TOWARDS THE ERADICATION OF HEPATITIS B IN TAIWAN
A Discussion Paper

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Table of Contents

Foreword

Viral hepatitides have long been important public health problems in humans. The etiologic agents were not identified, until around 1965 when Baruch S. Blumberg first found the relationship of Australia antigen and serum hepatitis. Further characterizations revealed the antigen to be the surface antigen of the hepatitis B virus. This epoch-making observation launched a new era in the diagnosis, prevention and treatment of hepatitis B. In about 15-20 years, the natural history of hepatitis B virus infection was elucidated, and more importantly, an effective vaccine against the infection became available. In the meantime, the routes of transmission were also made clear, rendering interruption of the transmission more specific and effective. The hepatitis B vaccine together with the effective means of interrupting the transmission routes contributed greatly to the control of hepatitis B virus infection. However, these measures can do very little to those who have already been chronically infected. Fortunately, specific therapies against chronic hepatitis B have started to appear about 10-15 years before and the treatments improved substantially in the last few years. Although far from perfect, now we do have some effective means to treat those who are chronically infected.

In Taiwan, acute and chronic liver diseases have been known to be rampant in as early as the beginning of the last century. Studies around 1975 showed an extreme high prevalence of chronic hepatitis B infection in the general population (15%-20%), and 80%-90% of the chronic liver diseases as well as hepatocellular carcinoma were caused by chronic infection with the hepatitis B virus. This important health problem, repeatedly addressed by the academia in Taiwan, finally caught the attention of the Government in the late 1970s, and a government-sponsored control program was finalized in 1981. Accordingly, a mass vaccination program against hepatitis B, primarily aiming at immunizing newborn infants, was launched on July 1, 1984. Twenty years after implementation of the program, the hepatitis B carrier rate in children covered by the program decreased 85%, from ~15% to <1%. Most importantly, the deadly sequela of hepatocellular carcinoma in the vaccinees was also found to decrease in parallel . This is the first time in history that a human cancer is prevented by vaccination. Despite the success, there are still some who were born after implementation of

the program but were not prevented from chronic hepatitis B infection and hepatocellular carcinoma. Non-compliance to vaccination schedule, breakthrough infection and intrauterine infection are the causes of the failure.

At present, we have effective measures in immunizing the susceptibles, interrupting the routes of transmission and treating the chronically infected people. The time of considering elimination or even eradication of hepatitis B virus infection has come. This is especially true for countries where hepatitis B infection is not endemic. Nevertheless, with the admirable results achieved in the past, Taiwan should also start to think about elimination/eradication of hepatitis B in the country, even though it will certainly be much more difficult than in the non-endemic countries.

Dr Suzanne Wait has spent substantial efforts and time in exploring the possibility of eliminating/eradicating hepatitis B in Taiwan. She reviewed the epidemiology of hepatitis B, and analyzed the problems that remain to be tackled in Taiwan. With this essay as an important reference, I hope that Taiwan can take further steps towards the elimination or eradication of hepatitis B.

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Executive Summary

The Hepatitis B virus (HBV) is the most common cause of viral infection of the liver in the world. More than two billion people worldwide have been infected with HBV and seventy-five percent of all chronic HBV infections occur in Asia.

The virus is transmitted by contact with the blood or body fluids of an infected person. In Asia, the main mode of transmission is from an infected mother to her newborn infant (mother-to-infant transmission). Other modes of transmission are child-to-child contact within households where a family member is infected, contamination through the reuse of unsterilised needles and syringes and sexual transmission (homosexual and heterosexual).

The natural history of hepatitis B is complex, as it starts off as an acute infection that may evolve into chronic disease. Hepatitis B is often called a 'silent disease' because symptoms may remain absent for several years and they are difficult to identify as they are not specific to hepatitis. .

When chronic hepatitis B does develop, it can lead to serious and debilitating liver disease if left untreated, including liver cancer. Liver cancer is the leading cause of cancer in Taiwanese men and accounts for 21.8% of male cancer deaths. It is the second-leading cause of cancer in women and accounts for 14.2% of female cancer deaths.

Hepatitis B is a preventable disease. Taiwan was the first country in the world to introduce a population-wide vaccination programme against hepatitis B for all newborns in 1984. This programme has been extremely successful at reducing the prevalence and mortality associated with HBV in children. However, prevalence remains high in adults, with more than 90% of the population having been infected with HBV in the past. It is estimated that there are between 2.5 and 3 million carriers of HBV in Taiwan today.

