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Editorial

This issue of *Viral Hepatitis* reviews topics covered at the meeting on **Prevention and Control of Perinatal Hepatitis B Virus (HBV) transmission in the WHO European Region,** held on March 15-17, 2006 in Istanbul, Turkey. The meeting was organized by the Viral Hepatitis Prevention Board (VHPB) in partnership with CDC/Atlanta, UNICEF and the WHO. National and international experts from eight countries of the WHO European Region participated in the meeting.

The countries of the WHO European Region have achieved a marked progress in the introduction and implementation of immunisation against HBV, including immunisation of newborns in countries with high HBV prevalence. However, in some countries, in particular those with a high proportion of home deliveries, timely immunisation of newborns remains a challenge. On the other hand, as a result of the success documented for current immunisation programmes and other priorities existing in many countries of the Region, HBV vaccination is in danger of losing the priority it deserves on the agenda of governments, as well as partner agencies and organizations. This is reflected by some agencies downgrading HBV vaccination-especially within the mother-and-child health context.

However, HBV burden is still substantial, with an estimated number of 350 million chronic carriers in 2000, which continues to rise worldwide, and 30-90% of children infected below one year of age becoming HBV chronic carriers. This is particularly critical in regions of intermediate and high HBV endemicity, such as the WHO European Region, where 70-80% of infections are acquired perinatally and in early childhood.

HBV vaccination is the most effective measure to prevent HBV infection and its consequences, thus contributing significantly to the control and eventual eradication of the disease. The primary strategy for preventing HBV infection and related disease in future cohorts is to promote the vaccination of newborns and infants.

The overall objective of the meeting was to further contribute to prevention and control of perinatal HBV transmission in the countries of the WHO European Region, by highlighting the importance of timely newborn HBV vaccination, within the broader framework of mother-and-child health services. In order to reach this objective, participants of the meeting reviewed issues relating to current epidemiology of perinatal HBV transmission, scientific evidence of prevention and control of HBV transmission through vaccination, and country experience and examples of good practices on prevention and control of perinatal HBV transmission. Specific topics covered included country experience and information exchange on current HBV epidemiology, disease surveillance and monitoring of the impact of HBV vaccination programmes, modalities and timeliness of birth dose administration, contraindications and barriers to HBV newborn vaccination, logistics of HBV vaccination programmes and vaccine procurement, and sustainable financing.

The meeting focused on the situation in the Central Asian Republics, Caucasus and Turkey, and discussions highlighted lessons learnt, progress achieved and challenges remaining, which is relevant to other countries of the Region as well. Lessons learnt included the need for enhanced capacity building; sustainable vaccine procurement and supply; as well as improved communication at all levels, targeting health professionals, the general public, politicians and the media. Presentations and discussions during the workshops and meeting, as well as feedback from pre-meeting country questionnaires all contributed to conclusions with a list of lessons learnt and recommendations relevant to future directions for prevention and control of perinatal HBV transmission in the WHO European Region and elsewhere. These lessons learnt mainly addressed key challenges remaining for successful implementation of HBV vaccination programmes, particularly administration of HBV birth dose.

Nedret Emiroğlu and Selim Badur,
on behalf of the Viral Hepatitis Prevention Board

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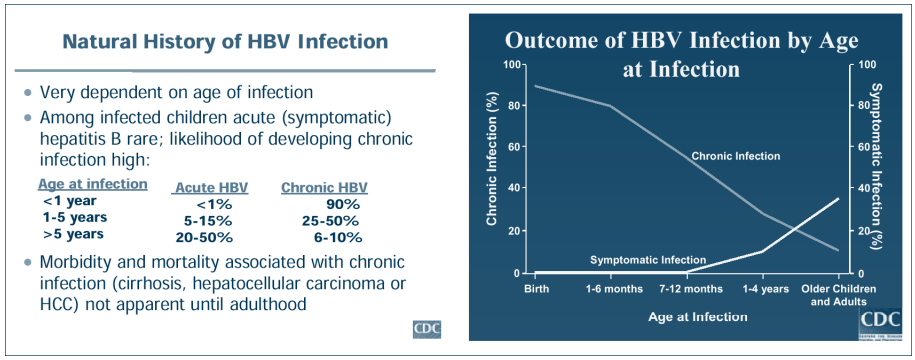
Prevention and Control of Perinatal Hepatitis B Virus (HBV) Transmission in the WHO European Region -a VHPB Symposium Report- Istanbul, Turkey, March 15-17, 2006

Epidemiology

Global estimates for hepatitis B disease burden

A true appreciation of the global disease burden caused by HBV is difficult because chronic HBV infections, accounting for most HBV-related morbidity and mortality in the form of cirrhosis and hepatocellular carcinoma (HCC), are not easily identified and reported.

HBV disease burden is also determined by the natural history of HBV infection, which is dependent on age of infection. Most children's infections are asymptomatic and go unrecognized: <1% of <1-year-olds develop acute symptomatic disease, yet 30-90% of them will develop chronic infection which will not be apparent until adulthood (see below).



The age at infection has also been shown to vary according to endemicity, with 70-80% of infections occurring perinatally and in early childhood in regions of high hepatitis B surface antigen prevalence (HBsAg ≥8%), versus <40% in regions of low prevalence (HBsAg<2%) [1].

Modes of HBV transmission in infants and children

There are two major modes of HBV transmission at early age: perinatal transmission from an infected mother to her infant and early childhood transmission (sometimes referred to as horizontal transmission) from an infected household contact to the child [2][1]. However, in some countries, e.g. Kyrgyzstan, children are also exposed parenterally.

Perinatal transmission of HBV infection from mother to infant generally occurs as a result of percutaneous and permucosal exposure to the mother's infected blood during birth. *In utero* transmission of HBV is rare, accounting for <2% of all perinatal infections [2]. Although HBV is found in low concentrations in breast milk, it has not been documented to be transmitted through breastfeeding.

The risk of perinatal transmission from an infected mother to her infant is related to the HBV viral load reflected in the serologic status of the mother's. The presence of hepatitis "e" antigen (HBeAg) indicates high viral load and increased infectivity: 70-90% of infants born to HBeAg positive mothers become infected, against 5-20% of infants born to HBeAg seronegative mothers.

Early childhood transmission of HBV most often occurs through household members with chronic infection. It may be facilitated by breaks in the skin barrier, such as scabies, leg ulcers, insect bites and dermatitis, that may be common in developing countries, especially in the tropics.

In regions of high and intermediate endemicity, perinatal and early childhood transmissions are the major sources of infection. Sexual transmission of HBV accounts for a high proportion of new infections among adolescents and adults in low and intermediate endemicity countries. Percutaneous exposures (such as unsafe injections and other unsafe percutaneous procedures) are a major source of HBV transmission in many developing countries [2].

[1]***Note**: For consistency purposes, "perinatal and early childhood transmission" terminology has been used in all parts of this report and according to Mast E, Mahoney F, Kane M, Margolis H. Hepatitis B vaccine. In: Plotkin SA, Orenstein WA, editors. Vaccine 4th ed. Elsevier; 2004. P 299-337, independently of terminology used in the speakers' presentations or during meeting discussions.*

Importantly, both perinatal and early childhood transmission can be prevented by vaccination of newborns and hepatitis B vaccine prevents perinatal transmission in up to 95% of infants when given soon after birth.

On the basis of HBV epidemiological data, a mathematical model was developed to estimate the global hepatitis B disease burden and vaccination impact [3]. The specific objective of this model is to evaluate the reduction in HBV-related morbidity and mortality with different vaccination strategies, and serve as a field tool at country level to facilitate introduction of hepatitis B vaccination, as discussed in the next section of this report.

HBV disease surveillance in selected countries of the WHO European Region

HBV endemicity per region			
Country	**Low endemicity <2%**	**Moderate endemicity 2-8 %**	**High endemicity ≥8 %**
Armenia	x		
Azerbaijan		x	
Georgia		x	
Kazakhstan		x	x
Kyrgyzstan			x
Tajikistan			x
Uzbekistan			x
Turkey		x	

Turkey

Turkey is a country of intermediate endemicity for HBV infection (3-8% HBsAg positivity), with a 1/3 of its population testing positive for anti-HBc. In 25% of chronic hepatitis cases, individuals are co/superinfected with hepatitis D virus (HDV); also, in 25% of cases, precore mutants are present, and genotype D is homogeneously represented (>99%).

Acute HBV infections compromise 29.7% of individuals aged 0-14 years in Turkey. In the pre-vaccination era, the number of reported HBV cases increased from an estimated 2000 cases in 1990 against ~5000 cases in 1998 while figures rose to >8500 in 2005. Of note, the increase after 1998 is partly to be attributed to better surveillance systems implemented after the introduction of routine vaccination. Several studies of aetiological classification of hospitalized acute viral hepatitis (VH) have shown HBV to be the leading cause of acute VH cases in the adult population (60.4%), followed by hepatitis A virus (HAV) (27.5%) whereas this situation is reversed in children (22.4% HBV vs 63.1% HAV).

As in regions of high HBV endemicity, HBV is the leading cause of HCC in Turkey whereas, in regions of low HBV endemicity, hepatitis C virus (HCV) is the leading cause of HCC.

HBV seroprevalence in Turkey is characterized by regional differences with significantly higher HBsAg and anti-HBc positivity in the Eastern part of the country. This is mainly explained by a lack of access to sufficient health services in that part of the country.

In Turkey, HBV transmission mainly occurs in early childhood, which is supported by HBsAg positivity rates which start to increase after age 5 and peak among 16-20 year-olds (~10%), when sexual transmission also plays an important role. This is also reflected in anti-HBc positivity rates peaking in the 11-14 year-olds (6.8%) and 15-19 year-olds (11.8%), respectively. However, studies which have looked at aetiological reasons for acute HBV cases in Turkey have shown a high level of unknown aetiology (up to 44.4%).

The importance of HBV transmission in early childhood and later in life is further reflected in the age distribution of HBV acute cases, peaking among 15-44 year-olds.

