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## **Strengthening Immunisation Systems and Introduction of Hepatitis B Vaccine in Central and Eastern Europe and the Newly Independent States**

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Report of a meeting organised by the Centers for Disease Control and Prevention, Children's Vaccine Programme at the Programme for Appropriate Technology in Health, the Global Alliance for Vaccines and Immunisation, the United Nations Children's Fund, the Viral Hepatitis Prevention Board, and the World Health Organization.

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## I. INTRODUCTION

Hepatitis B vaccine, which has been available since 1981, has an outstanding record of safety and impact<sup>1</sup>. Its introduction into routine national immunisation programmes is one of the most successful health measures ever achieved, protecting hundreds of millions of people from acute illness as well as from chronic infection leading to cirrhosis and liver cancer<sup>2</sup>. In 1991, hepatitis B vaccine became the first new vaccine added to the Expanded Programme on Immunisation (EPI) since the programme began in 1974. A year later (Table 1), the World Health Assembly endorsed the EPI goal of introducing hepatitis B vaccine into all national childhood immunisation programmes.

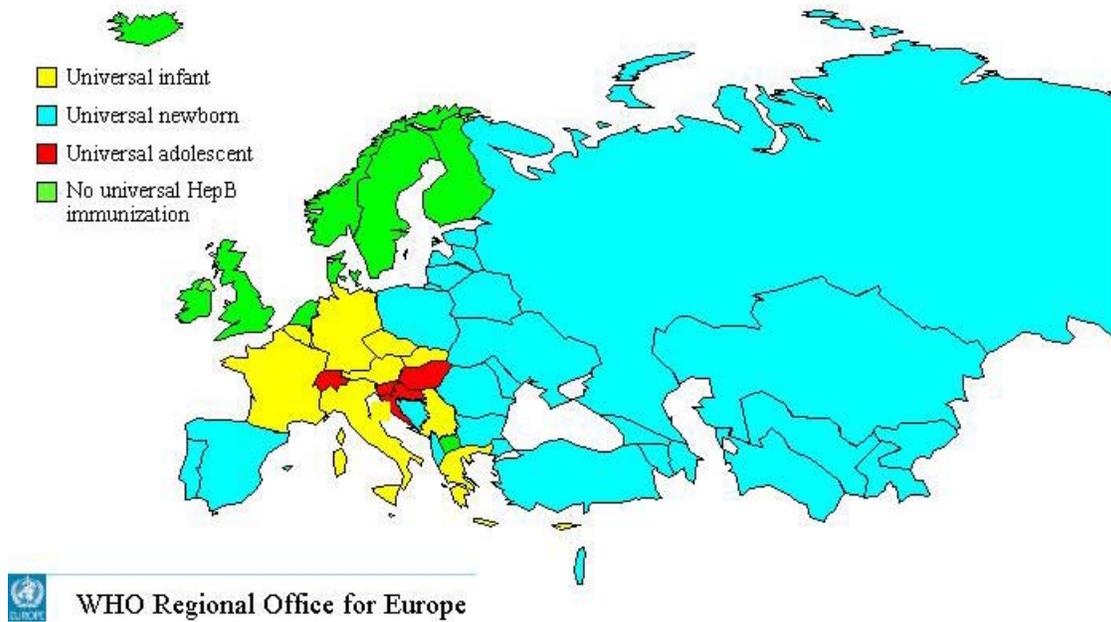
**Table 1**                    **Chronology: Hepatitis B and Immunisation**  
(Including Regional Conferences in the Countries of Eastern Europe and the Newly Independent States)

<b>1974</b>	Start of the Expanded Programme on Immunisation (EPI) targeting diphtheria, tetanus, whooping cough, polio, measles, and tuberculosis.
<b>1981</b>	Hepatitis B vaccines become available
<b>1986</b>	Recombinant hepatitis B vaccines become available
<b>1991</b>	EPI Global Advisory Board recommends inclusion of hepatitis B vaccine in national immunisation programmes in high endemicity countries by 1995 and in all countries by 1997
<b>1992</b>	World Health Assembly endorses EPI recommendation
<b>1994</b>	World Health Organization sets goal of 80% reduction in the incidence of new HBV carriers among children by the year 2001
<b>1996</b>	First regional conference on prevention and control of hepatitis B in Central and Eastern Europe and the Newly Independent States is held in Siofok, Hungary, October 6-9, 1996
<b>2000</b>	Global Alliance for Vaccines and Immunisation (GAVI) is established to help improve delivery of traditional childhood vaccines and introduce new ones
<b>2001</b>	Second regional conference on prevention and control of hepatitis B in Central and Eastern Europe and the Newly Independent States is held in St.Petersburg, Russian Federation, June 21-23, 2001
<b>2001</b>	World Health Assembly resolution sets new goal of 90% coverage with three-dose regimen of hepatitis B vaccine for all children by 2015
<b>2004</b>	Third regional conference on prevention and control of hepatitis B in Central and Eastern Europe and the Newly Independent States is held in Kyiv, Ukraine, May 25-28, 2004

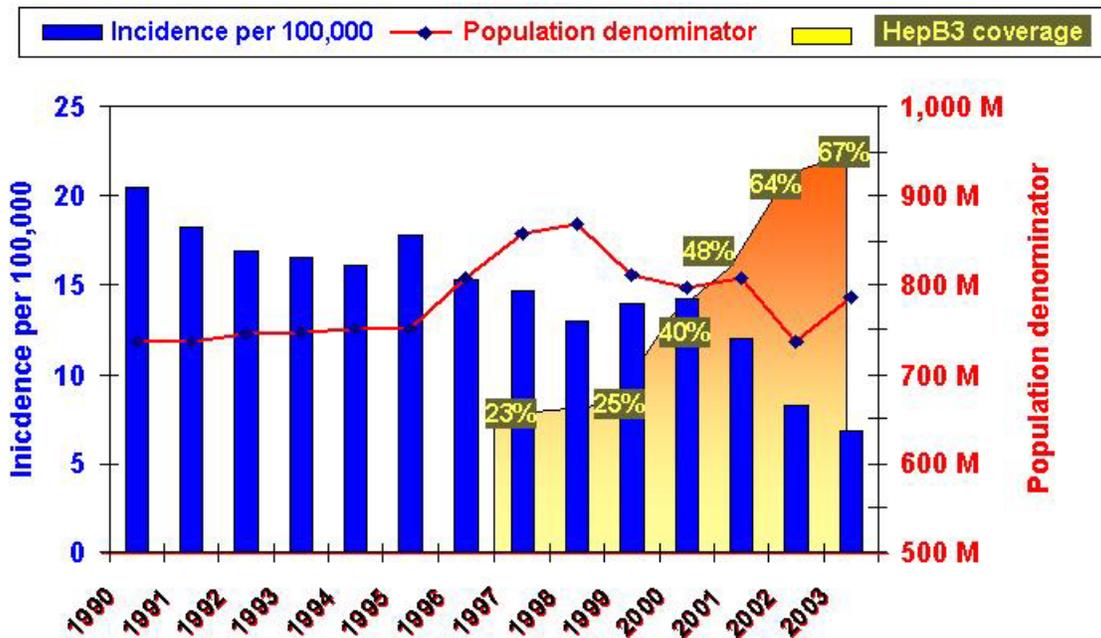
The countries of Central and Eastern Europe (CEE) and the Newly Independent States (NIS<sup>a</sup>) have made remarkable progress in reaching the EPI/WHO goal, with almost all 29 countries implementing hepatitis B immunisation programmes by 2004 (Figure 1, Table 2). The impact of these efforts is already evident in lowered regional rates of acute infection (Figure 2). Today, the countries of CEE and NIS are building on these successes to improve hepatitis B vaccine coverage for infants, children, and high-risk adults and ensure that national immunisation programmes are financially sustainable over the long-term.

<sup>a</sup> The list of Newly Independent States comprises Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, the Russian Federation, Tajikistan, Turkmenistan, Ukraine and Uzbekistan (hereinafter NIS, often also referred to as CIS (Commonwealth of Independent States)).