For those infected with HBV, appropriate management has been shown to substantially reduce the risk of long-term liver damage, including cirrhosis and liver cancer. Proper management of hepatitis B requires a combination of:

- *Prevention*: vaccination of newborns is the most effective means of preventing hepatitis B. Targeted prevention of groups at risk, accompanied by strong educational campaigns, is also important.
- *Screening of individuals at risk*: Given the absence of symptoms in the early stages of hepatitis B, many individuals do not know that they are infected. Screening programmes are thus necessary to contain the risk of infection by allowing individuals who are HBV-positive to follow the right course of care for themselves and take appropriate measures to avoid infecting others.

- *Diagnosis and monitoring*: Hepatitis B is under-diagnosed in Taiwan. Once diagnosis is ascertained, it is critical that individuals are monitored regularly to determine whether the disease has progressed and whether treatment should be initiated.
- *Treatment*: There have been important advances in the development of antiviral therapies to treat patients with hepatitis B, as are reflected in recent clinical guidelines in Asia and around the world. Early treatment is critical to prevent the progression of liver disease.

Despite a successful vaccination campaign and the existence of management options for patients infected with HBV, hepatitis B remains under-diagnosed and under-treated in Taiwan. Thousands of deaths per year are still attributed to HBV today.

Thus complacency cannot be allowed to develop. Some of the remaining challenges to achieving the optimal containment, and eventual eradication, of hepatitis B in Taiwan include:

- **Need for greater awareness and education:** Governments, including local agencies, must continue extensive screening programmes for hepatitis B and provide information to help the general population better understand the natural history of hepatitis B, the risks associated with being an HBV carrier and the importance of appropriate care. Efforts aimed at educating physicians are also critical as many practitioners lack the necessary knowledge of the best care to offer their patients.

- **Need to ensure continued success of the vaccination programme:** Careful quality control and monitoring of the outcomes of the vaccination programme must remain a public health priority for its success to continue. Further research is also needed into the evolving epidemiology of HBV in Taiwan to ensure that vaccination programmes are not missing out on any new risk groups that may develop over time.

- **Need to overcome geographic and social inequities in access to care:** Prevalence rates of HBV infection are higher in indigenous populations, in persons of lower socioeconomic status and in those living in remote areas. Moreover, most hepatologists and gastroenterologists are concentrated in the large urban centres and facilities for screening, diagnosis, monitoring and treatment may be very limited in remote areas.

- **Need to improve standards of care:** As in many clinical areas, there is inconsistency in practice in the management of hepatitis B. In particular, confusion remains around when to initiate therapy and for how long. Careful monitoring during treatment, using the most meaningful tests and procedures available, is needed to continually evaluate the efficacy

of treatment and to adapt treatment over time to prevent resistance to antivirals.

- **Need to remove financial barriers to care:** Some of the screening tests, diagnostic tests, procedures (including liver biopsy) and antiviral therapies for hepatitis B do not benefit from full reimbursement in Taiwan. Thus individuals must often pay for them out-of-pocket. Costs may be prohibitive and prevent individuals from receiving an appropriate diagnosis, attending regular monitoring check-ups or seeking and continuing treatment. Removal of these financial barriers is essential if patients are to be offered optimal care.

In conclusion: Hepatitis B continues to represent a tremendous public health burden in Taiwan. Yet clinical experience has shown that effective screening, diagnosis, monitoring and treatment of individuals affected by HBV can prevent progression to severe liver disease in patients and thus lead to a significant reduction in the burden of illness posed by HBV on Taiwanese society. However, sufficient resources are needed to ensure that individuals affected by HBV receive the best care as early as possible. Concerted actions amongst all stakeholders – policy-makers, health professionals and patient representatives – are needed if we hope to achieve the elimination and eradication of hepatitis B from Taiwan in years to come.

I. Introduction: Hepatitis B in Taiwan

The Hepatitis B virus (HBV) is the most common cause of viral infection of the liver in the world. More than two billion people worldwide have been infected with HBV. Of these, more than 350 million suffer from chronic HBV infection (WHO, 2000). Chronic hepatitis B is more prevalent than HIV (50 million cases worldwide) as well as chronic hepatitis C (170 million cases worldwide).

Seventy-five percent of all chronic HBV infections occur in Asia. The prevalence in Taiwan is between 15-20% and more than 90% of the adult population has been infected with HBV in the past. It is estimated that there are between 2.5 and 3 million carriers of HBV in Taiwan today (Department of Health, 2008). HBV carriers are at risk of transmitting the virus to others. Also, they face an absolute lifetime risk of death from liver-related diseases, including cancer, of 15-20% (Lin and Kirschner, 2004). Indeed, hepatitis B is the main cause of liver cancer, which is in turn the most frequent cause of cancer in Taiwan (Chen D-S, 2007).

Taiwan was the first country in the world to introduce a population-wide vaccination programme against hepatitis B starting from all newborns in 1984. This programme has been extremely successful at reducing the prevalence and mortality associated with HBV in children. However, detectable virus remains a concern within the adult population and prevalence rates have not decreased in adults over the age of 18 since the onset of vaccination (Chen CH *et al.*, 2007). Thus the burden posed by hepatitis B on society and on health care resources is likely to prevail for the considerable future (Mohamed *et al.* 2004).