Reported HBsAg positivity rates in pregnant women do not exceed those in the rest of the population, as shown from several studies conducted in several regions of Turkey in the 1990s (pre-vaccination era) and 2000s (post-vaccination era). Of note, the low HBeAg positivity rates, which may explain the low rates of perinatal transmission in Turkey, compared to countries, such as Taiwan, which may reach 40-50% rates.

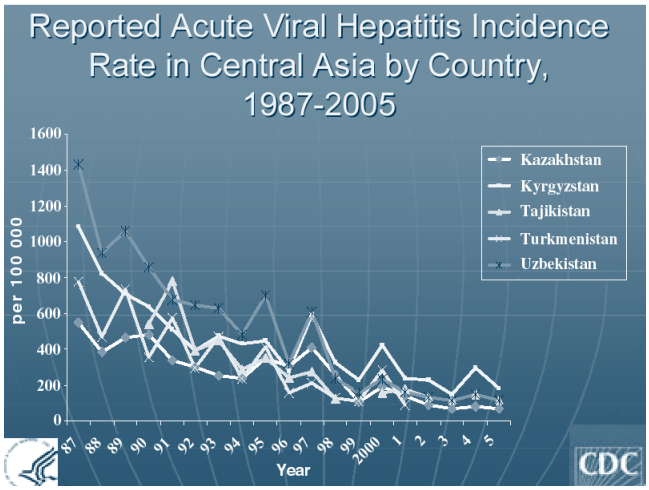
HBsAg Positivity in Pregnant Woman in Various Regions, Turkey, 1990s			
City	**Study Group**	**N**	**HBsAg (+) %**
Erzurum	Parlak M et al., 1994	**171**	**2.3**
Kayseri	Abaci IM et al., 1995	**400**	**3.8**
Istanbul	Çepni I et al., 1996	**4078**	**4.4**
Izmir	Erensoy S et al., 1996	**760**	**4.2** *(HBeAg 15%)*
Denizli	Kaleli I et al., 1997	**312**	**7.7** *(HBeAg 8.3%)*
Sivas	Poyraz Ö et al., 1999	**95**	**6.3** *(HBeAg 1.1%)*

HBsAg Positivity in Pregnant Woman in Various Regions, Turkey, 2000s			
City	**Study Group**	**N**	**HBsAg (+) %**
Ankara	Biri et al., 2001	**451**	**7**
Diyarbakir	Turhanoğlu M et al., 2001	**260**	**12.3** *(HBeAg 4.6%)*
Istanbul	Karaca Ç et al., 2003	**460**	**4.7**
Sanliurfa	Harma M et al., 2003	**136**	**7.3**
Afyon	Yilmazer M et al., 2004	**244**	**2.9**
Mersin	Börekçi G et al., 2004	**114**	**3.5**

Central Asia

VH is highly endemic in Central Asia. Over the period 1991-1998 in the pre-vaccination era, the estimated mortality rate due to acute VH in Central Asia was ~4/100,000 and >10/100,000 due to VH-related chronic liver disease (CLD). The estimated overall VH burden of disease in this region in the pre-vaccination era represented a total of ~220,000 cases of acute VH cases reported each year versus >1,000,000 cases of chronic hepatitis B.

High incidences of acute VH are reported in the region. However, as shown below, reported rates of acute VH dramatically decreased in all countries of Central Asia from pre- to post-vaccination era:



From a study conducted in Turkmenistan over the period 1989-1995 (pre-vaccination era), it was shown that reported new cases of CLD ranged from ~1,500/100,000 in 1990 to almost 2,200/100,000 cases in 1994.

Armenia

In the pre-vaccination era (prior to 1999) HBV incidence was high in Armenia and ranged from 7.5-23.1/100,000 while HBsAg seroprevalence reached 1-2%. However, the risk of HBV perinatal transmission was high, with high rates of chronic HBV infection.

Georgia

HBV burden of disease in Georgia in the pre-vaccination era was estimated from HBsAg seroprevalence measured among blood donors since no surveillance studies were carried out by the Ministry of Health in this period. Even if they are not comprehensive, these figures hint at the overall burden of disease in the country and indicate a progressive decrease from 6.2% to <1% in 2000.

Over the period 2000-2004, HBV seroprevalence data are available from several surveys conducted in high risk group populations, such as intravenous drug users (IDU), patients with sexually transmitted infections, sex workers, blood donors, patients with tuberculosis and pregnant women. In comparison with results from similar surveys conducted in the years before 2000, results have shown a shift from high to moderate HBV endemicity.

Kazakhstan

In 2004, six years after the introduction of the HBV vaccination programme, HBV was still an important aetiological agent for acute VH (16% of cases) after HAV (81%), in the region. However, the age distribution of acute VH cases had significantly shifted to older age groups. The incidence of acute HBV among children <1 year of age decreased from 24.7/100,000 in pre-vaccination period (1990) to 1.5/100,000 in 2005; from 87.3/100,000 to 0.2/100,000 among children aged 3-6 years; from 44.6/100,000 to 0.3/100,000 among children aged 7-14 years while the incidence of acute HBV among young adults increased for the observed period. In the 20-29-year age group, the incidence increased from 63.3/100,000 in 1990 to 79.0/100,000 in 2005.

Kyrgyzstan

In 2000, CLD was shown to be the 7th most important cause of death in Kyrgyzstan, with almost 20,000 years of potential life lost (YPLL) compared to 100,000 YPLL due to respiratory diseases and trauma, the primary causes of death in the region.

From the sentinel surveillance system of acute VH set up in 2000 in several cities of Kyrgyzstan with the support of the CDC office in the region, it appears that HAV has been the most significant disease for the past 5 years in this region while HBV is still playing an important role, with 20% of cases of VH attributable to HBV.

In a study conducted in the pre-vaccination era (1989) in Osh, the most endemic region of Kyrgyzstan, the distribution of chronic HBV infection by age ranged from >14% among 0-12 month-olds to <6% in >40 year-olds while overall HBV infection prevalence rates ranged from ~25% in 0-12 month-olds to ~60% in >40 year-olds (n=~2000 subjects).

HBV prevalence over the period 1998-1999 was studied in several cities of Kyrgyzstan and estimated to an average of 11.1% HBsAg and 43.8% anti-HBc, for the country.

In another study conducted in the same region among HBsAg chronic carriers (n=73) in the post-vaccination era (2005), results showed a rate of ~25% HBeAg prevalence versus 60% anti-HBe prevalence.

A case-control study which was conducted over the period 2000-2005 determined the major risk factors for acute VH in Kyrgyzstan. Significantly increased risk of developing acute hepatitis B, C or D was observed for children under 5 years of age undergoing blood transfusions and unsafe injections in health care settings.

Uzbekistan

A study conducted among ~2000 subjects in the pre-vaccination era showed a 13.3% HBsAg seroprevalence rate in the general adult population [4].

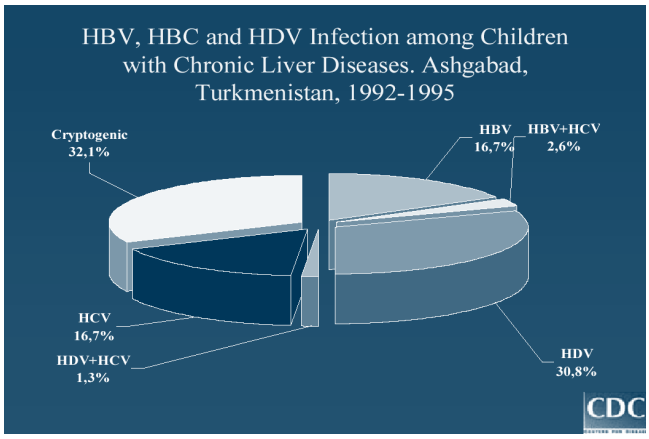
Hepatitis D virus in Central Asia

HDV infection is either acquired as a result of simultaneous co-infection with HDV and HBV, or as a result of superinfection, via HDV infection of an HBsAg-positive host. Since HBsAg carriers infected with HDV have a life expectancy <5 years, Central Asian children born in the pre-vaccination era are still dying from the disease today.

Overall, prior to HBV routine vaccination, there was an estimated case fatality of >2,000 individuals per year from acute VH and >12,000 from CLD, mostly among HBV+HDV co/superinfected individuals in Central Asia.

In a study conducted in Uzbekistan in 1995, the case fatality rate in children <14 years was significantly higher for those co-infected with HBV+HDV: 13% versus 1% for those infected with HBV alone.

The significantly higher proportion of co/superinfected individuals with HDV and HBV, compared to infection with HBV alone is reflected in another study on the aetiology of CLD in children from Ashgabad, Turkmenistan, over the period 1992-1995: 16.7% of cases infected with HBV alone, against 30.8% of cases co/superinfected HDV (see below).



