 1 st dose	Doses	Interval between doses			Booster dose	Considerations
			1 st to 2 nd	2 nd to 3 rd	3 rd to 4 th		
Option 1	As soon as possible after birth (<24h)	3	4 weeks (min) with DTP1	4 weeks (min) with DTP3		No	Premature and low birth weight Co-administration and combination vaccine
Option 2	As soon as possible after birth (<24h)	4	4 weeks (min) with DTP1	4 weeks (min) with DTP1	4 weeks (min) with DTP3	No	High risk groups

A 3 dose vaccine (1 monovalent birth dose followed by 2 monovalent or combined vaccine doses at the time of DTP1 and DTP3 vaccine doses) is recommended. However, 4 doses may be given for programmatic reasons (e.g. 1 monovalent birth-dose followed by 3 monovalent or combined vaccine doses with DTP vaccine doses). PEP for infants weighing less than 2000 grams include a dose at birth, which is not counted toward a ≥3-dose HepB vaccine series [20].

8.1.1 Lifelong immunity- the need of a booster dose?

A “booster dose” is a term referring to a vaccination given some time after a primary vaccination series. The aim is to provide a rapid protective immunity against a significant breakthrough hepatitis B virus infection clinical disease or serological test positive for HBV. The question whether it is a need for a booster dose, or not, have been posed several years back, at a time with limited data [52]. European Consensus Group on Hepatitis B Immunity published in the Lancet in 2000 that there is no need for a booster dose in healthy, fully vaccinated individuals [53]. In developing countries with high endemicity, this new recommendations meant a great decrease in costs savings [52]. Over the years, more data have been published including longer post-vaccination follow-up studies and the results are supporting the statement from year 2000. A follow up study from Thailand of infants receiving PEP after WHO guidelines, showed maintenance of immune memory and long-term protection after 22 years, among children that immunologically responded to the vaccine [54]. Additionally, a similar result was obtained

in a follow-up study from Italy; immune memory for HBsAg persists beyond the time at which anti-HBs disappears [55]. Presumably the immune memory persists through cellular immunity [50]. *The Journal of Infectious Diseases* published this year a 30-year follow-up study from Alaska that concluded that a booster dose is not needed, an overall of $\geq 94\%$ seemed to be protected (had anti-HBs ≥ 10 mIU/mL and/or responded to booster dose). Initial anti-HBs level and age at vaccination seemed to play an important role in the persistence of antibodies [49]. However, despite these findings, it is still not consensus about how long immune memory will last and whether a booster dose is needed or not [21]. Moreover, the so called “Alaska study” will continue to follow the participant at 35 years and announce that they will also look into cellular mediated immunity, included to the more well studied humoral immune memory, which is important “*especially in individuals that lose anti-HBs and fail to respond to a booster dose*” [21].

8.2 Current guidelines in Norway by the Norwegian Institute of Public Health

The incidence of acute hepatitis B in Norway has since 1975 decreased dramatically with an increase around 1995-2004 due to an outbreak among drug abusers. In the period 2008-2015 there were no reported cases of MTCT of HBV. Transmission between heterosexuals and through contaminated needles were the main anticipated mode of transmission, with a total of 14 incidences out of 19 reported cases of acute infections in Norway. According to the Norwegian Institute of Public Health, people in Norway with another ethnical background has a chronic HBV infection due to perinatal transmission or transmission in early childhood in their home country. In contrast, people born in Norway with a chronic HBV infection are likely to have the infection due to injection of contaminated needles. In the annually report by Norwegian Institute of Public Health published in 2015, there was reported 795 new cases of hepatitis B. Further it is estimated that about 25,000-30,000 persons are chronic carriers, with a recent increase due to immigration from medium- and high-endemic countries [31]. According to Resistance against Antivirals in Norway (RAVN) from 2015, the majority of all new cases are among immigrants for Somalia, Afghanistan, Vietnam, Thailand and Eritrea [56], but as previously mentioned, this has not led to any new cases of MTCT since 2008.