For those infected with HBV, appropriate management has been shown to substantially reduce the risk of long-term liver damage, including cirrhosis and liver cancer. However, a large proportion of HBV-infected individuals do not access appropriate and timely diagnosis, monitoring or treatment in many countries of the world, including Taiwan. This is due to a number of factors, the most important of which is low awareness of the urgency to seek medical advice about hepatitis B in the general population. This is compounded by incomplete knowledge by treating physicians of the most appropriate management options for patients and financial barriers due to limited reimbursement of diagnostic and treatment alternatives.

Thus much remains to be done to minimise the burden of illness posed by hepatitis B on Taiwanese society.

The purpose of this document is to present an up-to-date summary of the main facts surrounding the prevalence, mortality, natural history, and management of hepatitis B in Taiwan, to raise public awareness and to provide a platform for

discussion amongst patient representatives, leading scientific experts and policy-makers. It is hoped that this will assist all stakeholders to identify the key challenges and opportunities to be addressed if we are to move one step closer towards the elimination and eradication of hepatitis B infection in Taiwan.

II. What is hepatitis B?

The hepatitis B virus (HBV) is the most common of the different viruses (A, B, C, D and E) that cause hepatitis, which means inflammation of the liver (Lavanchy, 2005). Hepatitis B is transmitted by contact with the blood or body fluids of an infected person. Unlike hepatitis A or E, it cannot spread through contaminated food or water.

The virus survives out of the body for up to 7 days, thus the risk of infection upon exposure is very high. In fact, the virus is 100 times more infectious than HIV and 10 times more infectious than hepatitis C.

Who is at risk of becoming infected?

The main modes of transmission are:

- *Vertical* – when an infected mother transmits it to her child at birth
- *Horizontal* – health care workers exposed to sharp objects; sexual contact (heterosexual or homosexual) with infected individuals; shared contaminated needles amongst injection drug users; household contacts of chronically infected persons.

In Asia, the main route of transmission of HBV is from an infected mother to her newborn infant (m0ther-to-infant transmission). Other major modes of transmission are child-to-child contact within households where a family member is infected and contamination through the reuse of unsterilised needles and syringes in healthcare settings (Lavanchy, 2005).

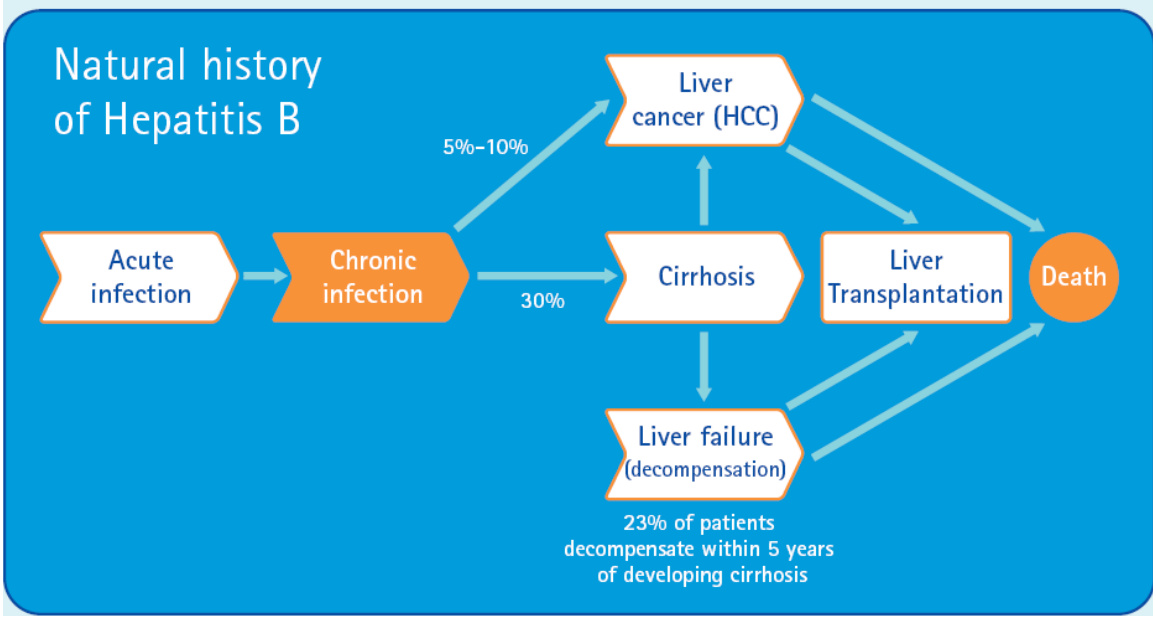
Natural history

The natural history of hepatitis B is complex, as it starts off as an acute infection that may evolve into chronic disease. Most cases of acute hepatitis B will resolve naturally without treatment. However, when chronic hepatitis B develops, it can lead to serious and debilitating liver disease if left untreated (see ***Figure 1*** below).