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[1] World Health Organization. Hepatitis B. World Health Organization Fact Sheet 204 (Revised October 2000). Accessed at http://www.who.int/mediacentre/factsheets/fs204/en/index.html on 15 December 2006

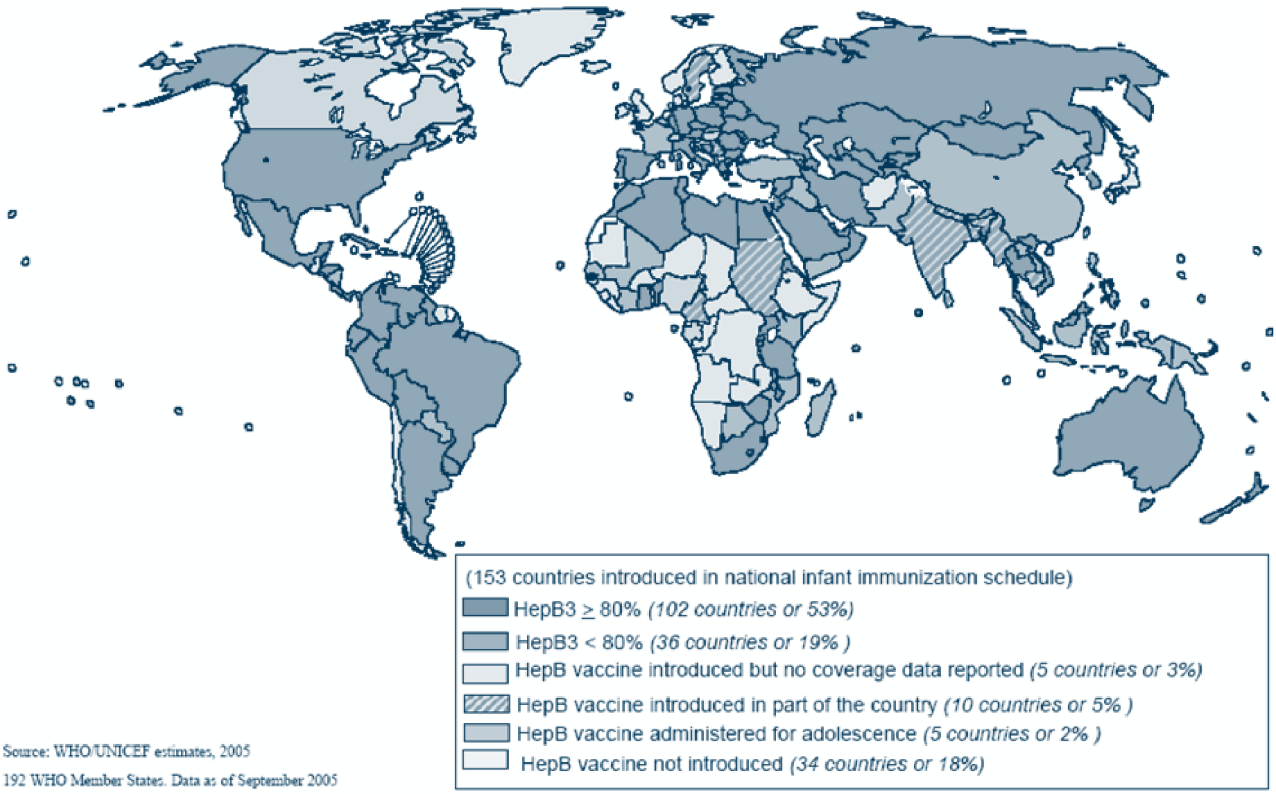
[2] Mast E, Mahoney F, Kane M, Margolis H. Hepatitis B Vaccine. In: Plotkin SA, Orenstein WA, Offit PA, editors. *Vaccines*. 4th ed. Philadelphia: Elsevier; 2004. p. 299-337.

[3] Goldstein ST, Zhou F, Hadler SC, Bell BP, Mast EE and Margolis HS. A Mathematical Model to Estimate Global Hepatitis B Disease Burden and Vaccination Impact. *Int J Epidemiol* 2005;34:1329-39.

[4] Ruzibakiev R, Kato H, Ueda R, Yuldasheva N, Hegay T, Avazova D, Kurbanov F, Zalalieva M, Tuichiev L, Achundjanov B, Mizokami M. Risk factors and seroprevalence of hepatitis B virus, hepatitis C virus and immunodeficiency virus infection in Uzbekistan. *Intervirology* 2001;44(6):327-32.

Based on presentations by S Wang, CDC, Atlanta, USA; L Mosina, CDC Regional Office in Central Asia; M Ciblak, Yeditepe University, Istanbul, Turkey; S Badur, University of Istanbul, Turkey; M Favorov, CDC, Dept of Health and Human Services, Central Asia Office, Almaty, Kazakhstan; A Hayrapetyan, Ministry of Health, WHO National coordinator for DPR, Yerevan, Armenia; P Imnadze, National Centre for Disease Control and Medical Statistics, Tbilisi, Georgia; S Jabirov, Republican Centrer for Immunoprophylaxy, Ministry of Health, Dushanbe, Tajikistan; J Kalilov, Republican Centre of Immunoprohylaxis, Bishkek, Kyrgyzstan; EI Musabaev, Scientific Research Institute of Virology, Ministry of Health of Uzbekistan Tashkent, Uzbekistan.

Countries having introduced HBV vaccine and infant HBV dose 3 coverage, 2004 [2]



Scientific evidence of control and prevention of perinatal HBV transmission through immunisation

Evidence of protective efficacy of newborn vaccination against HBV
Substantial progress has been made in implementing the 1992 WHO recommendation: by the end of 2005, 168 countries worldwide were implementing or planning to implement an immunisation programme for infants and/or adolescents. It is estimated that among the WHO Member States the global immunisation coverage with 3-doses of HBV-containing vaccines reached 51% in 2004, a sharp increase from the less than 10% coverage reported in the early 1990s [1, 2].

HBV vaccination starting at birth for all infants includes two prevention activities. HBV vaccination starting at birth provides a safety net for prevention of perinatally transmitted HBV infections among children born to HBsAg-positive mothers. Secondly, it also prevents HBV infections, including infections from early childhood onwards among children born to HBsAg-negative mothers.

Introduction of universal newborn vaccination and its effect on disease burden: country status and experiences
Data from several countries with intermediate and high HBV endemicity that started 10 years ago with effective implementation of universal newborn HBV immunisation programmes provide conclusive evidence of protective efficacy of newborn vaccination, as demonstrated by the dramatic reduction of carrier prevalence rates after implementation.

In the Eastern European region, considerable reduction in HBV incidence was achieved by implementing routine vaccination over the period 1990-2004.

Turkey
Turkey started its HBV immunisation programme in 1998; it includes universal 3-dose vaccination, beginning with a dose of vaccine administered at birth.

Despite initial obstacles to the introduction of HBV vaccine, substantial progress has been made. HBV vaccination coverage rates are variable depending on the region, ranging from <50% to 80-89% for the 3 doses, with lowest coverage in some regions in the Eastern part of the country. Continued efforts focus on follow up of protection in those children who were vaccinated as of 1998.

Armenia
Universal HBV vaccination was introduced in the national immunisation schedule in 1999, with the first dose to be administered at birth. As of 2003, a high global coverage rate of >90% was attained. The HBV incidence rate was significantly reduced after introduction of HBV vaccine in the national immunisation schedule, especially among children aged 0-14 years where up to a 9-fold decrease was observed. One of the remaining challenges is to improve the coverage rate in those regions where coverage is <90%.

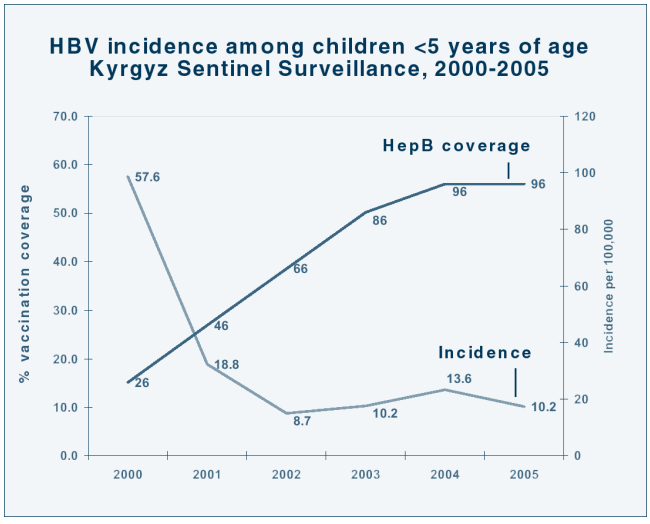
Georgia
HBV vaccine was introduced in Georgia between 2000 and 2003. The new vaccine was integrated into the existing immunisation schedule for children less than one year old, first in urban areas in 2000 and then countrywide in 2001. Maternity hospitals began vaccination of newborns in 2003, resulting in a new vaccination schedule: at birth, 2 and 4 months. Despite initial introduction difficulties, HBV immunisation coverage has increased in 2006 to 96% for the first vaccine dose but only 73% for the 3-dose series, which still requires improvement. The HBV incidence rate among children up to 5 years of age decreased significantly from 12.6/100,000 (1996) and 6.5/100,000 (2000) in the pre-vaccination era to 0.4/100,000 in 2004 and 2.6/100,000 in 2005.

Kazakhstan

Kazakhstan introduced routine newborn immunisation against HBV infection in 1998-99. Infants are immunized at birth, 2 and 4 months. The incidence rate of acute HBV dramatically decreased between 2000 and 2005 and the impact of vaccination was most remarkable through the absence of acute hepatitis in younger age groups. As already mentioned in previous section, the incidence of acute HBV dramatically decreased among children across all ages from pre-vaccination era (1990) to 2005. The serosurvey conducted in 2001 demonstrated that there were no cases of chronic HBV or HBV infection in the vaccinated cohort (children under 4 years of age) versus 4.8% prevalence of HBsAg and 14.3% prevalence of anti-HBc in the unvaccinated cohort (children at 8-9 years of age). It is estimated that 10,000 lives were saved per year by implementation of the regional viral HBV prevention programme.

Kyrgyzstan

Kyrgyzstan introduced universal newborn immunisation against HBV in 1999 in 5 out of 8 regions of the republic. All regions of the country are covered since 2001. In 2000, a sentinel surveillance for acute cases of viral hepatitis was started in Kyrgyzstan. In 2005 surveillance data were used to assess the impact of the HBV immunisation programme. According to this surveillance system, for the period 2000-2005 the percentages due to HBV and HCV were 18% and 4%, respectively, and the percentage due to HAV was 54%. Sentinel surveillance data demonstrate that among children aged <5 years, HBV incidence dropped from 57.6/100,000 in 2000 to 8.7/100,000 in 2002 and was 10.2/100,000 in 2005. Over the same period, 3-dose HBV vaccine coverage rates among infants rose to 96%. Field efficacy data demonstrate that more than 80% of chronic HBV and HBV infection cases were prevented by vaccination. This finding confirms the tremendous impact of the newborn immunisation programme.