**Figure 1 Hepatitis B immunisation policy WHO European Region 2004**



**Figure 2 Incidence of Hepatitis B in the European Region 1990-2003**



Courtesy of WHO Regional Office for Europe

## KYIV CONFERENCE, MAY 2004

Progress in hepatitis B vaccination was reviewed at a regional meeting entitled **Strengthening Immunisation Systems and Introduction of Hepatitis B Vaccine in Central and Eastern Europe and the Newly Independent States**, held in Kyiv, Ukraine, in May 2004. This meeting was the third in a series organised by the Viral Hepatitis Prevention Board (VHPB) in association with Ministries of Health, the World Health Organisation (WHO), the U.S. Centers for Disease Control and Prevention (CDC), and other partners.

**Table 2 Hepatitis B Immunisation Programmes in Central and Eastern European Countries and the Newly Independent States: 2000-2004**

<b>In 2000</b> 15 CEE and NIS countries had universal hepatitis B immunisation programmes:		<b>By 2004</b> an additional 14 CEE and NIS countries had universal hepatitis B immunisation programmes:	
<u>High endemicity countries (&gt;8%)</u>		<u>High endemicity countries (&gt;8%)</u>	
<b>Albania</b>		<b>Albania</b>	<b>Azerbaijan</b>
Kazakhstan		Kazakhstan	<b>Kyrgyzstan</b>
<b>Kyrgyzstan</b>		<b>Moldova</b>	<b>Tajikistan</b>
<b>Moldova</b>		<b>Turkmenistan</b>	<b>Uzbekistan</b>
<u>Moderate endemicity countries (2-8%)</u>		<u>Moderate endemicity countries (2-8%)</u>	
Belarus <sup>+</sup>		Belarus <sup>+</sup>	<b>Bosnia &amp; Herzegovina</b>
<b>Bosnia &amp; Herzegovina</b>		Bulgaria	<b>Georgia</b>
Bulgaria		(FYROMacedonia <sup>=</sup> ) <sup>ii</sup>	Lithuania
Lithuania		Romania <sup>+</sup>	Serbia & Montenegro <sup>=</sup>
Romania <sup>+</sup>		Turkey	
<u>Low endemicity (&lt;2%)</u>		<u>Low endemicity (&lt;2%)</u>	
Czech Republic <sup>^=</sup>		<b>Armenia</b>	Croatia <sup>^</sup>
Cyprus <sup>=i</sup>		Czech Republic <sup>^=</sup>	Cyprus <sup>=i</sup>
Estonia <sup>+</sup>		Estonia <sup>+</sup>	Hungary <sup>^</sup>
Latvia		Latvia	Poland <sup>+</sup>
Poland <sup>+</sup>		Russian Federation <sup>+</sup>	Slovakia <sup>=</sup>
Slovakia <sup>=</sup>		Slovenia <sup>^</sup>	<b>Ukraine<sup>+</sup></b>
<u>Figure legend</u>			
Endemicity data is taken from hepatitis B seroprevalence studies conducted between 1995 and 2003 by WHO/EURO, EUROHEP.NET ( <a href="http://www.eurohep.net">http://www.eurohep.net</a> ) and WHO Collaborating Centre at the University of Antwerp. All CEE and NIS hepatitis B immunization programmes provide universal coverage for newborns, unless otherwise noted by footnote:			
+ Infants, older children and adolescents, in addition to newborns			
= Infants			
^ Adolescents			
^= Infants and adolescents			
Countries that receive hepatitis B vaccines from the Vaccine Fund administered by the Global Alliance for Vaccines and Immunization (GAVI) are <b>in bold</b> .			
i Cyprus joined the WHO European region in 2004. Cyprus introduced hepatitis B vaccination in 1989.			
ii FYROMacedonia has planned introduction of hepatitis B vaccination for 2005			

At the time of the first conference, held in Siofok, Hungary in 1996, only 5 of the NIS and CEE countries (Albania, Bulgaria, Moldova, Poland, and Romania) included hepatitis B vaccination in their routine immunisation programmes, due largely to economic constraints. The goals of the Siofok meeting were to raise awareness of hepatitis B infection as a major regional health problem; to encourage and support efforts to evaluate local burdens of viral hepatitis; and to identify technical and financial resources for vaccine introduction<sup>3,4</sup>. The Viral Hepatitis Prevention Board (VHPB) in association with the World Health

Organization (WHO), and the U.S. Centers for Disease Control and Prevention (CDC) organized the Siofok meeting.

As presented at the second conference, held in St. Petersburg, Russian Federation in 2001, 15 NIS and CEE countries had introduced hepatitis B vaccine into childhood vaccination programmes, including 4 countries with high levels of hepatitis B infection and 5 with moderate levels (Table 2)<sup>5</sup>. The St. Petersburg meeting included, besides the three Siofok organizing partners, also UNICEF and two newly established international partners: the Children's Vaccine Programme at the Programme for Appropriate Technology in Health (CVP/PATH) and the Global Alliance for Vaccines and Immunisation (GAVI). The participation of these partners underscored the growing regional and international commitment to the elimination of vaccine-preventable diseases.

This document is the official report of the third regional conference, which examined the progress made over the past eight years and acknowledged the public and political commitment that has made it possible. The Kyiv conference included presentations on country experiences in introducing hepatitis B immunisation programmes; on impact of vaccination; on regional epidemiology and disease prevention; on immunisation safety and blood safety issues; and on vaccine procurement and financing. The conference also included workshops that explored four areas of major concern, including disease surveillance and programme monitoring; technical concerns regarding vaccine administration; management of vaccine safety crises, and financial sustainability planning.

## **II. GOALS, OBJECTIVES, AND ANTICIPATED OUTCOMES**

The conference participants included more than 100 public health leaders from the countries of Central and Eastern Europe and the Newly Independent States, as well as representatives from 6 supporting organisations (CDC, CVP/PATH, GAVI, UNICEF, VHPB, and WHO). The goal of the conference was to share experiences and knowledge that will help reinforce national immunisation programmes and facilitate the introduction of future vaccines.

The conference accomplished its stated objectives, which included:

- Providing an overview of the current epidemiological situation of viral hepatitis infection worldwide and in the European Region of the World Health Organisation
- Providing an overview of the Global Alliance for Vaccines and Immunisation (GAVI), the Vaccine Fund administered by GAVI, and related activities in the WHO European Region
- Providing an overview of the current status of hepatitis B vaccination globally and in the WHO European Region
- Discussing financial sustainability issues of hepatitis B vaccination in GAVI and non-GAVI countries in the WHO European region and sharing country experiences
- Discussing options for vaccine procurement for non-GAVI countries in Central and Eastern Europe and the Newly Independent States
- Reviewing vaccine safety issues and how to improve public health communication on safety topics
- Discussing transition issues related to the use of monovalent vaccines, combined vaccines, and new vaccines
- Discussing the roles of partner agencies and organisations in vaccination programmes

### III. EPIDEMIOLOGY AND PREVENTION

The meeting in Kyiv reviewed changes in the regional epidemiology of hepatitis B that reflect the impact of vaccination programmes, as well as efforts to reduce nosocomial transmission of bloodborne viruses. The meeting also discussed prevention of *Haemophilus influenzae* type b (Hib) infection and hepatitis C infection.