The risk of developing chronic disease depends on the age at which one becomes infected. Around 90% of individuals who are infected as newborns will develop chronic HBV infection, whereas this risk is much lower if one is

infected as a child younger than 5 years of age (25-30%) or as an adult (1-5%). For this reason, the main focus of vaccination programmes against HBV has been amongst newborns and children.

Figure 1: The natural history of hepatitis B



Adapted from Torresi et al, 2000 and Fattovich et al, 2003.

A silent disease

Hepatitis B is often called a 'silent disease' because symptoms are difficult to identify as they are not specific to hepatitis. They include loss of appetite, tiredness, vomiting, fever, joint pain, nausea, abdominal pain and jaundice. Even at the chronic stage of disease, many people are unaware of any symptoms.

Chronic hepatitis B may best be described as an evolving, dynamic set of interactions over time between the virus itself, cells in the liver (hepatocytes) and the person's immune system (Chen 1993; Liaw 2009b). The nature of these interactions defines the natural course of hepatitis B in several different phases. For persons infected at birth or during early childhood, there is usually a long initial phase termed the 'immune tolerant phase' during which the person does not exhibit any symptoms and the liver is not yet damaged.

The duration of these different phases, however, will vary from one individual to another. For this reason, it is critical that all persons known to be HBV-positive be monitored carefully so that appropriate steps may be taken to manage their disease as effectively as possible over the course of time.

Liver cancer

Once chronic disease starts causing liver damage, its consequences can be very serious. As is shown in ***Figure 1*** above, 30% of patients with chronic infection develop cirrhosis and nearly half of them will die from liver failure or liver cancer (more accurately referred to as hepatocellular carcinoma or HCC).

Hepatitis B remains the main cause of liver cancer in Taiwan, followed very closely by hepatitis C (Lee *et al*., 2009). Liver cancer is the leading cause of cancer in Taiwanese men and accounts for 21.8% of male cancer deaths. There were an estimated 7,159 cases of liver cancer in men in 2005, which represents an incidence of 62 new cases per 100,000 men every year (***Table 1***). Liver cancer is somewhat less frequent in women, in whom it is the second-leading cause of cancer mortality (2,757 cases in 2005 and 14.2% of female cancer deaths) (Lee *et al*., 2009; Department of Health, 2008).

Chronic liver disease and cirrhosis are the seventh most important cause of death in Taiwan. It is estimated that close to 11,000 people die every year in Taiwan due to liver failure or cirrhosis related to HBV (Mohamed *et al.,* 2004).

Table 1: Incidence of the five leading types of cancer in Taiwanese men, 2005 (Department of Health 2008)

Site of cancer	**No. of new cases in 2005**	**Crude incidence** (per 100,000)
Liver and intrahepatic bile ducts	7,159	62
Colorectal	5,497	48
Lung, trachea and bronchus	5,566	48
Oral cavity, oropharynx and hypopharynx	4,310	37
Prostate	2,704	23

A significant economic burden

In addition to its impact on morbidity and mortality, hepatitis B also poses a significant economic burden on society. Direct costs include the cost of treatment for acute and chronic hepatitis, cirrhosis, and liver cancer. Indirect costs result from lost productivity of patients with HBV in terms of the time they need to receive treatment or spend in hospital, time off work due to illness and premature death due to the sequelae of hepatitis B. As one would expect, costs increase significantly with progressively worsening disease state.

Most patients with sequelae of hepatitis B occur between 30-50 years of age. Therefore a large number of people affected by hepatitis B are men of working age who are very likely the sole supporters of their families. Their illness can thus have a significant economic impact on their family's welfare.

III.Managing hepatitis B disease: prevention, screening, monitoring and treatment

Proper management of hepatitis B requires a combination of prevention, screening of individuals at risk, monitoring of HBV-positive individuals to decide when to initiate treatment, and treatment of patients with chronic disease. A necessary companion to each of these aspects of management is thorough education and information of patients, their families and treating physicians to ensure that the optimal care is chosen for each individual affected by HBV infection.

Vaccination: the most effective prevention

Hepatitis B is a preventable disease. Because mother-to-infant transmission is the most important route of transmission, the most effective prevention method is vaccination of newborns and young children. A vaccine against HBV has existed since 1982 and HBV was included in the World Health Organisation Expanded Programme on Immunization (EPI) programme in 1991. Today, over 130 countries offer systematic vaccination to newborns against HBV.