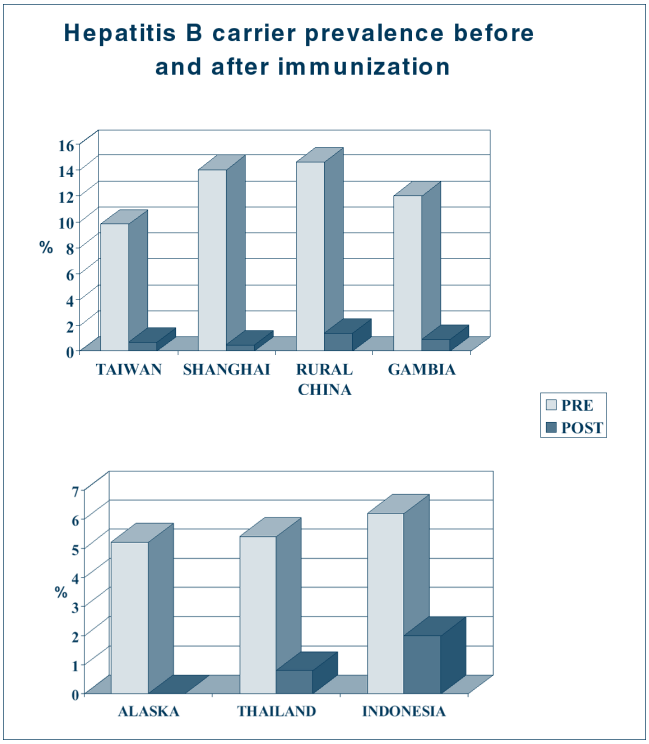
Tajikistan

Tajikistan introduced universal newborn immunisation against HBV in 2002. Since implementation, 3-dose vaccination coverage improved to rates above 80% in 2004 and further increased to 98% in 2006. To date, no survey has been performed to measure HBsAg and/or HBV anti-HBc prevalence in this region.

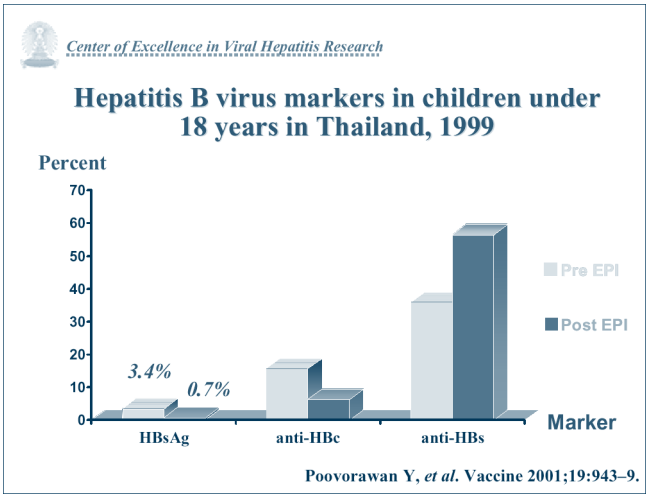
Uzbekistan

Universal newborn HBV vaccination was introduced in the national immunisation schedule in 2001. As of 2003, a high global coverage rate of >98% in newborns was attained, but coverage is highly variable depending on the region, with lower rates in mountainous, rural areas. The number of acute viral HBV morbidity cases among children aged 0-14 years as well as the seroprevalence of HBV markers among children has dramatically fallen (up to 6 times) in the 4-6 years following start of the universal vaccination programme.

A dramatic reduction of HBV carrier prevalence rates was also achieved by effectively implementing universal newborn HBV immunisation programmes in numerous countries with high HBV endemicity in other parts of the world, as shown in the graphs below.



For instance, in Thailand, HBV vaccine has been an integrated part of the expanded programme on immunisation (EPI) since 1992. Its impact on the countrywide prevalence of HBV infection and carrier rate was evaluated, based on serological data of viral hepatitis markers in five representative provinces in 1999. Among children aged 6 months to 18 years born after the implementation of this EPI strategy, only 0.7% were HBV carriers versus 3.4% before introduction of HBV vaccine in the EPI schedule [3].

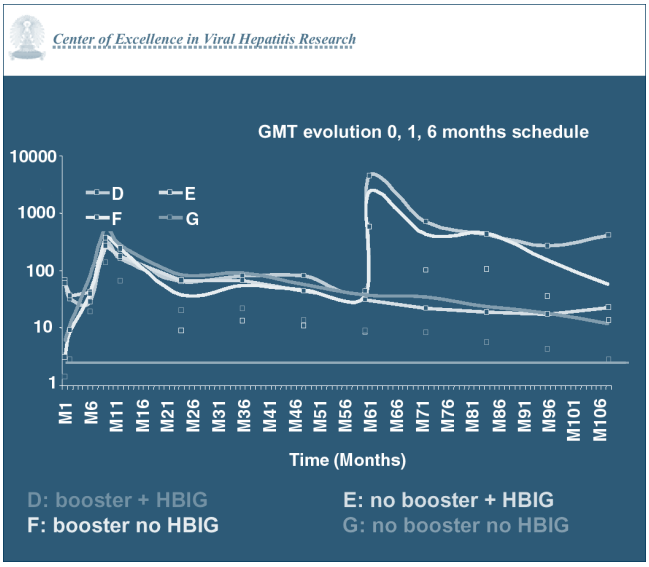


A more recent survey, conducted in 2004 in 4 different Thai provinces confirmed the further decrease of chronic carrier rate since 1999 in children aged <18 years.

Long-term immunogenicity and protection

Long-term studies carried out worldwide have shown that in spite of an observable decline in anti-HBs antibody levels to <10mIU/mL over time, long-term immunological memory persists among individuals who have responded to a complete HBV primary vaccination series [4]. Vaccinated infants develop an anamnestic anti-HBs response upon exposure to HBV later in life.

Long-term follow-up of immunity was evaluated in high risk neonates born in Thailand. One study followed a cohort of neonates of HBe positive mothers vaccinated against HBV starting at birth. The data showed that levels of anti-HBs antibodies >10mIU/ml persisted for 10-12 years, even in absence of a booster dose given at the age of 5 years [5] (see below).



No clinical signs of acute hepatitis were reported. Importantly, no new chronic infections (chronic appearance of HBsAg) were seen after month 24.

Vaccination of newborns thus not only provides a safety net against perinatal HBV transmission, it also elicits long-term immunity, conferring protection against all future exposures occurring later in life, such as transmission at childhood stage, and acute HBV disease at adolescent and adult age (e.g. due to sexual transmission). In addition, HBV vaccination confers protection against hepatitis D.

Based on currently available long-term follow-up data, routine booster doses following a universal vaccination programme are not advocated for any age group.

Combined vaccines and vaccine co-administration

Combined vaccines, such as diphtheria-tetanus-pertussis (DTP)-HBV, are widely accepted as an effective means of childhood immunisation. They present the benefits of increased compliance, time and cost savings for medical personnel administering the injections, as well as reduced work/school disruption. Combined DTP-HBV vaccines have been shown to provide similar or even higher anti-HBs immune response as compared to separate administration of monovalent DTP and HBV vaccines [6, 7]. The immunogenicity of 3 doses of combined DTP-HBV with and without single-antigen HBV vaccine at birth is also comparable [8]. In conclusion, combined DTP-HBV vaccines can be used following a birth dose of HBV vaccine. They have proven highly immunogenic and hence, replacing separate vaccines by combined DTP-HBV vaccines in areas of high HBV endemicity provides clinical, economic and strategic benefits.

The first dose of HBV vaccine at birth is co-administered with OPV and BCG in Azerbaijan, Tajikistan, Kazakhstan and Kyrgyzstan, and with BCG in Georgia (see Table 1 - page 11).

HBV vaccine given at birth simultaneously with BCG has been shown not to interfere with the development of the immune response to either HBV vaccine or BCG [9]. Moreover, BCG has been shown to promote the production of both Th1 and Th2 type cytokine responses to unrelated vaccines [10]. When BCG was administered at birth together with OPV and HBV, this resulted in an increased cellular and antibody response to HBV vaccine and an increased antibody response to OPV [10].

IPV vaccine has also been co-administered at birth with HBV vaccine, with similar immune responses to those observed after separate administration of each vaccine. Recently, a study conducted in Israel showed that the co-administration of IPV with HBV vaccine at birth provides early protection for both diseases [11].

In conclusion, there is sufficient evidence that OPV and IPV as well as BCG, can safely and effectively be co-administered with HBV birth dose.

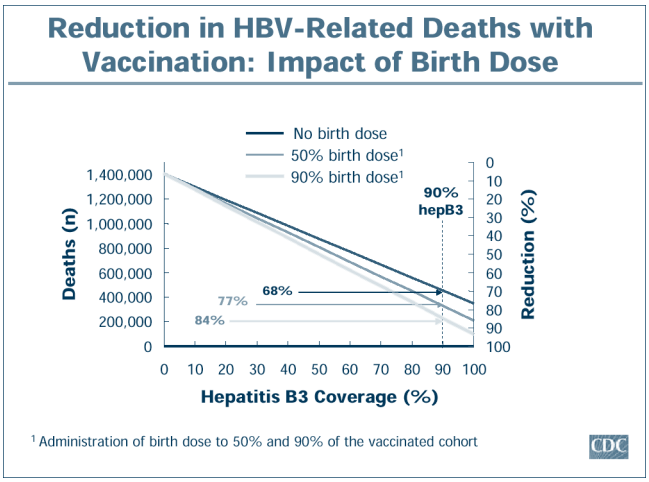
A mathematical model to predict impact of universal HBV vaccination

A flexible mathematical model which can be tailored to individual country situations was developed [12] to estimate HBV-related morbidity and mortality on country, regional and global level. This model also allows prediction of potential reduction in disease burden following different HBV vaccination strategies and thus can assist the policy-making process and implementation of HBV vaccine programmes.