WHO has since 1991 recommended all member countries to include the hepatitis B vaccine into their national vaccination programs. However, the Nordic countries and Great Britten has decided to only vaccinate groups at risk because of the low incidence of HBV infections [31].

8.2.1 Pregnant and neonatal prophylaxis

Norwegian Institute of Public Health recommends routine testing of pregnant women from medium- and high-endemic countries. When testing pregnant women, both HBsAg and anti-HBc should be screened for, see table 2 for abbreviation. Pregnant women born in Norway is only recommended to go through screening based on following indications, which also includes her sexual partner:

- Current or previous injection drug users

- Received blood transfusion out of Norway
- Sexual contact with an injection user or bisexual man
- Exposed in a job related setting
- Previous hepatitis B infection

The recommendations by Norwegian Institute of Public Health concerning PEP are more or less in coherence with WHO guidelines. Newborns should receive HBIG and the first vaccination dose after birth, followed by three doses at 1, 2 and 12 months. Twelve to fifteen months after birth it is recommended serological testing of HBsAg and anti-HBc to look for MTCT despite prevention strategies. This includes serological testing of anti-HBs to see if a booster dose is necessary. A booster dose is recommended for whom with antibody-response < 100 IU/l after last vaccination dose. Breastfeeding is encouraged throughout the period [48].

8.2.2 Norwegian Childhood Immunization Program

The hepatitis B vaccine is offered in the immunization program to children of parents from countries with a high incidence of the disease. In addition, the vaccine is offered free of charge to other people who [48]

- *Have an increased risk of becoming infected*
- *Have an increased risk of becoming chronic carriers if they become infected*

Already back in 2008 the Norwegian Institute of Public Health recommended reintroducing the hepatitis B vaccine into the Childhood Immunization Program, as WHO recommends to its member countries. The process started in spring 2015 and the vaccine will earliest be reintroduced in 2017. The institute poses multiple arguments why not only groups at risk should receive the vaccine. Increased globalization and immigration from regions with medium- or high-endemic countries are among some. The vaccine is also effective and there are a few reported side-effects [57].

8.3 Maternal screening methods

The majority of pregnant women with CHB infection will be asymptomatic, thus they will be identified through routine screening in the perinatal period [40]. Centre for Disease Control and Prevention (CDC) recommend testing for HBsAg in all pregnant women, including previously tested and vaccinated. There are currently no screening methods with high sensitivity and specificity, to identify chronic carriers of HBV pregnant, which are available in a low-resource setting [8]. Literature points out that such a method should ideally capture all HBeAg-positive women, but at a least women that are HBsAg positive. A study from China in 2012 looked more into that the proportion screened is often suboptimum, and that the prevention of MTCT failed at a level of identifying the positive mothers [58].

An occult HBV infection, also called “window period” or “silent” form in phase 5, is characterized by the presence of HBV DNA without HBsAg. Most are also without the presence of HBV antibodies [20, 59]. It

has important clinical significance in several conditions, e.g. in blood transfusion where HBsAg is used as the sole marker of infection in donor populations [60]. However this “window period” is not described in literature as a problem when it comes to MTCT due to the low viral concentration in blood [31].

8.4 Maternal vaccination strategies

Unvaccinated HBsAg negative mothers in a setting at risk for transmission should initiate vaccination [9].