#### A. HEPATITIS B INFECTION

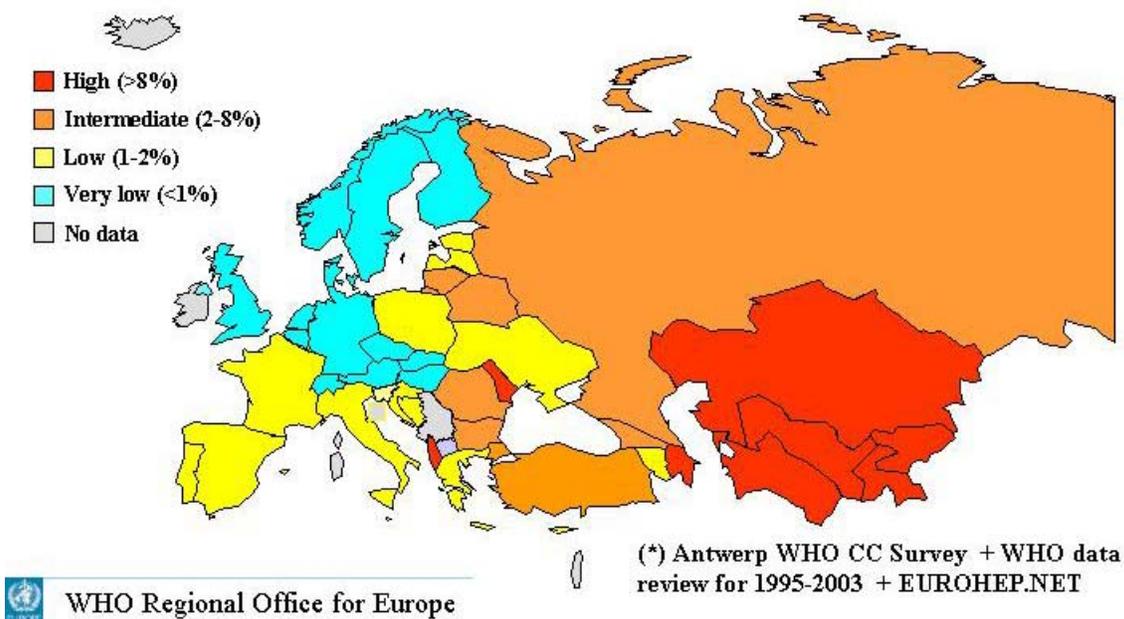
Globally, about 2,000 million people—nearly one-third of the world’s population—have antibodies to hepatitis B surface antigen (HBsAg) that indicate current or past infection. In high endemicity areas, most hepatitis B infections are acquired perinatally or during early childhood. Infections at this early age often lead to asymptomatic chronic infections that can cause severe liver damage (cirrhosis or cancer) over a period of years (Table 3). In high endemicity areas, most hepatitis B infections are acquired perinatally or during early childhood. 21% of HBV- related deaths result from infection in the perinatal period, and 48% of HBV-related deaths result from infection in early childhood. Three doses of hepatitis B are 90-95% effective in preventing hepatitis B infection and its chronic sequelae<sup>1,2</sup>.

**Table 3** Acute and Chronic Hepatitis B Infection Among Infants and Children<sup>6</sup>

<u>Age at Infection</u>	<u>Acute infection</u>	<u>Chronic infection</u>
<1 year	<1%	90%
1-5 years	5-15%	25-50%
>5 years	20-50%	6-19%

Central and Eastern Europe and the Newly Independent States includes 8 countries with historically high prevalence rates of hepatitis B (>8%; Figure 3 and Table 2); 9 countries have moderate rates (2-8% rates) and 12 have low rates (>2%). In high endemicity areas, where children under five are the largest group affected, perinatal transmission, child-to-child, unsafe injections, and blood transfusions are the main routes of transmission. In low endemicity areas, adolescents and adults are at highest risk, due to sexual transmission and injection drug use. In intermediate areas, people of all ages acquire hepatitis B infection.

**Figure 3** Viral hepatitis B endemicity, estimated prevalence of HBsAg carriers (\*)



**Regional Progress.** CEE and NIS countries have made great strides in preventing hepatitis B through vaccination, with lowered rates of acute hepatitis B reported throughout the region (Figure 2). Immunisation efforts are in good accord with the priorities established by WHO (Box 1), with 26 out of 29 countries targeting infants or newborns and infants. Three countries are only targeting adolescents. All high-endemicity countries provide a birth dose of hepatitis B vaccine, and the three-dose coverage rate is expected to approach the rates for diphtheria-tetanus-pertussis (DTP) and measles within a few years (Figure 4). Surveillance for viral hepatitis has been strengthened, and notification of cases of acute hepatitis B is mandatory in all NIS and CEE countries.

Across the region there is increased political commitment and support for hepatitis B vaccination. Immunisation is provided free of charge in all NIS and CEE countries, and vaccines are administered by well-trained, capable, and motivated public health personnel. Collaborative partnerships have been established between ministries of health and international partners, including WHO/EURO, VHPB, UNICEF, GAVI, CVP/PATH, and CDC.

NIS and CEE countries have also intensified efforts to prevent transmission of hepatitis B through unsafe injections, blood transfusions, and other healthcare-related procedures. These activities, which also prevent transmission of HIV and hepatitis C, are described further in the section on **Safety Issues**.

**Box 1****WHO's Global Hepatitis B Vaccination Strategy****Goal**

90% coverage with three-dose regimen of hepatitis B vaccine for all children by 2015

**Objectives**

- Primary: Prevent chronic HBV infection, cirrhosis, liver cancer, and death  
Secondary: Prevent acute hepatitis B infection

**Vaccination Priorities**

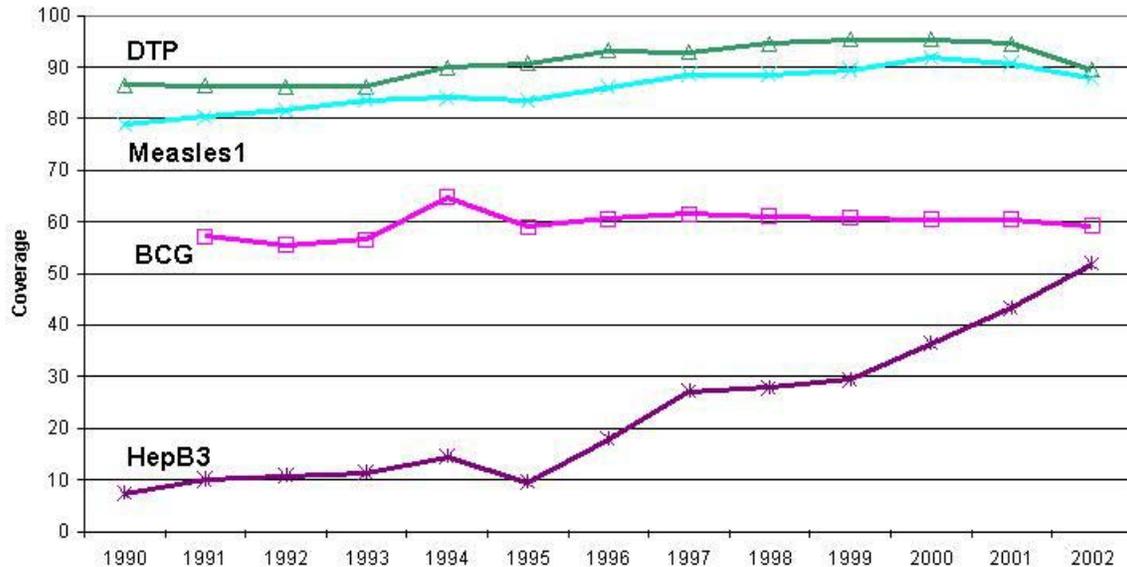
- Routine infant vaccination
- Prevention of perinatal transmission by providing the first dose of vaccine within 24 hours of birth (the birth dose)
- Catch-up vaccination for older children and adults at risk

**Challenges.** Obstacles to further regional progress in prevention and control of hepatitis B infection include economic and political instability in some NIS and CEE countries; unequal economic development of districts within countries; and difficult transitions from centralised to decentralised healthcare systems. There is also continued need for:

- Strengthened surveillance systems that monitor progress and identify problems
- Technical support on issues related to vaccine preparation, quality, administration, and management
- Improved public health communication when vaccine safety issues arise
- Financial sustainability planning to ensure that immunisation programmes are funded from year to year
- Public advocacy and political commitment
- Better programme management and evaluation of performance at all levels
- Improved communication and collaboration with stakeholders
- Better integration between private and public healthcare sectors

Four of these topics - disease surveillance systems, technical support, vaccine safety crises, and financial sustainability planning - were addressed at special workshops whose reports are provided in section VII.

**Figure 4 Immunisation coverage rates in the European Region, 1990-2002**



WHO Regional Office for Europe

## **B. HAEMOPHILUS INFLUENZAE TYPE B INFECTION**

*Haemophilus influenzae* type b (Hib) virus is responsible globally for more than 3 million cases of serious disease in young children, causing more than 400,000 deaths each year. Meningitis occurs in more than 30% of cases involving children less than five years old, sometimes leaving survivors with neurological deficits such as deafness or learning problems<sup>7</sup>

GAVI partners have chosen the Hib conjugate vaccine - which is 90% effective in preventing disease - as one of the new vaccines supported by the Vaccine Fund, along with hepatitis B vaccine and yellow fever vaccine. Like the hepatitis B vaccine, the three-dose Hib conjugate vaccine can be safely administered to infants in co-administration with other vaccines (i.e., DTP, oral polio vaccine [OPV], or hepatitis B vaccine) or in combined vaccines, making it relatively easy to integrate into EPI vaccine schedules.