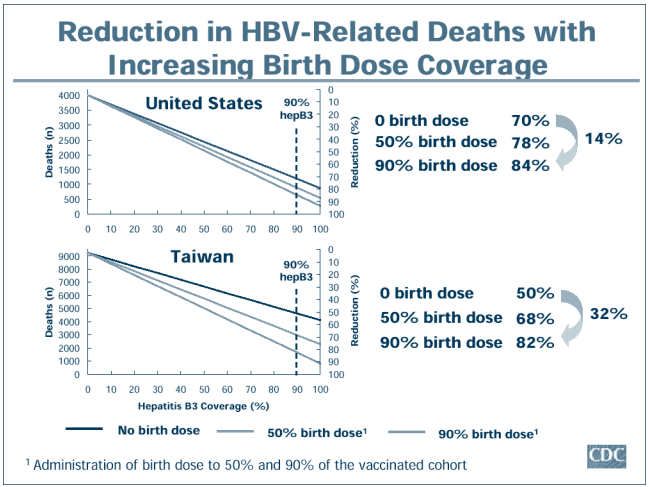
The model requires only limited population-specific information to calculate disease burden: (i) birth cohort surviving past the first year of life, (ii) prevalence of HBsAg and HBeAg among women of child bearing age, and (iii) prevalence of HBV infection (resolved and chronic) among 5-year-olds and >30-year-olds (i.e. anti-HBc). The reduction in disease burden from vaccination can already be calculated based on only two input parameters, i.e. (i) proportion of the surviving birth cohort expected to receive the birth dose of vaccine and (ii) proportion expected to complete the vaccination series.

According to model predictions, routine HBV vaccination of infants, without administration of a birth dose of vaccine to protect against perinatal HBV infection, would prevent up to 75% of global deaths from HBV-related causes, depending on vaccination coverage for the complete series. As coverage increases from 50% over 80% to 90%, the proportion of deaths prevented is estimated to increase from 38% over 60% to 68%, respectively.

Administration of a birth dose of vaccine has a substantial impact on the proportion of HBV-related deaths prevented. As shown below, with 90% complete vaccine series coverage, administration of a birth dose to 50% and 90% of the vaccinated birth cohort would increase the proportion of deaths prevented to 77% and 84%, respectively.



The predicted proportional decrease in HBV-related deaths by region, with 90% complete vaccination series coverage and 0, 50, and 90% birth dose coverage is shown in the following slide for the United States (US) and for Taiwan. The additional reduction in deaths with 90% birth dose coverage compared to no birth dose ranged from 14% points in the US to 32% points in Taiwan. The impact of the birth dose was most pronounced in the regions with the highest proportion of deaths attributable to perinatal infection.



In conclusion, the model estimates that inclusion of a birth dose of HBV vaccine, globally, could prevent more than 80% of HBV-related deaths. Findings from this model contributed to the recent update of the US strategy to eliminate HBV transmission. The new December 2005 Advisory Committee on Immunisation Practices (ACIP) recommendations [13] now focus on immunizing all newborns before hospital discharge in order to address gaps in eliminating perinatal and early childhood transmission.

Countries are encouraged to try and use this model as a field tool, entering their own country data. The model outcome should facilitate the choice of HBV vaccination strategies and their introduction in their specific country. The model is readily available as a user-friendly interface at http://aim.path.org/en/vaccines/hepb/assessBurden/model/index.html

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HBV birth dose administration and maternal screening

Prevention of perinatal HBV infection

Perinatal transmission is responsible for 35-40% of new HBV infections every year worldwide [1]. For a newborn infant whose mother is positive for both HBsAg and HBeAg (high-risk infants), the risk for chronic HBV infection is 70%-90% by age 6 months when no HBV vaccine or HBV immunoglobulin (HBIg)-prophylaxis is given [2-4]. For infants of HBsAg-positive but HBeAg-negative mothers (low-risk infants), the risk of chronic infection is <10% [5].

HBV vaccination and HBIg administration within 24 hours after birth, followed by two additional vaccine doses (at 1 and 6 months) in order to complete the 3-dose vaccine series, has been demonstrated to be 85%-95% effective in preventing acute and chronic HBV infection in high-risk infants [6]. The major factor that influences the efficacy of newborn intervention is the timing of the first dose of vaccine in relation to birth. No apparent effect on immunogenicity has been documented when minimum spacing of doses is not achieved precisely. Increasing the interval between the first 2 doses has little effect on immunogenicity or final antibody concentration [7].

HBV birth dose administration

A variety of schedules may be used for HBV immunisation in national programmes, depending on the local epidemiological situation and programmatic considerations. National strategies for the prevention of perinatal transmission of HBV should take into account the relative contribution of such transmission to the overall HBV disease burden and the feasibility of delivering the first dose of HBV vaccine at birth [8].

Efficacy is optimal when the vaccine is administered within 12-24 hours after birth but declines over time when the vaccine is offered later than 24h [9].

The universally agreed recommendation for the birth dose is "as near as possible to birth" (VHPB [10, 11], CDC [12]), and according to WHO this should preferably be within 24 hours [8]. In the US, infants born to HBsAg-positive mothers or mothers with unknown status, should receive HBV vaccine plus HBIg within 12 hours after birth; newborns from HBsAg-negative mothers should receive the first vaccine dose before hospital discharge [12]. In practice however, countries adopt more flexible schedules (up to 7 days after birth), even though they are not recommended, for infants born outside healthcare facilities, to reflect the realities in the field, e.g. in Indonesia.

Maternal screening and administration of HBIg

Different policies on maternal HBsAg screening exist: some countries do and others do not screen pregnant women for HBsAg. Countries that have chosen not to implement universal immunisation at birth, instead use HBsAg screening of pregnant women with immunisation of newborn infants born to HBsAg-positive mothers. If such an effective screening programme is in place, the routine birth dose can be omitted without lowering the benefit of vaccination. However, screening is costly and for some countries not always relevant in view of a birth dose programme. The screening strategy is usually not feasible in developing countries with high prevalence of disease. It may also not be the most reliable and convenient option, even in countries where HBsAg screening in pregnancy is well established [8]. In these countries, universal HBV vaccination at birth may help avoid the costly screening of the status of the mother.

A recently published review on HBV immunisation of newborns of HBsAg-positive mothers concluded that the combination of vaccine plus HBIg is superior to vaccine alone [13]. It is important to note that the primary outcome measure used in this paper was the occurrence of HBV, defined as a blood specimen positive for HBsAg, HBeAg or anti-HBc. However, the aim of immunisation is not the prevention of sub-clinical disease, as measured by the presence of serological markers. On the contrary, virus exposure at sub-clinical infection functions as a natural booster, triggering the memory immune response. When evaluating the benefit of HBIg therapy at birth, the most important target of immunisation programmes should be considered, i.e. prevention of chronic HBV infection. The review published by André and Zuckerman in 1994 [6] shows that, when focus is placed on protection against chronic carriage, the difference in protection provided by highly immunogenic recombinant DNA vaccines, administered with or without HBIg, is only 2-5% (ranging, depending on the study, from 90% to 100% without HBIg and from 92% to 100% with HBIg). Based on this literature review it is concluded that for highly immunogenic vaccines the vaccine efficacy is over 90% and HBIg co-administration is not necessarily recommended. For lower dosage HBV vaccines, which are less immunogenic, it is best to complement the vaccine dose with HBIg administration at birth.

In randomized placebo-controlled clinical trials, administration of HBV vaccine in a 3- or 4-dose schedule without HBIg, beginning <12 hours after birth has been demonstrated to prevent 70%-95% of perinatal HBV infections among high-risk infants. The data indicate that offering HBIg at birth adds only marginal advantage to protective efficacy provided by active immunisation with HBV vaccine alone. This approach to HBV prevention has important economic implications for countries where HBIg is scarce and relatively expensive. Based on the data available, existing national policies of giving HBV vaccine alone can be considered as justifiable.

As a rule, HBIg should be used as an adjunct to HBV vaccine. However, in full-term newborns, the protection against perinatal transmission achieved by immediate (<24 hours) HBV vaccination is not significantly improved by the addition of HBIg [8].

Strategies to improve timely HBV birth dose administration

Administration of HBV vaccine within 24 hours after birth to infants born in remote areas of high HBV prevalence countries, especially infants born at home, is logistically difficult due to poor infrastructure. Clearly, strategies are needed to improve timely administration of the HBV vaccine birth dose in these areas. Experimental data in China, Indonesia and Vietnam resulting from the evaluation of strategies to improve the timely administration (within 24 hours) of the birth dose are presented. These strategies include out of the cold chain (OCC) use of vaccine, use of a pre-filled monodose, autodisable (AD) device (Uniject™, a trademark of BD - see picture) and raising awareness on the existence of such strategies.

WHO recommendations on using vaccine out of cold chain

Currently, WHO recommends that vaccines with Vaccine Vial Monitors (VVMs) can be taken out of the cold chain only if health workers and others handling the vaccines have been trained to interpret VVM readings correctly and if any vial bearing a VVM that has reached its end-point is discarded. Managerially, however, it is wise to maintain vaccines in the cold chain for as long as possible during distribution. This ensures the maximum viable life in the field [14].

Still according to WHO, a policy can be developed at country level to allow vaccine OCC, either generally for all routine immunisation activities or on a limited basis in certain areas or under special circumstances, such as: national immunisation days; hard-to-reach geographical areas; immunisations provided in the home; cool seasons; storage and transportation of freeze-sensitive vaccines (including HBV vaccine) where the risk of freezing is greater than the risk of heat exposure [14].

Indonesia is currently the only country that uses an OCC strategy for HBV vaccine for the birth dose at a national level, but other nations are studying opportunities for similar approaches. WHO's Western Pacific Regional Office has drafted HBV birth dose guidelines that include procedures for using an OCC strategy for the birth dose. Since WHO Geneva guidance on OCC has not been widely disseminated [15], it was concluded at the meeting that WHO recommendations on OCC need to be clarified to help establish and implement OCC procedures at a country level.