8.5 Antiviral therapy

Newly published literature [8] suggests a shift of focus to decrease MTCT of HBV by reduction of the maternal viral concentrations before delivery. The ultimate goal in future is to completely eliminate the virus, which to date is not achieved by current antiviral therapy. Complete eradication is difficult due to the remaining cccDNA in the hepatocyte and the difficult induction of immune control of the virus [19]. As briefly touched upon earlier, studies points out that maternal concentrations of HBV DNA is the most important risk factor of MTCT, with a cutoff of 200 000 IU/mL (2×10^5 IU/mL) [14, 61]. Given what we know about the most common route of MTCT from exposure to maternal blood and secretions at delivery, viral concentration in maternal blood is of great significance [20]. The current immunoprophylaxis regime fails in 8-32% whom mothers have high levels of viremia ($>200\ 000$ IU/mL), even when administrated after the guidelines [62]. According to AASLD guidelines there are only three antivirals studied in pregnant women; lamivudine, telbivudine and tenofovir [45]. Several studies can show results of lowering the risk of HBV transmission when given antiviral treatment to high-risk women along with standard immunoprophylaxis [14, 63]. A retrospective study from 2013 including pregnant women with levels of HBV DNA $>200\ 000$ IU/mL and HBeAg positive that had been given tenofovir disoproxil fumarate (TDF) during second and third trimester, reduced the perinatal transmission. Vaccine and HBIG were administrated according to WHO guidelines [64]. However literature points out that the levels of HBV DNA could be further reduced if starting treatment earlier, but that there are insufficient data upon the timing [12]. A meta-analysis published this year in *Hepatology*, included 26 studies and its findings showed that antiviral therapy reduces MTCT in women with chronic HBV infection and high viral load [65].

8.5.1 Current recommendations by AASLD of CHB in pregnancy [45]

- *The infants of all HBsAg-positive women should receive immunoprophylaxis (HBV vaccination ± hepatitis B immunoglobulin, per WHO/Centers for Disease Control and Prevention recommendations).*
- *Antiviral therapy was started at 28-32 weeks of gestation in most of the studies.*
- *Antiviral therapy was discontinued at birth to 3 months postpartum in most of the studies. With discontinuation of treatment, women should be monitored for ALT flares every 3 months for 6 months.*
- *There are limited data on level of HBV DNA for which antiviral therapy is routinely recommended.*

The level of >200,000 IU/mL (1 million copies/mL) is a conservative recommendation.

- *For pregnant women with immune-active hepatitis B, treatment should be based on recommendations for nonpregnant women.*
- *Breastfeeding is not contraindicated. These antivirals are minimally excreted in breast milk and are unlikely to cause significant toxicity. The unknown risk of low-level exposure to the infant should be discussed with mothers.*
- *There are insufficient long-term safety data in infants born to mothers who took antiviral agents during pregnancy and while breastfeeding.*
- *C-section is not indicated owing to insufficient data to support benefit.*

Current recommendations recommends against the use of antiviral drugs in HBsAg-positive pregnant woman with an HBV DNA $\leq 200,000$ IU/mL [45]. Present-day drug labels do not recommend breastfeeding in combination with TDF or lamivudine. However, studies show that the infants are exposed to higher drug doses during pregnancy. Moreover TDF is one of the drugs included in the WHO guidelines for breastfeeding in HIV-positive mothers on antiretroviral treatment (ART) [66]. AASLD points out that the safety of lamivudine and tenofovir during breastfeeding has not been well studied in women infected with CHB, but refers to data from the existing HIV literature [45].

8.5.2 Are there any effects on obstetric or infant parameters?

TDF or lamivudine given during second and third trimester has not shown any different in obstetric or infant parameters, such as congenital abnormalities or neonatal growth centiles [63, 65]. The antiviral drug tenofovir has neither showed any adverse outcome to mother or child [65]. TDF given in first trimester to 1370 women did not show any increase in birth defects according to Antiretroviral Pregnancy Registry.

8.6 Postpartum strategies

Minimizing the exposure of the newborn to maternal serum and amniotic fluid after birth may reduce the risk of HBV infection. It can be done by avoiding contact and cleaning the respiratory tract and skin of the newborn [7]. Administration of HBIG keeps the incidence of this mode of transmission low [12]. However immunoglobulin is not widely available due to out-of-hospital births and storage criteria. Moreover, it is expensive, all obvious factors to take into consideration in resource-limited countries [8]. Knowledge about the virus and vaccination guidelines is in literature also described as important factors of MTCT of the virus [67]. Unskilled health attendants and home deliveries are both risk factors for infants to get infections, thus education and access to health facilities play a role in the postpartum strategies to prevent MTCT [68].