Over the past eight years, 32 of 52 WHO/EURO member countries have introduced Hib vaccine into routine immunisation programmes, including 25 Western European countries and 7 CEE countries (Croatia, Czech Republic, Hungary, Latvia, Lithuania, Slovakia and Slovenia). Data from the European Union Invasive Bacterial Infection Surveillance (EU-IBIS) Network confirm that significant decreases in Hib incidence have occurred in countries that have introduced Hib vaccine<sup>8</sup>. Far fewer young children are infected, and the rate of meningitis is decreasing, reflecting the infrequent occurrence of Hib-related meningitis in older children or adults.

Population based studies were recently conducted in Bulgaria, Poland, and the Russian Federation with support from WHO and demonstrated relatively low levels of Hib incidence.

Several additional NIS and CEE countries are assessing the disease burden of Hib and costs and benefits of introducing Hib vaccine into childhood vaccination programmes, using a rapid Hib assessment tool developed by WHO (Box 2). The decision on whether to implement a national Hib immunisation programme typically takes into account disease prevalence rates, cost-effectiveness, political commitment, long-term sustainability, and past experience with introducing the hepatitis B vaccine.

### **Box 2                      Rapid Assessment of the Disease Burden of *Haemophilus influenzae* type B**

WHO's rapid assessment tool (RAT)<sup>9</sup> uses locally available data - such as a retrospective estimate of the incidence of meningitis in children less than five years of age or an overall estimate of mortality in children less than five years of age - to calculate the prevalence of *Haemophilus influenzae* b (Hib) infection.

RAT assessments have also been performed in:

- Albania (2001)
- Kyrgyzstan and Uzbekistan (2002)
- Armenia, Moldova, and the Ukraine (2003)
- Bosnia and Herzegovina (2004)

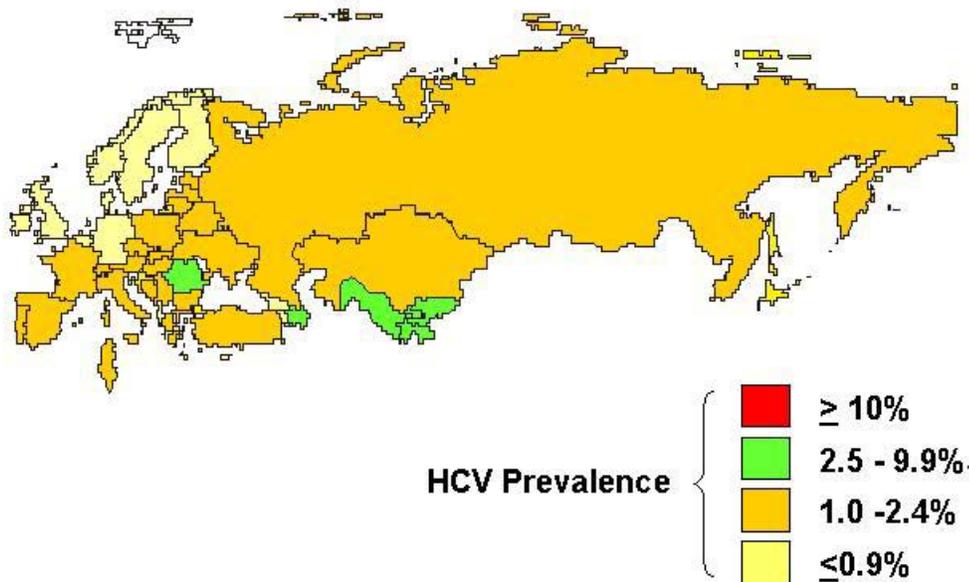
Estimated Hib meningitis rates in these countries ranged from 3-15 to 5-25 cases per 100,000 children under 5 years of age, suggesting that introduction of Hib conjugate vaccine in some of these countries could have an impact on children's health.

RAT can also be used to assess the potential cost-effectiveness of vaccine programmes. RAT calculations suggest, for example, that the introduction of Hib vaccine into Moldova would be cost-effective if the cost of vaccination were USD 1.5 per child or USD 0.5 per dose, and into the Ukraine if the cost were USD 2.7 per child or USD 0.9 per dose.

## **C. HEPATITIS C VIRUS INFECTION**

Hepatitis C is endemic in most parts of the world, though substantial regional differences exist in terms of prevalence, incidence, and risk factors. As indicated in Figure 3, most European countries have low (1-2.4%) or moderate (2.5-9.9%) prevalence of hepatitis C infection. However, these estimates include much uncertainty. Prevalence data from laboratory-based sources (e.g., blood bank records) are often unrepresentative of the general population, while incidence data from syndrome-based surveillance systems do not distinguish among infections caused by different hepatitis viruses. In addition, syndromic surveillance systems exclude the large number of asymptomatic infections, of which the chronic component might be reported, but only when liver disease is far advanced.

**Figure 5**      **Prevalence of HCV infection**



**Source:** WHO, *International Travel and Health*

<http://www.who.int/ith/index.html>

Around the world, injection drug use and unsafe medical practices (especially untested blood transfusions and unsafe injections) account for most hepatitis C infections. Unsafe medical practices are major risk factors in countries with high endemicity of hepatitis C, while injecting drug use is the major risk factor in countries with low endemicity. Because there is as yet no vaccine against hepatitis C, prevention efforts focus on addressing these risk factors.

***Healthcare-Associated Transmission.*** In countries where hepatitis C virus (HCV) is spread in medical settings through contact with contaminated blood, the most effective preventive activities include:

- Introducing transfusion services that always screen all blood units and discourage blood donation from people in high risk groups
- Implementing injection safety practices and discouraging unnecessary medical injections
- Ensuring proper sterilisation and disinfection of syringes and medical equipment
- Encouraging the use of non-reusable syringes and needles
- Establishing infection control precautions in all healthcare settings to reduce the risk of exposure to contaminated blood

***Injecting Drug Use.*** As noted above, injecting drug use is the predominate risk factor for hepatitis C infection in low-endemicity countries. When a country experiences a steep increase in hepatitis C infection, it is often due to an increase in injecting drug use behaviour and/or the introduction of HCV into the IDU

population. Hepatitis C virus is rapidly acquired after initiation into drug use and is more common among drug users than HIV<sup>10</sup>. Hepatitis C prevention activities should therefore be integrated into programmes that address substance use and harm reduction (see below, Part D).

## **D. INTEGRATED PROGRAMMES FOR PREVENTION AND SURVEILLANCE OF VIRAL HEPATITIS AND HIV**

Prevention activities can be integrated into hospital and clinic-based programmes for the prevention of HCV, HIV, and hepatitis B, as well as into programmes that address substance use and corrections health. These programmes can provide a variety of prevention services in an integrated and cost-effective manner (e.g., vaccination against hepatitis B and counseling on how to avoid bloodborne or sexual transmission of viral hepatitis viruses and HIV). Healthcare workers can identify people in high risk groups, test them for HIV, HBV, and HCV, counsel them about harm and risk reduction, vaccinate against hepatitis B and refer them for medical evaluation or substance use treatment, as necessary.

This approach presents significant challenges. It requires funding or referral sources for laboratory tests, vaccination, and medical care. It requires well-trained counselors who can provide information on several different diseases. It also requires cooperation among managers of health programmes that receive funding from different sources (e.g. programmes on HIV, sexually transmitted infections (STIs), drug treatment, and corrections health). Despite these obstacles, most experts agree that the integration of disease prevention activities can provide major public health benefits.

***Integrated Disease Surveillance.*** Integrated surveillance programmes that target diseases with overlapping risk factors can be an efficient and useful way to track diseases of public health importance. Five Central Asia Republics - Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan - are implementing integrated programmes for sentinel surveillance of infection due to viral hepatitis viruses (A-D) and to the HIV virus. Risk factor data from these programmes will be used to develop integrated prevention programmes that target those at highest risk (e.g., injecting drug users and people exposed to unsafe medical practices).

A description of the Kyrgyzstan Acute Hepatitis Surveillance System is provided in Section IV: Country Experiences, and examples of sentinel surveillance studies conducted in Kyrgyzstan and Kazakhstan are provided in Box 3.