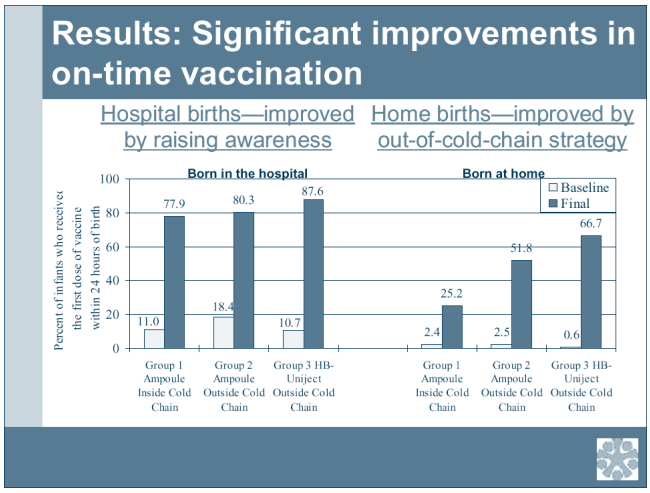
Country experiences of timely HBV birth dose administration

China

A national survey conducted in 1999 in China found that among children who had received the first dose of HBV vaccine, only 38.9% had received it on time (within 24 hours after birth). Among children born at home, who represent at least 27% of the birth cohort (3.2 million children annually), on-time administration of the first dose was even lower, not exceeding 16.7%.

To improve the on-time delivery of the HBV vaccine birth dose to children born at home, studies were undertaken in remote areas of China to evaluate the safety and effectiveness of using village doctors to provide children born at home the HBV vaccine birth dose, when stored OCC in the doctors' homes. Also, the impact of using a prefilled, monodose device (Uniject™) was studied. Village-based doctors and midwives were trained as vaccine providers, and social mobilization was conducted to emphasize the importance of HBV immunisation and on-time delivery of the birth dose.

Approximately 40% of the children in the study areas were born at home. Increases in on-time administration (within 24 hours after birth) were seen, with more substantial improvements occurring in the OCC groups (see overleaf).



Among children born at home, OCC storage of vaccine and administration of vaccine at the village level substantially improved on-time administration of the first HBV vaccine dose. Since many children are born at home and hospital-based immunisation requires long-distance travel, more efficient use of available village-based health workers is an effective way to improve immunisation access for hard-to-reach populations.

Among infants born in hospitals where vaccine was not stored OCC, on-time administration of the HBV birth dose increased substantially without introducing any new tools or procedures other than increasing awareness, provider training, and supervision. This finding highlights the importance of ongoing oversight and programme support in optimizing the results of new programmes such as HBV vaccine birth dose introduction.

Seroconversion was comparable among groups with vaccine stored in the cold chain or OCC. This indicates that storing HBV vaccine OCC does not reduce vaccine potency, especially when used with VVMs so that any heat-damaged vaccine can easily be recognized and discarded. Accidental vaccine freezing due to cold chain user error or equipment malfunction is documented in many countries. This could be prevented by OCC storage of HBV vaccine in countries with no risk of freezing as a result of weather conditions.

Indonesia

Since Indonesia is mainly rural, with 90% of its rural births taking place at home, an alternative to conventional facility-based immunisation was needed to timely provide the birth dose of HBV vaccine. Indonesia uses a 7-day interval for assessment of timely birth dose administration, since the recommended 24h is not achievable in these regions.

Initial attempts to use trained village midwives to vaccinate newborns in their homes proved difficult due to the limitations of the cold chain, high wastage of multidose vials, and injection safety concerns.

The pilot introduction of the Uniject™ device, prefilled with HBV vaccine and stored OCC by midwives in their homes was studied in 1995 in Indonesia as a way to make HBV immunisation at a home visit more feasible [16]. The combination proved effective: midwives were able to vaccinate newborns more quickly since they did not need to collect the vaccine from the health centre cold chain. VVMs allowed midwives to determine whether the vaccine had received too much heat exposure, and a serosurvey confirmed that HBV vaccine stored OCC retained its potency [17]. The AD and prefilled features of Uniject™ made it more convenient and safe for use during home visits, while its single-dose format eliminated the wastage common to multidose vials. Although more expensive per dose than multidose vial vaccine, a cost study showed Uniject™ to be cost saving compared to multidose vials when multidose vial waste is higher than 33% [18].

Based on success of the pilot introduction of OCC delivery during home visits using HBV-Uniject™, the approach was incorporated into the Indonesian national policy in 1996. By 2000, Indonesia was able to introduce a programme for birth dose delivery using HBV-Uniject™ and, with GAVI support, the programme was expanded in 2003 to target all of Indonesia's 4.5 million annual births. Currently, the rate of birth dose delivery is about 65% when considering a 7-day interval after birth.

Vietnam

In rural areas in Vietnam, children are often born at home or in commune health centres where vaccines, including HBV birth dose, are only available once a month. To overcome this limitation to on-time delivery of the birth dose, PATH and the Vietnamese EPI conducted a pilot OCC project where single-dose HBV vaccine vials with VVMs are stored at the commune health centre OCC, making vaccine immediately available for newborns born at the health centre or in the surrounding community. This pilot has demonstrated the feasibility and benefits of the OCC approach: delivery of the birth dose within 24 hours increased from 44% to 78%. VVMs were effective in preventing the use of heat-damaged vaccine. A serostudy showed no difference in seroconversion rates between in-the-cold-chain and out-of-cold-chain groups [15]. The national EPI is monitoring the study results and is also reviewing the international guidelines and experience with OCC storage, to determine the feasibility of expanding the program to the entire country.

Cambodia

In Cambodia, the immunisation programme is being rebuilt after years of war, but due to the limitations in numbers of health workers, only fixed health posts can be used to introduce the HBV birth dose. No OCC strategy has been introduced because the Ministry of Health feels that insufficient global policy guidance exists. Nonetheless, through awareness-raising efforts on-time birth dose coverage has reached 50% in the pilot province.

Furthermore, the following experiences with respect to timely delivery of the birth dose were shared by the represented countries:

- In Georgia, 22% of birth doses given in maternity hospitals are not administered on-time. A substantial difference between monitored coverage rates for HBV dose 1 (81% in 2004 and 82% in first 6 months of 2005) versus BCG vaccine (87% in 2004 and 92% in 2005) was observed. This is mainly explained by contraindications, misconceptions, as well as safety concerns (of both parents and medical staff) with the newly introduced HBV vaccine.
- In Armenia, the use of monodose HBV vaccine in AD syringes has significantly reduced the number of missed opportunities, leading to an increased coverage rate for the birth dose administered within 24h.
- The overall proportion of home deliveries in Tajikistan is 30%. A survey was conducted in rural, mountainous districts with more than 50% home deliveries. Preliminary findings indicate that children born in the maternity unit receive the first HBV vaccine dose on the 3rd day but children born at home are only vaccinated on the 15th day.

HBV birth dose administration to preterm neonates

WHO specifies only two contraindications to HBV vaccination: allergic reaction to any component of the vaccine [8] and anaphylaxis to a previous dose [19]. Still, the country survey revealed that in practice, in some countries, other arguments serve as a reason for not providing the HBV vaccine dose at birth (e.g. acute illness in Georgia).

One common misconception about contraindications is the deferral of HBV vaccination in preterm newborns with low birth weight (< 2 kg), as discussed in the next section of this report.

Earlier initiation of HBV vaccination provides timely protection of vulnerable preterm infants who are more likely to get exposed through receipt of multiple blood products and surgical interventions [20]. Also, HBV vaccines are safe and well-tolerated by preterms. Initially, the American Academy of Pediatrics (AAP) recommended that, based on their lower antibody response to HBV vaccination [21, 22], in preterms with birth weight <2,000g born to HBsAg-negative mothers the first dose of HBV vaccine should be deferred until they reach 2,000g or 2 months of age [23]. The current US recommendations (AAP and ACIP) for preterm newborns include screening the HBsAg status of the mother and administering a birth dose plus HBIg to all newborns who are at high risk of HBV exposure [12, 24]. In preterms with birth weight <2,000g, born from HBsAg-positive mothers or no maternal HBsAg screening available, the first HBV vaccine dose should be administered at birth and a total of 4 HBV vaccine doses are recommended [24]. Only in low risk infants with birth weight

<2,000g the birth dose may be deferred to 30 days of age.

Based on scientific evidence and review of international guidelines, it was concluded that gestational age and birth weight should not be limiting factors in delaying HBV vaccination of clinically stable infants. WHO recommendations for countries that opt for schedules with a birth dose were re-emphasized: preterm infants should be vaccinated at birth and subsequently enter the respective national HBV vaccination schedule. Even if the birth weight is <2,000g, the birth dose should still be given by 24 hours but the vaccine dose at birth should not be counted towards the primary series; three additional doses (not two) should be given [8].

Table 1: Country questionnaire (2006): Vaccination programmes and HBsAg screening

Country	Universal HBV newborn vaccination implementation	Timing of birth dose	Vaccination schedule*	Coverage rate# (%) Dose 1, 2, 3	HBsAg screening pregnant women	Delivery in/outside health care facilities (HCF)	Other birth vaccines
Azerbaijan	2001‡	0-24h	0, 1m, 5-6m	-	No	98.1% in HCF (birth dose <24h) 1.9% out HCF (birth dose <24h)	BCG, OPV
Georgia	2003	0-24h	0, 2m, 4m	96.5 77 73.4	No	95% in HCF 5% out HCF	BCG
Kazakhstan	1998	0-24h	0, 2m, 4m	99 99 99	No	99.9% in HCF	BCG, OPV
Kyrgyzstan	1999-2000	0-24h	0, 2m, 5m	98.9 98.5 97.4	No	98% in HCF	BCG,OPV
Tajikistan	2002‡	0-24h > 72h	0, 2m, 4m	98 96 94	No	71% in HCF (birth dose <24h)	BCG, OPV
Turkey	2003	0-24h 24-48h 48-72h	0, 2m, 9m	94 90 85	Not systematically	77% in HCF (birth dose <24h) 23% out HCF (birth dose <72h)	-
Uzbekistan	2001	0-24h	0, 2m, 6m	99.2 98.4 98.9	Yes, 92% 13% is HBsAg+	95% in HCF 5% out HCF	BCG, day 3-5

* None of the countries uses combined vaccine for the 2nd or 3rd HBV vaccine dose
‡ Phased introduction in selected regions, currently nationwide
# Based on routine administrative reporting of HBV vaccination for newborns

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Keys and challenges to the successful implementation of HBV vaccination programmes

This section of the report focuses on keys and remaining challenges to the successful implementation of HBV vaccination programmes identified during the meeting, on the basis of:

- presentations relating to individual country experiences of the WHO European Region;
- alternative strategies to improve birth dose administration in China, Indonesia, Vietnam and Cambodia;
- presentation and discussion of the scope of current international guidelines and the need for future guidelines to be developed, based on new/updated recommendations;
- issues addressed in questionnaire (see Table 2 below) filled out by individual countries of the WHO European Region and related shared experiences during meeting workshops.