8.7 Preventing MTCT of HBV at a structural level: technical strategies to update national strategies

WHO published in May 2015 a review in the *Journal of Viral hepatitis* called “Where next for hepatitis B and C surveillance?” The background for the publication was the need for an evaluation of future common strategies, e.g. case reporting. Case reporting was stated as a fundament for comprehensive epidemiologic assessments of the burden of hepatitis B and C, allowing decision-makers to maximize the interventions against the burden of disease. The variability in reported cases including sources of data, such as serologic status, reflects the difference in testing and reporting practices. The review uses the lack of differentiation between an acute and chronic HBV infection as an example. Moreover WHO emphasizes that the public health response to hepatitis B (and C) has been “*disproportionately small in relation to the enormous burden of disease presented by these infections and in comparison with other communicable diseases with a similar disease burden*”. WHO highlighted the lack of epidemiological estimates as one of the reasons why prevention and treatment strategies have been in variable quality. However, as the review discuss, it is worth mentioning that the surveillance of HBV is more difficult than other diseases. The review points out many asymptomatic individuals, availability of testing services and the complex laboratory diagnosis as some of the difficulties [69]. WHO published in September 2015 a technical report to “*provide guidance to public health professionals asked with managing a response to viral hepatitis*”. The manual is still provisorial and will be presented to the World Health Assembly in 2016 for adoption by Member States [70].

One other important aspect to highlight is the actual use and implementations of the guidelines. Despite global guidelines published by WHO, national recommendations and routine practice varies. It is estimated that in 2014 half of all countries were following the recommendations by WHO. There are different explanations, and the problems are somehow complex. One aspect pointed out is the availability, including limitation in storage, and costs of HBV monovalent vaccine and HBIG. This affects especially less developed countries [8]

Looking at Norwegian guidelines published by the Norwegian Institute of Public Health concerning case reporting of the virus, the procedure is quite clear. The hepatitis B virus is classified as a group A disease which means that the patient full identity should be registered at Norwegian Surveillance System for Communicable Diseases (MSIS), including both acute and chronic carriers. The criteria are based on laboratory techniques of either one, or in combination, of the following tests: HBsAg, HBeAg, HBV-DNA and anti-HBc IgM [31].

9. Factors associated with failure to PEP

There are no quick answer to why PEP sometimes fails. On one hand, despite timely prophylaxis, the MTCT of HBV occur in 5-15%, on the other hand, there are multiple factor associated with deviation from

the PEP guidelines. Failure to PEP despite of timely treatment with prophylaxis is associated with maternal HBeAg positivity, high HBV DNA levels, nonresponse to the vaccine, and rarely, HBV mutations [9]. As pointed out earlier, AASLD explains the failure as a result of HBeAg- positive mothers with a viral load greater than 200 000 IU/mL [45]. Delay in receipt of the HepB birth dose, failure to complete the vaccine series and failure to receive HBIG are some of the deviations from the guidelines [9]. A deeper understanding of PEP failure, with focus on two high-endemic countries will be presented below.

10. Perinatal transmission of HBV in Vietnam and Cambodia: An introduction to two high-endemic countries

In Asia, and in particular in highly endemic East Asia, vertical transmission during the perinatal period is the main cause of the transmission of HBV. The region has one of the worlds highest prevalence of the virus (>5%) [20] and the virus is one of the major infectious cause of death in the region, ahead of malaria, tuberculosis and HIV [5]. As previously described, MTCT occurs in 50% of unvaccinated children with HBsAg positive mothers. 90% of these will develop to chronic carriers, with the complications that follow [6]. In contrast, <5% of the horizontal transmissions to adults, leads to chronic carriers [4]. The regional goal for Western Pacific by 2017 of reducing the prevalence of hepatitis B chronic infections to less than 1 % among children has been achieved. Even though this means an 89% reduction in prevalence compared to the period prior to vaccine introduction and the averment of seven million hepatitis related deaths, there are still great challenges and differences among countries within the region. Vaccination coverage according to guidelines and birth dose within 24 hours is pointed out to be the main reason for that, with Vietnam as one of the countries with the highest number of perinatal infections [5].