**Box 3****Sentinel Surveillance for Acute Viral Hepatitis in the Central Asian Republics**

Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan are using sentinel surveillance for acute hepatitis to assess the impact of their immunisation programmes and to evaluate risk factors for transmission of viral hepatitis. Examples of sentinel surveillance studies include:

- **Evaluation of the Hepatitis B Vaccination Programme (Kyrgyzstan).** A study of the incidence of acute hepatitis B cases in newborns between 2000 and 2003 found that the rates of infection were 2.9 per 100,000 vaccinated children versus 760 cases per 100,000 unvaccinated children. This finding confirms the tremendous impact of the newborn immunisation programme.
- **Etiologies of Acute Cases of Viral Hepatitis (Kazakhstan).** Sentinel surveillance projects conducted in 2003 found that 76.2% of acute cases of viral hepatitis are caused by hepatitis A virus, 20% by hepatitis B virus, 3.1% by hepatitis C virus, and 0.04% by hepatitis D virus. Due to the success of childhood immunisation programmes, the majority of acute cases of hepatitis B were reported in adults.
- **Etiologies of Acute Cases of Viral Hepatitis (Kyrgyzstan).** In 2003 the percentages due to hepatitis B and C were 26% and 7% and the percentage due to hepatitis A was 43%. As in Kazakhstan, most of the cases of hepatitis B and C in 2003 were in young adults, suggesting that parenteral transmission (through injecting drug use or unsafe medical procedures) and sexual transmission may be contributing factors.
- **Risk Factors for Bloodborne Viral Hepatitis (Kyrgyzstan).** A case control study analysed following risk factors for infection with hepatitis B, C, or D: blood transfusion, surgery, injections administered in a hospital, injections administered in a polyclinic, blood sample collection in a polyclinic, visit to a surgeon, dentist, urologist, or gynecologist, blood donation, multiple sex partners, STI diagnosis. In response to these findings, Kyrgyzstan is improving blood safety and injection safety at blood banks, hospitals, and clinics.

## IV SAFETY ISSUES

Safety issues - including vaccine safety, injection safety, and blood safety - were a major theme of the Kyiv conference. A WHO/EURO list of the most frequently asked vaccine safety questions is provided in Box 4.

Conference presentations on safety issues included:

- How WHO ensures the safety and quality of vaccines distributed by UNICEF
- How vaccine safety issues may be investigated and addressed
- How vaccines can be optimally managed, stored, and distributed
- How to prevent healthcare-related transmission of hepatitis B

**Box 4****Frequently asked Questions About Safety of Hepatitis B Vaccines**

- Q.** Which hepatitis B vaccines are recommended for use by WHO?
- A.** All commercially available hepatitis B vaccines are safe and effective, including those made in Belgium, Cuba, India, South Korea, Switzerland, and the United States
- Q.** Is it acceptable to have thiomersal-containing vaccines offered through the Vaccine Fund and UNICEF, even though some countries use thiomersal-free vaccines?
- A.** Absolutely. Expert consultations and reviews by the Global Advisory Committee on Vaccine Safety have found no evidence of toxicity in thiomersal-containing vaccines (see also Box 6).
- Q.** Are thiomersal-containing hepatitis B vaccines safe enough to be offered at birth?
- A.** Yes. The European Technical Advisory Group of Experts on Immunisation (ETAGE) endorses the continued use of hepatitis B vaccines in national immunisation programmes, including administration of thiomersal-containing and thiomersal-free vaccines to newborns for prevention of perinatal transmission<sup>11</sup>.
- Q.** Can a birth dose of hepatitis B vaccine be given simultaneously with BCG vaccine?
- A.** Yes. A recent study suggests that co-administration of BCG and hepatitis B vaccine even increases the immune response to hepatitis B, with no increase in adverse events following vaccination<sup>12</sup>.

## **A. VACCINE QUALITY AND SAFETY**

Hepatitis B is the first vaccine that prevents both infection and cancer. It protects newborns from perinatal transmission, children from person-to-person transmission, adults from sexual transmission, and people of all ages from bloodborne transmission via unsafe transfusions or injections.

Hepatitis B vaccines consist of purified preparations of hepatitis surface antigen (HBsAg) that are prepared by harvesting antigen from the plasma of people with chronic infections or by producing HBsAg in genetically engineered yeast or bacteria. The overwhelming majority of hep B vaccine manufactured is now recombinant. All WHO-pre-qualified vaccine and therefore, all vaccine purchased by UNICEF is recombinant. Aluminium phosphate or hydroxide is often used as an adjuvant, and thiomersal (ethyl mercury) may be used in some of the currently available hepatitis B vaccines to prevent bacterial contamination that may occur after multi-dose vaccine vials are opened. Some countries manufacture their own vaccines while others purchase them directly from private manufacturers or procure them through UNICEF with external financial assistance. (see also **Vaccine Procurement and Financing**).

***Prequalification of Vaccines Distributed by UNICEF.*** WHO advises UNICEF on vaccine safety and efficacy and ensures that vaccines distributed by UNICEF meet standards for potency, thermostability, labeling, and shipping conditions. All vaccines prequalified by WHO ([http://www.who.int/vaccines-access/quality/un\\_prequalified/prequalification\\_system.htm](http://www.who.int/vaccines-access/quality/un_prequalified/prequalification_system.htm)) must be assessed by the national regulatory authority (NRA) of the country in which the vaccine is manufactured. The NRA reviews production processes and quality control procedures and tests vaccine lots to ensure consistency. A joint NRA/WHO team makes periodic factory visits and prepares an assessment every two years.

As of May, 2004, pre-qualified hepatitis B vaccines - all recombinant products - are available from

- Berna Biotech (previously Korea Green Cross), Switzerland/South Korea
- Center for Genetic Engineering and Biotechnology, Cuba
- GlaxoSmithKline Biologicals, Belgium
- LG Life Sciences LTD, South Korea
- Merck and Co. Inc, United States
- Shanta Biotechnics Private Ltd., India

These vaccines are made by different processes and are not identical “generic” products. In terms of effectiveness, however, they are interchangeable<sup>13</sup>. WHO standards for vaccine quality are the same for all vaccines, regardless of the country of manufacture. Also combined vaccines, DTP-hep B and DTP-hepB-Hib have been pre-qualified.

**Addressing Concerns About Vaccine Safety.** In spite of the vaccine’s impressive safety profile (Box 5), questions have been raised about possible linkages between hepatitis B vaccine components and particular diseases (Box 6). Reviews and investigations by the Global Advisory Committee on Vaccine Safety (GACVS; [http://www.who.int/vaccine\\_safety/en/](http://www.who.int/vaccine_safety/en/)) and other experts have found no scientific basis for these concerns (Box 6).

#### **Box 5 Safety Profile of Hepatitis B vaccine**

- Pain and tenderness at the site of injection in 15% (3-19%) of those vaccinated
- Fever greater than 37.7 °C in 1-6% of those vaccinated
- Fever, headache, muscle aches and pain, nausea, vomiting, loss of appetite, and fatigue occur at same rate as when a placebo is given
- Anaphylactic reaction occurs in 1 per 600,000 doses
- No association with group B streptococcus infection (GBS)
- No association with diabetes
- No association with hair loss
- Cases of rheumatoid arthritis, thyroiditis, lupus, hematological disorders and multiple sclerosis have been reported, but no causal link has been demonstrated

More information on the Safety Profile of hepatitis B vaccine is available at:  
[http://www.vhpb.org/files/html/Meetings\\_and\\_publications/VHPB\\_Meetings/Kyiv2004/pdf/S51enDuclos.pdf](http://www.vhpb.org/files/html/Meetings_and_publications/VHPB_Meetings/Kyiv2004/pdf/S51enDuclos.pdf)

The safety of hepatitis B has been confirmed by many independent groups, including:

- Agence Nationale d’Accréditation et d’Evaluation en Santé (ANAES)<sup>14</sup> (<http://www.anaes.fr/HAS/has.nsf/HomePage?ReadForm>)
- Agence Française de Sécurité Sanitaire des Produits Santé (AFSSAPS)<sup>14</sup> (<http://www.agmed.sante.gouv.fr>)
- U.S. Institute of Medicine (IOM)<sup>15,16,17</sup>
- Viral Hepatitis Prevention Board (VHPB)<sup>18,42</sup> (<http://www.vhpb.org>)
- European Association for the Study of the Liver (EASL)<sup>17</sup> (<http://www.easl.ch>)
- European Technical Group of Experts (ETAGE)<sup>19</sup>

Nevertheless, rumors and mistaken associations between vaccination and disease have created undue fear in the public, reduced vaccination coverage and a huge amount of work for health authorities.