Keys to successful HBV vaccination programmes

Integrated political framework and policy instruments

An integrated approach of disease surveillance and laboratory strengthening was recognized as a key element to an appropriate definition of the epidemiology of disease. Such instruments should allow for an adequate

Table 2: Country questionnaire (2006): surveillance and impact studies, vaccination contraindications/barriers, vaccine procurement and logistics

Country	Vaccination coverage: source information	Vaccination Impact monitoring	Contraindications to HBV newborn vaccination	Barriers/Challenges to HBV vaccination programme	Vaccine procurement	Adapted cold chain storage for larger HBV distribution	Vaccine freezing assessment
Azerbaijan	Routine administrative reports	Immunisation reports	-	-	Central through UNICEF	-More frequent deliveries/collections -Refrigeration capacity enlarged -More cold boxes	No
Georgia	Routine administrative reports	-Immunisation reports -Coverage survey	-Acute illness -Fever >38.5°C	-Inadequate public acceptance -Media propaganda	Central through GAVI	-Refrigeration capacity enlarged -More cold boxes	Yes
Kazakhstan	Routine administrative reports	-Immunisation reports -Disease surveillance	-Early delivery -Low birth weight -Other	First dose delay requested by neonatologists	Central through tender	-Refrigeration capacity enlarged -More cold boxes	2002 via UNICEF
Kyrgyzstan	Routine administrative reports	-Immunisation reports -Disease surveillance	Low birth weight	Financing	Central through UNICEF/GAVI	Refrigeration capacity enlarged	No
Tajikistan	Routine administrative reports	-Immunisation reports -Coverage survey	WHO guidelines implemented	-	Central through UNICEF/GAVI	-Refrigeration capacity enlarged -More cold boxes	No
Turkey	Routine administrative reports	-Immunisation reports -Disease surveillance	None	-	Central through tender	Refrigeration capacity enlarged	September 2005
Uzbekistan	Routine administrative reports	-Immunisation reports -Coverage survey	-	-Training needs -Cold storage capacity	Central through UNICEF	-Refrigeration capacity enlarged -More cold boxes	Yes (via WHO)

quantification of the burden of disease and support the development of comprehensive prevention strategies in the form of sustainable and cost-effective vaccination programmes.
Such programmes have been put in place in the five republics of the Central Asian region which have received support from the CDC Central Asian Office since 1996 in the form of a close collaboration with national Ministries of Health. Technical support was also provided by the Division of Viral Hepatitis of CDC, National Centre for Infectious Diseases (NCID), WHO and UNICEF in order to identify adequate resources to implement programmes while financial support is received from the USAID, GAVI and the World Bank

The success of HBV vaccination programmes in countries from Central Asia - which represent the most endemic area of the WHO European Region - was acknowledged during the meeting, with an overall coverage rate of >95% achieved for the 3-dose HBV vaccination course, as well as an increased coverage rate for the timely administration of the birth dose. Several alternative strategies were also shown to be successful in ensuring a better coverage of timely birth dose administration in difficult areas of high HBV prevalence countries, such as China, Indonesia, Cambodia and Vietnam, with very high percentages of home deliveries.

Such efforts have led to a dramatic reduction of HBV incidence among children and thus represent a real opportunity to prevent HBV perinatal transmission and the development of chronic infections. Indeed, if administered soon after birth, HBV vaccine is highly effective in preventing infection in up to 95% of infants.

In particular, the successful implementation of HBV vaccination programmes has been facilitated in those countries with a favourable political and public health context where immunisation has been recognized as a major priority at governmental level. In some cases, immunisation policy has also been supported by efficient complementary measures, such as efforts to reduce home delivery and the set up of vaccination catch-up programmes in adolescents and risk-group populations.

Strategies to overcome "field difficulties"
In the previous section of this report, several strategies were presented to overcome "field difficulties" otherwise impeding the successful implementation of vaccination programmes among rural, difficult-to-reach populations with a high proportion of home deliveries in areas of high HBV endemicity.

Such successful initiatives have involved HBV birth dose administration to infants born at home by village-based doctors and midwives trained as vaccine providers. In some instances, this strategy has been coupled with OCC use of HBV vaccine, and the use of Uniject™ and VVM devices in order to reduce vaccine wastage while guaranteeing vaccine quality and safe injection, which is particularly important when vaccine is administered by trained village healthcare workers. A more commonly applied strategy has also involved the use of existing infrastructures, such as village healthcare centres, replacing traditional immunisation posts. Field experience from Indonesia is illustrated in the slide below:

Training and communication programmes
Country experience has revealed the importance of training and communication as key factors to successful immunisation programmes. Training of healthcare workers is organized in several countries from the Central Asian region with the support of CDC, aiming at the timely delivery of the appropriate vaccine to the right populations, in particular with regards to the proper introduction of HBV birth dose. Such training sessions also include more specific and logistical aspects, such as freezing problems and waste disposal.

Healthcare workers, family doctors, pediatricians and epidemiologists are also trained and educated on a broader level, on the importance of HBV immunisation, in particular awareness is raised on the timely delivery of HBV birth dose.

Country experience was shared from Vietnam where PATH and the national EPI team jointly introduced a supportive supervision system in which supervisors and healthcare workers work more closely together to solve problems and conduct on-the-job skills training.

In terms of communication, several successful strategies were described, such as the development of information booklets about vaccination in Armenia or the introduction of a communication programme in Vietnam, using a variety of print and broadcast media. A nationally televised family quiz show, using immunisation-related quiz questions, has been successful in increasing awareness of immunisation issues.

Another information initiative was conducted in Tajikistan between January and February 2006, with the support of GAVI and WHO. The objective of this survey was to provide information on coverage, timeliness and completeness of HBV immunisation with special emphasis on administration of the HBV first dose. Such information aimed at:

- identifying problems and constraints affecting HBV immunisation (mainly concentrating on those related to home deliveries);
- identifying strengths and weaknesses of immunisation programmes in the country (missed opportunities, training needs, existing knowledge, attitudes, practice and satisfaction of families to understand traditions and constraints towards immunisation, in particular newborns);
- making recommendations on the complete and timely administration of HBV vaccine injections.

In spite of the general enthusiasm and positive appreciation of the critical steps taken toward successful HBV immunisation programmes, representatives of countries at the meeting identified a number of impediments and remaining challenges to be faced.

Remaining challenges to successful HBV vaccination programmes

Surveillance weaknesses and lack of vaccination impact studies
Independently of problems encountered by individual countries regarding the implementation of adequate surveillance systems, the general difficulty in appreciating the real burden of disease caused by HBV is aggravated by the fact that chronic HBV infections are not easily identified, yet they heavily contribute to HBV morbidity; hence the critical importance of tools such as the HBV disease burden model [1] as an interface for countries to use at national level, supporting public health exercises.

In addition, a number of disease surveillance weaknesses were underlined by meeting participants, in particular with regard to the lack of accuracy and reliability of national reporting systems and existing discrepancies between official statistics collected at national level and regional sentinel surveillance systems.

The lack of surveillance data before the introduction of HBV vaccination programmes was identified as a limiting factor in most countries while the need for improved knowledge of disease epidemiology was recognized, in particular for the identification of risk-groups and accurate target populations.

More specifically, the need for improved case definitions (e.g. in order to make the difference between chronic and new case numbers), and standardized diagnosis and test methods were cited in the context of surveillance studies while the lack of vaccine follow-up studies and the need for proper impact assessment studies in cohorts of vaccinated individuals, using adequate serological markers, were also mentioned.

Healthcare system weaknesses and poor logistics of vaccination programmes

Several countries, such as Turkey and Tajikistan, deplored healthcare system weaknesses, in particular with regards to a >50% proportion of home deliveries in rural areas, linked to difficult access and transportation conditions, but also resulting from costly and poorly cared delivery departments. Such factors were identified as impediments to the timely administration of HBV birth dose and were said to contribute to regional coverage discrepancies, in particular in difficult geographical areas where outreach immunisation sessions should be organized.

In most countries, the poor quality of medical documentation in healthcare facilities was raised, in particular in terms of observed discrepancies between entries in immunisation registries and immunisation passports and the lack of implementation of official entry forms, hence the need for systematic supervision visits at immunisation centres, coupled with staff training and assistance.

Specific areas of improvement were also identified in customized immunisation programmes, such as home births not being reported to midwives acting as vaccine providers, private practices not administering HBV vaccine to neonates, and the more general need for improved coordination and integration of HBV birth dose in mother-and-child-care services.

Several other problems linked to poor logistics of vaccination programmes were discussed, such as the lack of control of migrating populations, vaccine shortages in healthcare facilities, and other general management problems regarding the need for improved monitoring of vaccine freezing when used OCC (especially in countries with cold temperature and power cuts), implementation of injection safety policy and proper disposal of safety boxes and disposable injectors in designated incinerators.