It is estimated that 9% of the total population in Cambodia have a chronic disease. Seroprevalences show great provincial differences in HBsAg-positive children, ranging from 0,33 to 3,45, with higher prevalences in rural areas [71]. Figure 5 and 6 present the vaccine coverage in Cambodia and Vietnam, based on data for WHO databases [72, 73]. The vaccines was introduces in Cambodia in 2006 [71] and by 2014 the country had 97% coverage of 3-dose hepatitis B vaccine (HepB3) and 87% coverage of birth dose (HepB_BD). Vietnam, on the other hand, introduced the 3-dose vaccine nationwide in 2002 and birth dose in 2003 [74] and data from 2014 reveals coverage of 95% of HepB3 and 55% of HepB_BD. The country has an estimated seroprevalence of >8% of chronic infections and an average 2,7% for children [74].

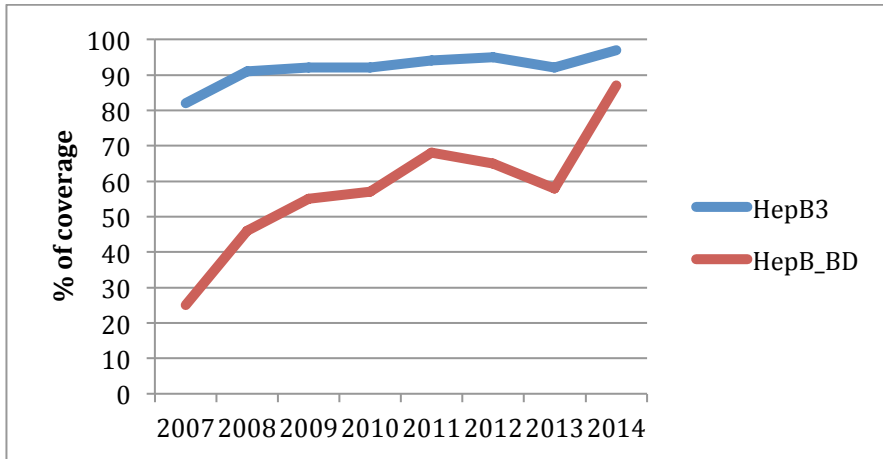


Figure 5. Vaccine coverage in Cambodia between 2007 and 2014

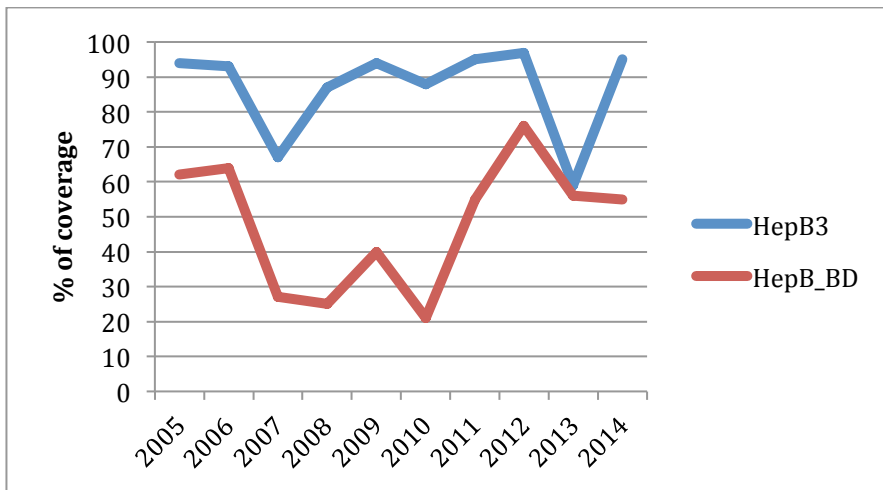


Figure 6. Vaccine coverage in Vietnam between 2005 and 2014

As figure 6 indicates, the country has confronted some challenges along the way, looking at the incidences in 2007 and 2013 with particular interest. *Vaccine* published in 2016 an article that looked further into why there was a substantial reduction in hepatitis B vaccination coverage during the particular period and estimated the extent of impacts. It was estimated that 130,675 chronic HBV infections and 25,197 HBV-related deaths would occur in children born in 2013 due to the decrease in coverage. The article points out public concern over vaccine safety and the media coverage as the main cause of the incidence [75].