**Box 6****Investigations of Hepatitis B Vaccine Safety Issues**

Expert investigations conducted between 1999 and 2004 have found no evidence of adverse health effects related to the use of the hepatitis B vaccine or its components. Safety topics have included:

**Thiomersal and Health Effects**

In 1999, the U.S. Food and Drug Administration reported that the cumulative amount of mercury involved in childhood vaccinations exceeds the threshold set for methyl mercury by the U.S. Environmental Protection Agency. However, as vaccine experts have noted, the ethyl mercury (thiomersal)—the only mercury compound used in childhood vaccines—is chemically distinct from methyl mercury and has a long history of safe use<sup>20,21,22</sup>.

Over the past few years, associations have been suggested between thiomersal and specific diseases<sup>20,21,22</sup>. For example, a 2001 research article reported a possible association between hepatitis B vaccination and acute lymphoblastic leukemia (ALL) and suggested that thiomersal might play a role<sup>23</sup>. However, an expert review found that the study contained statistical errors and epidemiologic bias and a series of epidemiologic studies found no evidence to support suggested linkages between thiomersal and ALL,<sup>24</sup> diabetes,<sup>25</sup> or developmental disorders such as autism<sup>26,27,28</sup>.

**Aluminum Compounds and Health Effects**

Aluminum phosphate or hydroxide is often used as an adjuvant in childhood vaccines, including hepatitis B vaccines. In some individuals, the intramuscular injection of these vaccines can lead to the development of macrophagic myofasciitis (MMF), a localised histopathologic lesion that contains macrophages and aluminum. In 1999, a review by the Global Advisory Committee on Vaccine Safety confirmed that local MMF lesions are due to immunisation but found no evidence of linkage between MMF and systemic illness<sup>29</sup>.

**Multiple Sclerosis and Hepatitis B Vaccination**

In 1999, the Government of France suspended the national school-based adolescent vaccination programme because of case reports that linked multiple sclerosis (MS) cases to hepatitis B vaccination. However, a national pharmacovigilance survey concluded that the association was coincidental: the age and sex distribution of the MS cases associated with hepatitis B vaccination were similar to the expected distribution of MS in the general population. Large epidemiologic surveys do not support a causal relationship between MS and hepatitis B vaccination<sup>1,16,18,19,24,30</sup>.

**Conclusion:** There is no evidence of linkage between hepatitis B vaccination and systemic disease.

As discussed by Workshop C: 'How to manage a vaccine safety crisis', public health leaders must be prepared to address whatever safety issues may arise. They must investigate all rumors, keep careful records of adverse events following immunisation, and maintain clear, accurate, consistent and continuous communication with the public via the newsmedia. Public health communication is critical to public trust in vaccines, trust in the health system, and trust in international organisations and vaccine suppliers.

**Vaccine Management.** Effective immunisation programmes depend on good vaccine management and good transport and storage practices. In 2003, WHO and UNICEF issued a joint statement listing Global Criteria for Effective Vaccine Store Management (EVSM) related to these topics:

- Pre-shipment and arrival procedures
- Storage within temperature ranges
- Storage capacity of the facility
- Equipment and transport
- Maintenance of buildings, equipment, and vehicles
- Effective stock management
- Quality of deliveries to the next level
- Vaccine wastage during transport
- Standard operating procedures
- Adequate human and financial resources

In regard to hepatitis B vaccine, one of the most important vaccine management issues is that the **vaccine must not be frozen during storage or transport**. If ice packs are used during transport they must be “conditioned” (i.e., kept at ambient temperature for about one hour so that they are warmed to 2-4<sup>0</sup>C degrees) or replaced with chilled water packs (icepacks kept in refrigerators).

The WHO/ATT (Access To Technology) Effective Vaccine Store Management website (<http://www.who.int/vaccines-access/vacman/csci/csci.htm>) provides materials that help vaccine managers appraise current practices and meet the Global Criteria, including a model National Vaccine Quality Management Plan, an Assessment Questionnaire, and Guidelines for Self-Appraisal. The site also provides information on the Global Training Network, and vaccine management training courses organised in English, French, Russian, and Spanish, which are located at WHO and UNICEF Country Offices (<http://www.who.int/vaccines-access/vacman/VMTC/VMTCmain.htm>).

Other vaccine management issues were discussed by Workshop B: ‘Technical aspects of hepatitis B vaccines’, which covered a range of issues related to vaccine use (schedules, cold chain maintenance, waste management), duration of protection, use of boosters, pre- and post-vaccine testing, and management of non-responders.

## **B. INJECTION SAFETY AND BLOOD SAFETY**

Hepatitis B virus - like HIV and hepatitis C virus - can be spread to patients through unsafe injections and blood transfusions and to healthcare workers via needle sticks. NIS and CEE countries have made progress in reducing these health risks, making use of programmes or tools developed by WHO, Safe Injection Global Network (SIGN) ([http://www.who.int/injection\\_safety/en](http://www.who.int/injection_safety/en)), UNICEF, and other partners.

***Injection Safety Practices.*** In many NIS and CEE countries, routine medical treatment includes injections that may be administered with used needles and syringes and after administration, needles and syringes are not always disposed of correctly. The majority of injections administered worldwide are for therapeutic purposes and injection safety efforts must address both therapeutic and vaccine injections. Other challenges to injection safety include mis-use of disposable syringes; increased volume of waste due to use of disposable syringes; increased costs for equipment and waste disposal; and risk to providers during sharps disposal.

WHO/EURO is working with more than 20 member countries to improve injection safety by:

- Assessing injection and waste disposal practices
- Training healthcare workers in best practices for safe injections
- Identifying affordable options for improving injection safety and sharp waste management, as needed, based on pilot projects and cost-effectiveness studies
- Promoting the purchase of supplies (e.g., disposal or auto-disable syringes and safe containers for sharps)
- Raising public awareness of injection safety issues
- Recommending the creation of safety committees at hospitals and clinics
- Revising national healthcare policies and drafting plans of action

UNICEF-Uzbekistan has developed a Safe Immunisation Programme that was implemented in the country in 2002. Programme components include assessing injection practices, training healthcare workers, providing educational outreach to the general population, and constructing incinerators for safe disposal of injection safety equipment. Data from a project in Karakalpakistan (Uzbekistan) indicate that a safe injection program improved injection practices: There was a reduction in the number of unnecessary medical injections, which also reduced treatment costs, and triggered consistent proper disposal of used needles and syringes.

**Safe Disposal of Syringes and Sharps.** Injections performed with contaminated needles expose healthcare workers (as well as patients) to unnecessary risk. Needle sticks may occur during recapping, collection, disassembly, soaking, rinsing, recycling, or transport of sharps to the site of burning, burial, or incineration. A pilot study conducted in Uzbekistan to improve injection safety and safe sharps collection is described in Box 7.

**Box 7                    Improving Injection Safety and Safe Sharps Collection in Uzbekistan**

A risk factor assessment conducted by the Uzbekistan Ministry of Health reported a high risk of bloodborne transmission of HIV and viral hepatitis due to unsafe injection practices and out-of-date technologies for disposal of sharps. The most significant risk factors for patients were medical injections, surgery, and blood transfusion.

A pilot study in Samarkand implemented training interventions for healthcare prescribers and providers that led to:

- A reduction in the number of patients receiving unnecessary medical injections from more than 50% to about 15%.
- An increase in the number of safely handled sharps from 10% to almost 100%
- A decrease in the annual number of needle stick injuries per injection provider from 2.25 to 0.5.

Implementation of these interventions is ongoing at hospitals and clinics.

Safe injection equipment may include:

- **Auto-disable (AD) syringes.** A joint statement by WHO, UNICEF, and the United Nations Population Fund (UNFPA) calls for the use of auto-disable syringes by all nations by 2003 (<http://www.who.int/vaccines-documents/DocsPDF99/www9948.pdf>). AD syringes are now at a comparable price with disposable syringes; safe practices for re-cycling them are under consideration by WHO and others.
- **Safety containers.** The use of safe disposal boxes to contain sharps - even sharps that are disinfected and decontaminated - is highly recommended to prevent injuries and disease transmission. A wide range of containers is available, usually made of plastic or reinforced cardboard.
- **Mechanical needle removers, pullers, or destroyers.** This type of equipment reduces the risk posed when needles are separated from syringes by hand before recycling.