Taiwan was the first country to introduce a universal vaccination programme against HBV in 1984 (Chen *et al*., 1987). The programme has evolved over the years, and today, it covers all newborns, who receive a vaccine dose at 0, 1 and 6 months. Catch-up vaccinations are also given to all preschool children who did not receive vaccination at the neonatal period, to all first-graders and all children <15 years of age. Coverage of infants is in the order of 97% (Ni *et al*., 2001). Vaccination is also offered to all susceptible health-care workers (Mohamed *et al.,* 2004).

As a result of the vaccination programme, the rate of chronic hepatitis B infection amongst children in the Taipei City under the age of 15 years has decreased from 9.8% in 1984 to 0.7% in 1999 (Ni *et al*, 2001). The liver cancer rate in children aged 6-14 years has fallen from 0.7 per 100,000 in the early 1980s to 0.36 per 100,000 in the early 1990s (Chang *et al,* 1997). Moreover, the vaccination programme has resulted in decreased rates of horizontal transmission amongst children (Chien *et al.*, 2006).

Targeted prevention of high-risk groups

Other prevention efforts exist to encourage individuals at risk to modify their behaviours to minimise their risk of becoming infected by HBV. Tactics include promoting condom use to avoid sexual transmission (heterosexual and homosexual), implementing safe syringe use and sharps disposal for medical personnel, and providing needle-exchange programmes to intravenous drug users.

Screening

Screening for HBV is a critical means of identifying individuals who are at high risk of being infected by HBV but do not present any symptoms (asymptomatic HBV carriers), to ensure that they receive appropriate monitoring, treatment and counselling and that they do not unknowingly infect others. Given that universal vaccination was only introduced in 1984, individuals born before that time are still at high risk of carrying the HBV. Screening is the only way to ensure that all cases of HBV infection are identified before diseases become apparent.

To be successful, screening programmes must be accompanied by appropriately targeted public information campaigns, to ensure that individuals follow up screening with necessary actions.

Screening policies for HBV differ significantly from country to country. In Taiwan, screening is done at blood donation, when entering school, the military or new employment. In China, children and adolescents are screened before admission to kindergarden, school and university and hospitalised patients are all screened systematically for HBV markers. In Singapore, all persons applying for residential visas are screened (Hou *et al.*, 2004).

Diagnosis

Identification of the hepatitis B virus is done by various tests, where one looks for hepatitis B viral or serological markers (signs for HBV in the blood).

Unfortunately, a great majority of HBV patients remain undiagnosed, mostly because of the silent nature of hepatitis B. In addition, many diagnostic and monitoring tests are not reimbursed in Taiwan. Therefore inability to pay is often an obstacle to receiving appropriate care for many poorer patients with hepatitis B (Mohamed *et al.* 2004, Hou *et al*., 2004). This is particularly true in the case of recent molecular assays. Additionally, many physicians seeing individuals who are carriers for HBV may not be fully aware of the most effective diagnostic and monitoring tests available (Liaw 2009a). Finally, individuals who suspect they are infected with HBV may be reluctant to seek diagnosis for fear of stigmatization.

Monitoring

Diagnosis is the first step towards appropriate management of HBV, however, initial diagnosis must be followed by continuous monitoring of the patients' viral load to determine whether treatment is needed, at what point it should be initiated and for how long. These questions remain critical issues of discussion among leading experts of hepatitis B in Taiwan and elsewhere in the world (APPROACH 2008).

Monitoring is done via periodic assessment of key parameters such as HBV DNA levels as well as liver disease progression. The critical role of HBV DNA as a marker for liver cirrhosis as well as liver cancer was ascertained in world-acclaimed studies conducted mainly in Taiwan (Chen C-J *et al*. 2006; Iloeje *et al.*, 2006). The conclusions of these studies have allowed for much greater precision in determining at what point to initiate antiviral treatment for HBV-infected patients and whether treatments administered are being effective.

The most recognised means of identifying the stage of progression of liver disease is liver biopsy. Yet many patients are reluctant to undergo liver biopsy for fear of the invasiveness of the examination.

Existing guidelines offer recommendations as to the most meaningful markers and the most effective monitoring techniques (Liaw *et al.*, 2008). However, practice varies significantly and patients may fail to present for annual monitoring check-ups in the absence of symptoms. As a result, they may only present to physicians for treatment at a stage when cirrhosis or extensive liver damage has already begun. The fact that many monitoring tests are not comprehensively reimbursed in Taiwan poses an additional financial hurdle to appropriate patient management.

Treatment

The ultimate goal of HBV treatment is to permanently inhibit replication of the HBV, as this has been shown to be the most important factor in reducing the risk of long-term liver damage and progression to cirrhosis and liver cancer. It is

thus critical to initiate treatment early using the most meaningful markers for viral replication to prevent significant liver damage from occurring. Early treatment also allows preventing the significant health care costs associated with subsequent advanced liver diseases.