Literature empathizes that routine newborn HBV vaccination in Vietnam is highly cost-effective from the payer’s perspective and cost-saving from both societal and health care perspective [76]. The complications to a chronic infection put a substantial financial burden not only at an individual level, put also on the Vietnamese health care system and society [28]. Home births in Cambodia is common and children born at home without a skilled birth attendant will have two times the chance of missing a birth-dose within 24 hours, compared to those born in proper health facilities. The chance is even greater if the place is in the rural districts, and the difference is largely attributed to access to health facilities and/or

skilled birth attendants. Another important aspect concerning factors associated with under-vaccination in Cambodia is the mother's educational level. If the mother had received primary or secondary school, there are 30% less of a chance of unvaccination with timely birth dose (<24 hours). However Cambodia Ministry of Health has acknowledged the problems with out-of-hospital birth and has among others implemented simple injection devices (e.g. Uniject) to reach infants born at home. Additionally the true number of children receiving appropriate vaccination is often unknown and national serosurveys are needed. Furthermore, training and education of skilled birth attendants are needed [71]. Vietnam has faced some of the similar difficulties upon timing and coverage and their national immunization program has raised awareness over the importance of a birth-dose holding seminars among public health decision makers, re-training health-care works and initiation of awareness campaigns. Another important aspect pointed out is the need to improve access and demand to poor ethnic groups with high HBsAg often living in remote areas [74]. In addition, blood safety and sterilization in medical settings should be further improved to avoid parenteral transmission [77].

Despite all the challenges, hepatitis B prevalence among children has dramatically decreased. However looking into the future, vaccination at birth with the timely birth dose and complete infant hepatitis B vaccination series, is still number one prevention strategies of MTCT in the region. Additional strategies such as antiviral therapy for pregnant women may be necessary in high endemic countries such as Vietnam and Cambodia where perinatal transmission still occurs. At a regional level, new goals beyond 2017 should be completed. Total elimination of MTCT should be in reach. The Western Pacific Region has this year launched plans to hepatitis prevention by developing a regional action plan that includes treatment, screening and vaccination [5].

11. Discussion

It has become obvious that hepatitis B is a major public health problem and should be recognized as a burden of disease in line with tuberculosis, HIV and malaria, not only at an individual level, but also at a socio-economic level. This assignment has focused on the consequence of MTCT of hepatitis B and looked into the prevention strategies as an important component of reducing the global burden of CHB infections. It appears like vertical transmission of the virus is the major route of transmission in less developed countries, while horizontal transmission dominate in countries such as Norway. However some researchers put a question mark whether MTCT is the most important factor for developing a persistent HBV infection. It could be overestimated as different genotypes and genetic polymorphism might contribute to higher prevalence in East Asia compared to Europe.

One of the challenges with MTCT is that the risk of chronicity is inversely proportional with age and most of the newborns (90%), to hepatitis B positive mothers, will get the virus without any prevention strategies. Moreover, infection in infancy is usually asymptomatic until later in life, at a time where the virus has caused severe liver disease. Clinically its impossible to differentiate the virus from other virus-

caused hepatitis, neither distinguish between an acute and chronic infection, hence laboratory confirming is essential. However, hepatitis B is a resource-demanding virus to diagnose. There are currently no screening methods available in resource-limited settings with sufficient test properties to capture HBsAg-, and ideally also HBeAg-positive women. The result is often a suboptimum proportion been screened and the prevention of MTCT fail at a level of identifying the positive mothers. Bearing both the diagnostic and screening challenges in mind while looking at the possibilities for treatment, status quo is unfortunately that there are no definite treatment to cure the infected mother or child from hepatitis B, thus vaccination is essential to prevent MTCT of the virus. The vaccination is cost-effective and with few reported side-effects, however it has to be administered timely and with proper number of doses to accomplish complete prophylaxis. Moreover GAVI don't support the monovalent dose, which makes is less available. The advisable immunoglobulin, on the other hand, is both expensive and requires storage in cold environment, obviously making it less available in resource limited countries.