Most priority countries from CEE and NIS countries use AD syringes and safe container boxes. Eleven of these countries receive injection safety funds from GAVI. In the future, several countries may initiate local manufacture of safety containers and AD syringes, keeping prices lower.

**Box 8****Improving Blood Safety Procedures in the Central Asian Republics**

A pilot study in the Central Asian Republics assessed region-wide blood safety procedures, identified unsafe practices, and implemented interventions to reduce blood borne disease transmission.

**Assessment.** Serological testing confirmed that blood transfusions were a significant source of risk to both patients and healthcare workers. The most significant risk factor for hepatitis C was plasma donation, apparently due to the collection of blood in reusable bottles. Risk factors for healthcare workers included exposure to blood, injuries in the workplace, and re-use of gloves.

The assessment also identified weaknesses in blood donor recruitment (e.g., the use of paid blood donors and lack of comprehensive blood donor screening), as well as in the diagnostic capacity of blood bank laboratories. Most laboratories interpreted serologic tests visually rather than by quantitative optical scanning, and inadequate blood transfusion processing supplies led to reuse of contaminated materials.

**Interventions.** Interventions included strengthening Blood Center laboratories and training laboratory managers and technicians. As part of this effort, Blood Center managers toured the Jordan National Blood Center to share ideas and experiences.

As a result of these activities, Blood Centers have reduced the risk of nosocomial infection by:

- Implementing blood donor screening and blood unit testing
- Introducing laboratory quality control and quality assurance procedures
- Training staff members in blood safety principles
- Discouraging the use of blood donations from Blood Center Staff

**Blood Safety Practices.** NIS and CEE countries in which blood transfusions are major risk factor for viral hepatitis are working to improve the safety of their blood supplies by introducing blood donor screening and serological testing of donated blood units into blood bank procedures. Rapid progress has been made in the Central Asian Republics of Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan, working in collaboration with the International Consortium on Blood Safety (ICBS) and USAID (Box 8).

The improvement of blood safety practices typically requires improvements in laboratory capacity and laboratory control, supply of reagents, training of healthcare workers, and procedures for interviewing and screening potential blood donors. Countries that have instituted these improvements report that making blood transfusions safer is one of the easiest and most effective ways to prevent transmission of viral hepatitis and HIV/AIDS.

## V. VACCINE PROCUREMENT AND FINANCING

**Vaccine procurement and financial sustainability planning** was another major theme of the Kyiv conference. Presentations included:

- An overview of changes in market conditions that affect supplies of hepatitis B and other childhood vaccines.
- A discussion of group procurement as a potential approach to purchasing affordable vaccines.
- A description of the steps involved in financial sustainability planning to ensure that immunisation programmes have adequate and reliable long-term financing.

## A. VACCINE SECURITY

Since the 1970s, when EPI began, vaccine production has shifted from the public to the private sector. As a result, vaccine production objectives are now based primarily on market considerations (costs, prices, competition) rather than on public health needs. This trend was accelerated in the 1990s by mergers and consolidations that led to more streamlining and less flexibility in vaccine production.

The vaccine market has been diverging into two tracks: products that are “high-tech” and expensive (i.e., vaccines made through genetic engineering) and products that are “low-tech” and less expensive (i.e., vaccines made from whole cell preparations). Due to large price differences between these products (Table 4), the greatest profitability is in the high-income market. Thus, although UNICEF buys 40% of the global volume of vaccine doses, the total cost of vaccines procured by UNICEF represents only 5% of total market value.

**Table 4** A Diverging Market for Hepatitis B Vaccine

<u>Country Income</u>	<u>Vaccine Preparation</u>	<u>Cost</u>
Low	Hep B vaccine: Monovalent & combination with DTwP <sup>i</sup>	32-90 cents
High	Acellular: Combination with DTaP <sup>ii</sup>	9 dollars

i DTwP: diphtheria, tetanus, and whole cell pertussis vaccine  
ii DTaP: diphtheria, tetanus, and acellular pertussis vaccine

In response to recent vaccine shortages - due in part to market changes - UNICEF has developed a Vaccine Security Strategy for ensuring an uninterrupted supply of affordable vaccines of assured quality ([http://www.unicef.org/supply/index\\_vaccine\\_security.html](http://www.unicef.org/supply/index_vaccine_security.html)). In accordance with the strategy, UNICEF’s role has evolved from vaccine buyer to strategic partner of vaccine producers. UNICEF makes future (“forward”) commitments to buy vaccines from a variety of manufacturers in both industrialised and developing countries. UNICEF provides these manufacturers with rolling forecasts of demand for EPI vaccines for a period of 3 years. The rolling forecasts and long-term supply arrangements provide lead-time for ramping up production, which typically takes two to three years (longer if new factories are built).

UNICEF reports that vaccine manufacturers are responding positively to the new approach. There are on average two to four suppliers for all EPI vaccines, larger stocks of each vaccine, and smaller price variations among manufacturers.

UNICEF’s Vaccine Security Strategy includes new procedures for ensuring safe delivery of vaccines. Since May, 2003, each UNICEF vaccine shipment has been inspected by a country official who fills out a Vaccine Arrival Report to ensure that problems (such as heat exposures) are detected and delivery practices are improved.

## B. GROUP PROCUREMENT OF VACCINES

During 2002, NIS and CEE countries purchased approximately 160 million doses of hepatitis B vaccine, 80% by self-procurement (Box 9) and 20% through UNICEF (primarily via the Vaccine Fund). In 2003 the Children's Vaccine Programme at PATH raised the possibility of developing a third approach, as described in a document entitled *Group Procurement of Vaccines for CEE and NIS: Feasibility, Issues, and Options*<sup>31</sup>.

### Box 9 WHO/EURO Vaccine Procurement Survey

In 2002, WHO/EURO conducted an e-mail survey of vaccine procurement practices in 15 NIS and CEE countries: Bulgaria, Croatia, the Czech Republic, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Macedonia, Romania, Serbia & Montenegro, Slovakia, Slovenia, Turkey, and the Ukraine. Twelve of these countries (80%) are self-procuring.

The survey determined that national vaccine procurement systems may be strengthened by:

- Revising vaccine legislation to improve contract management and allow competing bids
- Building the technical capacity of the national regulatory authority to ensure vaccine quality and document adverse events following vaccination
- Developing multi-sector organisational structures for vaccine procurement
- Forecasting future vaccine needs, taking into account shortages, wastage, and reserve stock
- Implementing financial sustainability planning on an annual basis
- Exploring opportunities for group procurement

Group procurement might help resolve these issues:

- High vaccine prices or prices that vary widely from country to country
- Insufficient transparency and competition in the vaccine procurement process
- Limited selection of vaccines
- Irregular supply of vaccines
- Inadequate quality assurance in some countries

Prepared in conjunction with WHO and other partners, *Group Procurement for CEE and NIS* is based on a regional survey of vaccine prices, as well as in-depth discussions with ministries of health in Croatia, Macedonia, Lithuania, and Romania. The report concludes that group procurement may be especially beneficial for middle income countries with GNP/per capita income greater than \$1000. Models include the PAHO revolving fund ([http://www.paho.org/english/hvp/hvi/revol\\_fund.htm](http://www.paho.org/english/hvp/hvi/revol_fund.htm)) and the Gulf Cooperation Council vaccine fund.

Despite its potential advantages, there is limited regional interest in group procurement at the present time, because many countries prefer the flexibility of self-procurement or have legal obstacles to changing their procurement practices. However, four countries in the Region (Bulgaria, Latvia, Lithuania and Estonia, are considering group procurement as a future option. Group procurement could save these countries between 200,000 and 800,000 Euros per year (not including operating costs) for hepatitis B vaccine, Hib vaccine, and mumps/measles/rubella (MMR) vaccine.

CVP/PATH suggests that these countries take a step-wise approach to implementing group procurement, with WHO as a primary partner. The first step would be to share information on prices, types of vaccines, and experiences with suppliers and vaccines ("informed buying"). The second step would be to create a database of regional vaccine information. Interested countries could then move on to preparing a joint market survey (coordinated buying), group negotiations with individual procurement (group contracting), and then - as a final step - centralised contracting (group procurement).

## C. FINANCIAL SUSTAINABILITY PLANNING

All countries that receive vaccines and resources from the Vaccine Fund are required to prepare a financial sustainability plan (FSP) during their second year of GAVI support. Although national self-sufficiency is the ultimate goal, the short-term aim is to help each country mobilise domestic and external resources to achieve target levels of immunisation.