Treatment options

The past few decades have seen tremendous advances in the discovery of effective and safe antiviral agents against HBV. Two main antiviral treatment options exist currently: interferon-α, and nucleoside/nucleotide analogues. Interferon is given by injection, whereas nucleoside/nucleotide analogues are administered orally. Because of the high prevalence of HBV infection in Asia, many of the clinical trials testing these medicines have taken place in Asia in Asian patients. Thus significant experience has been gained that has demonstrated the ability of antiviral treatments to stop viral replication, prevent the occurrence of cirrhosis and reduce mortality in patients affected by chronic hepatitis B (Liaw *et al.*, 2009a). Studies have also shown that effective therapies against HBV may reduce the healthcare costs associated with chronic hepatitis B in Taiwan (Hsieh *et al.*, 2004).

An evolving evidence base

As in other therapeutic areas, evidence and knowledge about the effectiveness of different treatment approaches is constantly evolving. At the same time, important insights into the natural history of hepatitis B have been gained in recent years.

On the basis of this combined evidence, experts from around Asia have written a consensus statement on the management of chronic hepatitis B, the most recent version being updated in 2008 (Liaw *et al*., 2008). These guidelines look in depth at which particular treatments are most appropriate for specific groups of patients in accordance with their viral load tests, liver function tests and other clinical parameters. They also provide guidance as to which treatments should be initiated when, and for how long.

Under-treatment

Despite the emergence of these guidelines, too few patients actually benefit from treatment in Asia, in cludingTaiwan. An international survey estimated that only 4% of patients diagnosed with HBV in Asia received treatment, as opposed to rates of 20% in the United States and 17-28% in Europe (Decision Resources 2006).

These low treatment rates are due to many factors. These include: low awareness amongst carriers as to the need for monitoring, insufficient

knowledge on the part of physicians of the importance of timely treatment and financial barriers in access to treatment in Taiwan.

Complex disease management

As has been described above, the pathways of care for hepatitis B are complex. Many health professionals may not have had the opportunity to fully understand the management options available to patients infected with HBV. Yet this knowledge is essential if patients are to be offered the individualised counseling, assessment and explanation of care options necessary to optimise their chances of successful outcomes (Liaw *et al*., 2008).

Recognition of the need for dedicated training on hepatitis B was a key driver behind the recommendations of the APASL. Also, a number of helpful pocket guide books (Liaw 2006; Liaw 2006b), journal supplements and internet-based outreach educational programmes have been developed in Taiwan to try to help primary care physicians, internists, gastroenterologists and hepatologists improve the standard of care offered to patients infected with HBV (Liaw 2009a).

Financial barriers to treatment

Only some of the antiviral therapies advocated in the APASL guidelines benefit from full reimbursement in Taiwan (Liaw 2009a). As a result, patients must pay for treatment out-of-pocket.. Only a very small minority of patients have private insurance to cover full treatment costs. Fortunately, the Bureau of National Health Insurance has recently lifted some key hurdles in financial barriers, and the improvements are anticipated.

IV. Challenges to containing hepatitis B in Taiwan

A huge success story…

The Taiwanese vaccination programme against hepatitis B is a true success story. It is also a promising example of how many diverse institutions – the local governments, the Department of Health, the Ministry of Education, the Ministry of National Defence, academic institutions, non-profit organisations and local government – can work together to achieve a common public health goal.

The programme was also made possible thanks to a strong public health infrastructure, highly trained nurses and an active public education campaign that took place for at least three years before the onset of vaccination in 1984.

Moreover, Taiwan has also made important efforts to improve the management of patients infected with HBV. In 2003, the Taiwanese Center for Disease Control initiated a pilot programme entitled '*Strengthening of treatment for chronic hepatitis B and C under the National Health Insurance*'. The programme tries to ensure that all cases of hepatitis B (and hepatitis C) are registered so that individuals affected may benefit from appropriate diagnosis, monitoring and treatment. The ultimate goal of the project is to reduce the incidence of liver cirrhosis and liver cancer in Taiwan.

Finally, the comprehensive disease registry and death certification system in Taiwan have helped identify and monitor cases of hepatitis mortality and liver cancer in children over the years and evaluate the success of the vaccination programme (Chien et al, 2006).

…Yet challenges remain:

Despite this success, hepatitis B remains a major public health problem in Taiwan, resulting in thousands of deaths per year. Moreover, a number of studies have shown that general awareness of hepatitis B remains inadequate within the Taiwanese population despite repeated public educational efforts on behalf of the Taiwanese government. For example, a survey of 1025 adults aged 30 years and above in Taiwan found that only 52% knew about chronic HBV infection and only 46% knew of the existence of effective treatments. Fewer than half of individuals infected with chronic hepatitis B knew that they were infected (IMS Health Taiwan 2005). Similar results were found in Taiwanese university students, with several studies finding that up to one-quarter of students who were HBV-carriers were unaware of their status or of the necessary actions they needed to take to prevent disease from developing over time and to avoid infecting others (Wang *et al*., 2009; Wang *et al*., 2006). These worrying results are not unique to Taiwan and are a sobering reminder of the lack of knowledge about HBV in the general population and the need for greater efforts to use settings such as universities and schools to help raise awareness of the disease.