Sustainability of vaccination programmes

Several factors were identified as critical in order to ensure sustainability of vaccination programmes, including a strengthened status, role and participation of the Interagency Coordination Committee (ICC) in HBV immunisation and support; the reinforcement of immunisation policies, such as risk-group and adolescent catch-up programmes (e.g. in Turkey and Kyrgyzstan); and the validation of alternative immunisation strategies or updated recommendations in international guidelines (e.g. WHO), so as to provide unequivocal support on current issues such as the implementation of OCC and use of VVMs [2], delayed birth dose administration beyond 24h after birth, and use of single-dose injecting devices (e.g.Uniject™).

Sustainable vaccine procurement was also mentioned as an issue in some regions, in particular those with political instability. Financing monovalent HBV dose and the use of combined vaccines was regarded as an impediment in several countries and the need for fund raising activities was mentioned, as well as the need for a more adequate use of financial resources within countries. The cost of vaccine was mentioned as a cause of lower coverage in rural areas (e.g. China).

Training and communication needs

In spite of existing training programmes in most of the countries represented at the meeting, the need for revision of current training programmes, reinforced communication and increased public awareness, as well as specialist education (including neonatologists, neuropathologists and pediatricians but also medical students, healthcare workers and managers of public health centres) was mentioned in order to increase vaccine acceptance, in particular with regards to HBV birth dose administration.

The need for specialized training of medical staff was also mentioned, such as keeping of medical records or training midwives to overcome fear of injecting newborns, in particular those with low birth weight.

Several commonly widespread misconceptions relating to vaccination, in particular in terms of misconstrued vaccine-related adverse events (e.g. misconception of thiomersal), and perceived contraindications to administration of HBV birth dose (e.g. CNS pathology, convulsions, birth injury, birth weight <2kg, prematurity, asphyxia, pulmonary atelectasis; Down's syndrome, harelip, cephalocele, anemia, hemolytic disease, AIDS, syphilis, contact with influenza, use of corticosteroids, anaphylaxis, acute clinical condition and fever >38.5°) were identified as impeding factors to the acceptance of new vaccination guidelines and innovative strategies.

The low dissemination of WHO guidelines on vaccination of preterm babies [3] was also said to contribute to poor implementation of programmes and the need to alert WHO regional office and EPI national managers was expressed, hence the role of international advisory boards such as the VHPB.

In order to break those conceptual barriers and block the impact of anti-vaccination propaganda in the media, an integrated communication strategy is needed, focusing on information relating to vaccine preventable diseases and the development of new vaccines.

Such information campaigns should help raising awareness of the medical profession and the public toward HBV-related serious health problems among children and convince them of vaccine quality, efficacy and safety. Parents should be better informed of the benefits of vaccination as well as the risks for unvaccinated children and other susceptible groups of people.

Suggestions for specific initiatives in this area were made, including production of information materials and fact sheets in the language of the country; enhanced communication with professionals on success stories and achieving goals of vaccination efforts; improved interactions with the media, key opinion leaders and decision-makers in the country; and, when appropriate, insisting on free delivery of vaccine in countries where it is the case.

However, country representatives also underlined the problem of costs relating to media activities described and urged for the continued support of international boards present at the meeting.

Example of country experience with factors interfering with successful implementation of HBV vaccination (Georgia):

Main Reasons Interfering HepB Vaccination in Maternity Hospitals

Acute disease with clinical symptoms	76%
False contraindications	50%
Refusal from parents	40%
Refusal from doctors	12%
Mass-media influence	17%
Shortage of vaccine (last two months in 2004)	72%

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Conclusions

Meeting outcomes were presented within the framework of meeting rationale and objectives, as defined in the introduction of this report.

A review of the current epidemiology of viral hepatitis and perinatal HBV transmission in Central Asian countries, South Caucasus and Turkey revealed that:

- HBV is the leading cause of CLD in high-endemicity countries in comparison to HCV in low-endemicity countries;
- Countries have intermediate or high HBV endemicity, with variations in prevalence rates across countries, including socioeconomic and rural/urban differences;
- Very high rates (up to 20%) of HDV were reported in some countries;
- Transmission is predominantly perinatal although the route remains unknown in many cases; early childhood, parenteral and sexual routes are also significant;
- Higher HBeAg positivity results in increased transmission rate;
- Results of questionnaire from 8 countries showed that 2006 surveillance data were comprehensive and of improving quality, thus contributing to a better definition and quantification of disease burden, necessary for the implementation of national vaccination strategies.

An overview was provided of current recommendations and country practice on universal HBV vaccination programmes, birth dose administration, maternal screening and HBIg administration:

- All countries have introduced universal HBV vaccination, with a major effort to administer the birth dose within 24 hours, and with flexibility on the timing of the third dose (as a function of existing vaccination programmes); all using monovalent HBV vaccine for the birth dose; high coverage rates were reported in all countries, with improvements in cold chain functioning. All countries have centralized vaccine procurement, mostly through international agencies;
- The universally agreed recommendation (VHPB, WHO, CDC) for the birth dose is "as near as possible to birth", and preferably within 24 hours. However, outside healthcare facilities, more flexible schedules (even up to 7 days after birth) are adopted (even though not recommended), to reflect realities in the field;
- Considerable variations were reported in % of births within healthcare facilities (often >95%) or at home (30% or more in some countries or regions);
- There is no specific contraindication to the use of HBV vaccine in neonates other than WHO-specified allergic reaction to any vaccine component or anaphylaxis to previous dose. However, results from questionnaire in 8 countries revealed numerous false arguments;
- For preterm babies (<2kg): low birth weight is not a contraindication to HBV vaccination. HBV vaccine is safe but with possibly reduced immunogenicity, therefore preterm babies should receive birth dose within 24h , followed by three (and not two) subsequent doses;
- Different policies and practice were reported across countries on maternal screening; maternal screening is costly and not necessarily relevant in view of a birth dose programme;
- Current data indicate that HBIg administration only adds marginal advantage to protective efficacy; existing national policies of giving HBV vaccine alone are therefore justifiable.

Based on a presentation by D FitzSimons, WHO, Geneva, Switzerland.

Scientific evidence on prevention and control of HBV transmission through vaccination was summarized and country experiences were shared:

- Data from several countries provide conclusive evidence of the protective efficacy of HBV newborn vaccination;
- Many studies testified the significant reduction in disease and infection rates that followed HBV vaccination programmes;
- Routine booster doses following HBV universal vaccination programmes are not advocated in the national hepatitis B programmes;
- A flexible mathematical model can be tailored to individual country situations and can be used to assist the policy-making process and implementation of HBV vaccination programmes.

On the basis of presentations, discussions and feedback from workshops, as well as results from questionnaire in 8 countries, a list of keys and challenges to successful HBV vaccination programmes were identified, regarding:

- Importance of a favourable political and public health framework allowing for adequate disease surveillance, reliable case reporting systems, improved healthcare capacities and sustainable vaccination programmes;
- Strategies to overcome field difficulties, such as OCC (combined with new tools, such as Uniject™ and VVMs) and better use of existing structures and staff;
- Development of training and communication programmes for the public and medical profession in order to raise general disease awareness and redress widespread misconceptions, e.g. false contraindications to vaccination.

The role of the following partner agencies and organizations was reaffirmed and a pledge was made to them to continue to prioritize HBV vaccination:

- WHO, UNICEF, World Bank, Asian Development Bank, GAVI, Government of Japan, VHPB;
- Governments and national ministries, especially of health and finance, agencies (e.g. CDC, US Agency for International Development) and universities;
- Foundations and nonprofit organizations, e.g. Bill and Melinda Gates, PATH, Vishnevskaya-Rostropovich Foundation (VRF);
- New partnership: 5 United Nations Agencies (Mother and child health context).

Lessons learnt and recommendations

- Bring vaccine delivery to the neonate: participating countries have achieved success in vaccinating neonates, but challenges remain in terms of coverage and timeliness;
- HBV vaccination provides a safety net against perinatal HBV transmission, and also prevents early childhood, parenteral and later sexual transmission; HBV vaccination also protects against HDV;
- HBV vaccine can be administered successfully and effectively with other vaccines (e.g. BCG and OPV);
- Combined vaccines have good immunogenicity and can replace monovalent vaccines, except for the birth dose in areas of high HBV endemicity;
- Ensure sustainable vaccine procurement by involving finance and health ministries;
- Clear specifications are needed in vaccine tenders: e.g. provide vaccines with VVMs, restate open vial policy, provide instructions in appropriate languages;
- Flexible strategies are needed to modify cold chains (OCC does not mean putting the vaccine in the cold when there is a threat of freezing);
- New tools (e.g. Uniject™, autodisable syringes, VVMs, OCC approaches) are accepted and training is essential in order to improve vaccine delivery;
- Data on HBIg confirm that countries' existing policies of giving HBV vaccine alone are defensible;
- Guidelines may need revision and/or restatement on cold-chain strategy, administration of birth dose within 24 hours, HBIg administration and open-vial policy;
- Maternal screening is acceptable if already in place but it is not a high priority compared with universal HBV vaccination of neonates, which is a "worthwhile investment". In countries of high HBV prevalence, maternal screening may not be feasible or the most reliable or convenient option;
- A mathematical model exists showing that the impact of vaccination is highest in countries with highest rates of perinatal HBV transmission; this model is available and accessible for application of national data;
- Surveillance systems need to be supported by laboratory systems and there is a general need for capacity building of health systems;
- Disposal of medical waste is a very general problem without ready solutions;
- Successes need to be communicated to health professionals (including medical schools) in appropriate language and format: digests of information, fact sheets, etc;
- There is a need for improved communication at all levels: general public, politicians, and media in appropriate languages;
- This meeting focused on Central Asian countries, South Caucasus and Turkey, yet conclusions are applicable to many more countries;
- International fora and workshops are most valuable for exchanging information and relaying important messages and concerns to intergovernmental agencies.

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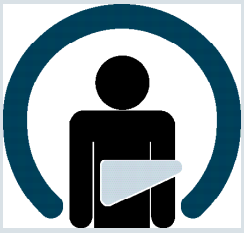

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