Looking at the different modes of transmission of the virus it is evident that less developed countries have greater challenges. However it is easy to fall into the same old conclusion of lack of infrastructure, history of poor political governance, corruption and economic challenges. It's very general and count for almost all global health problems. Vietnam and Cambodia have higher rates of out-of-hospital births, challenges concerning skilled health workers and appropriate antenatal care, poor health facilities, poverty and difficulties with establishing national serosurveys, essential for national guidelines and policies. One factor is often leading to another, and all factors are pointed out to negatively affect the extremely important birth dose, given within 24 hours. With the risk of generalizing, implementing these challenges into other resource-limited countries seems reasonable. Furthermore, WHO estimates that only half of all countries were following their recommendations in 2014, understandable taking the situation in Vietnam and Cambodia into consideration. However, this assignment has been an eye-opener to how intricate the prevention of MTCT can be, things are often more complicated than they seemingly appears to be. This has might become a weakness, understanding MTCT goes beyond a few headlines and the way it is portrayed in this assignment is probably very simplified, important aspect might have been excluded due to lack of literature or poor research strategy.

Concerning vaccination coverage, estimates by WHO show that these two countries are going in the right direction, however they have still huge challenges and every day thousands of children develop chronicity and will be needed resource demanding follow-up and treatment in many years to come.

Looking at the WHO and CDC guidelines, recommendations regarding the vaccine should be better supported by research. Research gaps have become clear, and there are gaps between current knowledge and practice, e.g. concerning a booster dose. There is a need of longitudinal cohort studies in under-researched populations such as children, young adults and pregnant women with CHB. Some is obvious difficult to perform due to ethnical limitations, others could be a consequence of less profit in research concerning health related questions in resource-limited countries. The expensive HBIG has been questioned; the mechanism and benefits are not well documented. Lowering the mothers viral load (VL) with antiviral treatment before delivery might replace the HBIG in future, but the risks and benefits

during pregnancy and breastfeeding needs additional surveillance. Whether we need a booster dose or not is also questioned, both highly resource demanding measures. The mechanism concerning why neonates develop CHB infection is still unclear, a central mechanism to understand MTCT. Further research concerning both mechanism of the transmission and development into chronicity and population based surveys are needed.

12. Conclusion

Throughout the process of writing this assignment it became clear that the focus on MTCT of hepatitis B is disproportionately small in relation to the enormous burden of disease presented by the virus. Despite the heavy burden of HBV-related deaths, new infections can effectively be prevented through timely completion of three doses hepatitis B vaccination and administration of HBIG. Number one priority for future strategies to combat MTCT will be to increase the coverage, with focus on increasing compliance of the birth dose. Improving health system infrastructure, raising awareness in the general population, increase the vaccine availability are among some of the key strategies. Continued public health efforts to control transmission of HBV by prevention programs and effective strategies to screen and identify positive mothers, monitor, and provide effective treatment for mothers with chronic infection, are necessary to reduce and eliminate MTCT of HBV. Lowering maternal HBV DNA levels of the virus to the minimum during third semester of pregnancy are a key factor, thus supplementary evaluations of antiviral treatment is needed. Further research is needed to guide future policy recommendation. This assignment can hopefully contribute to put focus on the global burden of HBV and prevention strategies and may be the starting point for an article in a Norwegian paper or journal regarding the possible reintroduction of the HepB vaccine into the Children Immunization Program in 2017.

Finally, as long as the prevalence of the virus remains high in East Asia it will be a constant pool of potentially transmissions from mother to child. To combat the spread of the virus at a global level, we need to improve prevention of MTCT in East Asia.

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