Thus complacency cannot be allowed to develop, and further efforts to ensure that appropriate prevention, screening, diagnosis and treatment are offered to the entire population, are still urgently needed.

Some of the remaining challenges to achieving the optimal containment, and eventual eradication, of hepatitis B in Taiwan include:

1. *Need for greater awareness and education*

i. ***Need for greater emphasis on the importance of screening and regular monitoring of HBV**:* Screening for hepatitis B is critical to ensure that all individuals infected by HBV are aware of their status, adopt appropriate preventive behaviours and seek appropriate care. Governments, including local agencies, must continue extensive screening programmes for hepatitis B. In addition, significant efforts are needed to ensure that individuals infected with HBV are monitored regularly for disease progression using the most meaningful tests and procedures and that physicians are aware of protocols to be followed and optimal tests and techniques to be used.

ii. ***Inadequate understanding of hepatitis B amongst treating physicians:*** Many practitioners lack the adequate knowledge to identify individuals at risk of infection, thus hepatitis B remains under-diagnosed in Taiwan. It is also under-treated, as many physicians lack sufficient knowledge of the pathways of care that are available to patients infected with HBV, limiting their ability to offer individualised advice to their patients. The importance of early treatment in particular needs to be recognised (Liaw *et al*., 2008)

iii. ***Poor understanding of hepatitis B in the general population:*** Hepatitis B is a complex disease. Understanding its natural history, the risks associated with being an HBV carrier and the importance of appropriate care requires dedicated educational efforts specific to each risk group. There have been a number of public awareness campaigns in Taiwan, yet further efforts are needed, particularly to encourage individuals to undergo screening. Also, it is important to recognise that stigma about being HBV-positive may inhibit certain individuals from seeking appropriate screening as they fear discrimination within their communities and possible repercussions on their employment status if they are known to be HBV-positive (Tan and Cheah, 2005). This fear may also make them reluctant to undergo diagnosis and appropriate care.

2. *Need to ensure continued success of the vaccination programme*

i. ***Continuous evaluation of the quality and impact of vaccination:*** Continued success of the vaccination programme in Taiwan requires the availability of high-quality vaccines, prevention of vaccine failure and careful monitoring of outcomes of vaccination. These must remain a

public health priority for the public health impact of the HBV vaccination programme to continue in Taiwan. (Lee *et al*, 2009; Chang *et al*, 2005)

ii. ***Adapting to a changing epidemiology of HBV:*** Further research is needed into the natural history and evolving epidemiology of HBV in Taiwan to ensure that vaccination programmes are not missing out on any new risk groups that may develop over time. For example, although waning immunity of the vaccine after 15-20 years has not, as of yet, been observed to the extent that a booster is generally recommended after this time period, the possibility that this situation may change should be monitored closely.

3. Need to improve standards of care for the management of hepatitis B

i. ***Lack of compliance with clinical guidelines:*** As in many other clinical areas, there is inconsistency in practice in the management of hepatitis B. Continuing educational efforts are needed to disseminate the 2008 revised APASL guidelines and ensure that care is harmonised across different treatment centres. In particular, decisions about when to initiate therapy and for how long should be based on the most up-to-date evidence, as there remains considerable uncertainty as to what the optimal duration of antiviral therapy should be in different groups of HBV-infected patients.

ii. ***Resistance issues with many antivirals:*** An already emerged issue with the use of some of the antivirals, particularly the older ones, is that the HBV may become resistant to some of these drugs, particularly after prolonged treatment. Thus careful monitoring during treatment is needed to adapt treatment over time. Many of the newer antivirals do not seem to exhibit the same resistance patterns as some of the older agents (Liaw, 2009b).

4. Need to overcome geographic and social inequities in access to care

i. ***Higher prevalence of hepatitis B infection in vulnerable populations:*** Despite vaccination, prevalence rates of hepatitis B infection are higher in indigenous populations, in persons of lower socioeconomic status as well as those living in remote areas (Huang *et al*., 2009). Particular prevention, screening and monitoring efforts are thus needed with these difficult-to-reach populations.

ii. ***Lack of medical clinics in rural areas:*** In Taiwan as in many Asian countries, there are limited facilities offering diagnosis, screening and treatment for HBV in rural areas. Moreover, most hepatologists and gastroenterologists are concentrated in the large urban centres. Thus innovative ways to provide targeted outreach programmes to individuals residing in these remote areas are needed.

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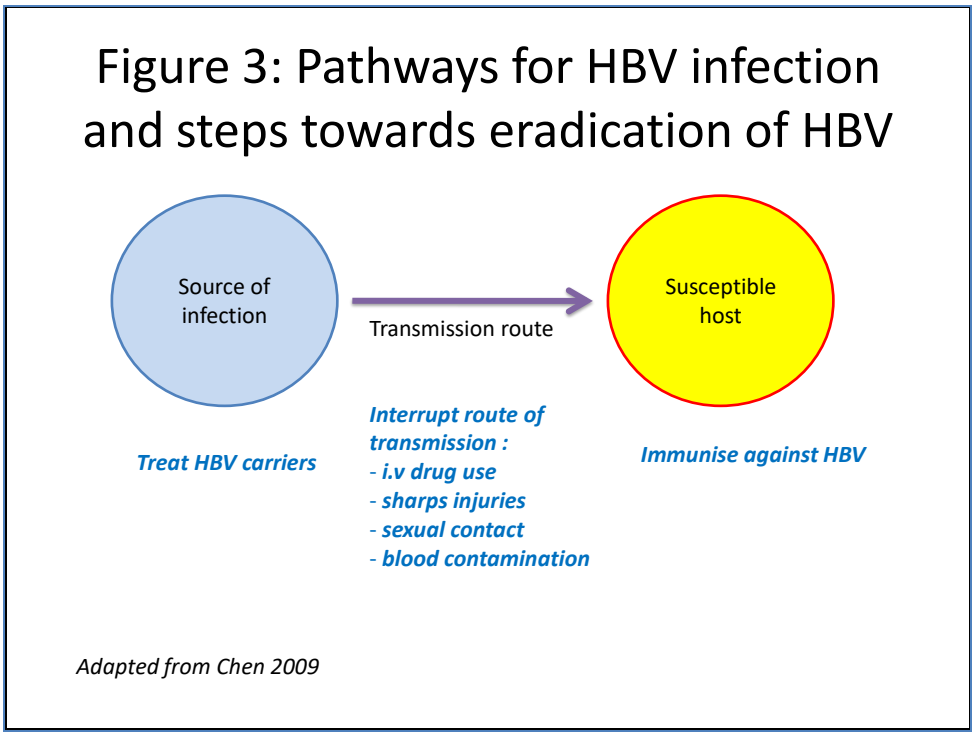
V. The way forward

Twenty-six years after the introduction of its vaccination programme against hepatitis B, Taiwan is at an exciting juncture with respect to hepatitis B. More than any other country, it can realistically contemplate the possibility of eliminating and eradicating the disease from its population, perhaps within the next 50 years.

Though possible, eradication of hepatitis B in Taiwan will require concerted efforts in a number of key areas. As was stated by Professor DS Chen:

> *Eradication of hepatitis B in Taiwan requires 'long-term commitment to continue the vaccination as well as interrupting the routes of transmission, treating the chronic HBV carriers, so that the infection is completely stopped*.' (Chen D-S, 2009).

These three areas of focus are illustrated in ***Figure 3*** below.



- First and foremost, susceptible individuals must be immunised – The continued success of the vaccination programme should not be taken for granted and continued efforts to achieve high coverage levels and monitor the outcomes of the vaccination programme on the epidemiology of HBV in Taiwan are needed.
- Secondly, the actual source of infection should be suppressed to a maximal extent. In other words, HBV-infected individuals should be treated in order to reduce the viral load of HBV to undetectable levels to prevent the spread of infection. For this to occur, rates of diagnosis, monitoring and treatment need to increase significantly in Taiwan. And most importantly, barriers in access must be removed to ensure that individuals affected by HBV are properly identified, that their disease is carefully monitored and that they receive timely and appropriate treatment.
- Thirdly, routes of transmission must be interrupted. Primary prevention measures targeted at high-risk individuals need to be implemented and compliance with such measures encouraged through public awareness campaigns. Targeted screening programmes are needed across the entire population.

In conclusion, hepatitis B continues to represent a tremendous public health burden in Taiwan. It is the main cause of liver cancer, which in turn is the leading cause of death in men and the second cause of death in women. Yet clinical experience has shown that effective screening, diagnosis, monitoring and treatment of individuals affected by HBV can lead to a significant reduction in the burden of illness posed by HBV and prevent progression to severe liver

disease in patients. If sufficient resources are devoted to continuing vaccination and improving access to screening, diagnosis and treatment for hepatitis B in Taiwan, then complete eradication of hepatitis B may indeed be a long-term possibility. In the meantime, concerted efforts are warranted to minimise the burden of hepatitis B on Taiwanese society and ensure that individuals affected by HBV achieve the best outcomes possible.

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