NIS countries that have developed or are in the process of developing FSPs include:

- Kyrgyzstan (2001)
- Albania, Armenia, Azerbaijan, Turkmenistan, Tajikistan, and Uzbekistan (2003)
- Bosnia & Herzegovina, Georgia, Moldova, and the Ukraine (2004)

The FSP describes how a country's national immunisation programme plans to match programme objectives with financing over the medium to long term. It requires an assessment of financing gaps and a strategy for addressing them. Typically, the FSP is developed by a multi-sector team, in consultation and negotiation with many stakeholders. Team members may include policy and financial experts at the ministries of finance and health, as well as representatives of an Interagency Coordination Committee for Immunisation established to oversee use of GAVI funds.

Steps in the planning process include estimating vaccine costs in pre-GAVI years; projecting resource needs for future years; analyzing programme development scenarios and options for covering financial gaps; and developing long-term strategies for financial sustainability. Technical assistance in preparing the FSP is available on request from GAVI, the World Bank, and WHO. In addition, CVP/PATH has developed an e-learning tool that provides assistance with all parts of the planning process (<http://aim-staging.stanford.edu>).

**Benefits.** FSPs can help Ministries of Health and Finance identify specific actions that increase the likelihood of long-term financial sustainability for immunisation programmes. FSP development provides a detailed picture of the financial underpinnings of national immunisation programmes. FSPs provide baseline information for year-to-year programme monitoring and can be shared with stakeholders and donors and used as advocacy tools.

**Challenges.** In many CEE and NIS countries, the current system of healthcare planning involves line-item budgeting rather than programme analysis, as required for the FSP. As a result, the healthcare sector may lack experience with economic evaluation studies and with the use of performance indicators and incentives to improve the quality of services. Lack of long-term planning may also lead to overlapping services and inefficient resource use.

Management problems that may arise during FSP planning and implementation include:

- Vaccine procurement and delivery systems may be managed by different offices (i.e., public health authorities and healthcare authorities) and may not be well coordinated.
- Data collection may not be standardised among services and an operational data audit system may be lacking
- There may be inadequate quality assurance procedures for cold chain maintenance, injection safety, and vaccine storage
- There may be a lack of established channels for interagency discussions or negotiations on operational policy issues

These and other challenges were discussed in **Workshop D**. Examples of financial sustainability planning are described in Box 10 (Development of a financial sustainability plan in Uzbekistan) and Box 11 (Implementation and evaluation of a financial sustainability plan in Kyrgyzstan).

### **Box 10            Developing a Financial Sustainability Plan**

In 2003 the National Immunisation Programme of Uzbekistan prepared its first Financial Sustainability Plan, in collaboration with other colleagues from the Ministry of Health and the Ministry of Finance. The planning team identified these immunisation goals:

- Maintaining coverage rates for all EPI vaccines, including hepatitis B
- Reducing measles morbidity to less than one case per 100,000 people
- Minimising the level of post-vaccination complications
- Reducing vaccine wastage
- Maintaining a reliable cold chain
- Ensuring injection safety through staff training and the use of auto-disable (AD) syringes
- Ensuring safe waste disposal

The team took stock of past immunisation costs—salaries, costs of building maintenance and repair, transport costs, injection-safety training costs, and purchase of vaccines, syringes, and cold chain equipment—and used this data to estimate future expenses. The team identified management problems and financial gaps and developed strategies to address them.

Benefits included:

- Developing financial skills for analyzing expenses and estimating line item costs
- Developing a multi-sector approach to problem-solving
- Learning how to keep everyone “on the same page” by providing a written record of all decisions
- Learning that financial planning is a reiterative process rather than a one-time event

### **Box 11            Implementation of a Financial Sustainability Plan**

In 2003, the National Immunisation Programme (NIP) of Kyrgyzstan conducted an evaluation of its 2002 Financial Sustainability Plan (FSP) by:

- Reviewing new trends in operations and financing
- Updating cost projections for the coming year
- Revising the projected financing gap in light of programme changes and new sources of funding
- Assessing the implementation of FSP aims and strategies over the past year (e.g., raising funds for additional vaccines; financing depreciation of cold chain equipment and vehicles, and finding new sources of funds to replace GAVI/VF procurement funds).

Because the NIP benefits from political support for the healthcare sector and for the government’s child development and community development agendas, the FSP was not needed as an advocacy tool. However, it helped expand and strengthen the NIP by providing data to support grant applications to government agencies, development banks, and international donors.

## **VI. COUNTRY EXPERIENCES**

The Kyiv conference included presentations on hepatitis B vaccination programmes in Georgia, Turkey, the Russian Federation, Kyrgyzstan, and Kazakhstan. A presentation was also given on the use of integrated sentinel disease surveillance to monitor hepatitis B vaccination programmes in the Central Asian Republics of Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan (Box 3).

### **A. GEORGIA**

Hepatitis B vaccine was introduced into Georgia (a high-endemicity country) between 2000 and 2003, with assistance from CDC, GAVI, UNICEF, and USAID. The new vaccine was integrated into the existing immunisation schedule for children less than one year old. It was used in urban areas in 2000 and provided countrywide in 2001. Maternity hospitals began vaccination of newborns in 2003, resulting in a change in vaccination schedule from 2 months, 3 months, and 8 months to birth, 2 months, and 4 months.

Initially, hepatitis B vaccination was not as well accepted as expected, because HBV infection was not considered an important public health problem by all physicians, and some parents and healthcare workers had doubts about the safety of the new vaccine. In some cases, infant immunisation was delayed due to misinterpretation of contraindications for vaccination of newborns. There were also financial and management impediments related to the decentralisation of the healthcare system.

Despite these difficulties, hepatitis B immunisation coverage with three-dose of vaccine has increased. The incidence of hepatitis B infection decreased significantly between 2000 and 2003 for all age groups.

Continuing efforts to strengthen immunisation include:

- Training healthcare professionals, including epidemiologists, pediatricians, neonatologists, and heads of health facilities.
- Establishing mobile immunisation teams to reach unimmunised children
- Improving healthcare management and data collection
- Raising awareness among parents and health workers about the dangers of hepatitis B and the effectiveness and safety of vaccination
- Making better use of the national Interagency Coordination Committee to advocate for sustained funding for hepatitis B immunisation.

### **B. TURKEY**

Turkey is a moderate-endemicity country for hepatitis B infection. Among children, approximately one-third of acute viral hepatitis cases are caused by hepatitis B virus, while 60% of adult cases are caused by hepatitis B. Almost one-third of the population has been exposed to hepatitis B virus at some time in their lives, and about 5% (3 to 4 million people) are chronically infected. Major disease risk factors include being a hemodialysis patient, or a female sex worker.

Turkey's Hepatitis B Prevention and Control Programme is based on five strategies:

- Immunisation of newborns, infants and high-risk adults
- Laboratory-based disease surveillance
- Education of the public, people at high risk, and healthcare workers
- Screening of blood donations and blood products
- Implementation of safe injection practices.

Turkey's hepatitis B immunisation programme started in 1998 and includes universal 3-dose vaccination of infants, beginning with a dose of vaccine administered within 72 hours of birth. It also includes vaccination of adults at high risk (e.g., medical and nursing students, haemodialysis patients, recipients of blood products, injecting drug users, household contacts of chronically infected people, female sex workers, people with multiple sex partners, people with chronic liver disease, prisoners, travellers to high-endemicity countries, and barbers and hairstylists). Secondary immunisation targets include people in institutions for the developmentally delayed, firemen, military troops, and selected police units and other groups who provide assistance during accidents and disasters.

Initial obstacles to the introduction of hepatitis B vaccine included difficulty in reaching all infants; low coverage and high drop-out rates in some provinces; and compliance problems due to public misperceptions about vaccination. Despite these problems, the hepatitis B coverage rate among infants has reached 88% for the first dose and 66% for all three doses, with some variation among provinces.

Substantial progress has also been made in disease surveillance. The ministry of health has established a notification system for acute cases of hepatitis B, improved the collection and management of data, and adopted a standardised case definition for hepatitis B infection. Other major improvements include routine blood bank testing of donated blood units and intensive training of healthcare workers in injection safety and and waste disposal practices.

## **C. THE RUSSIAN FEDERATION**

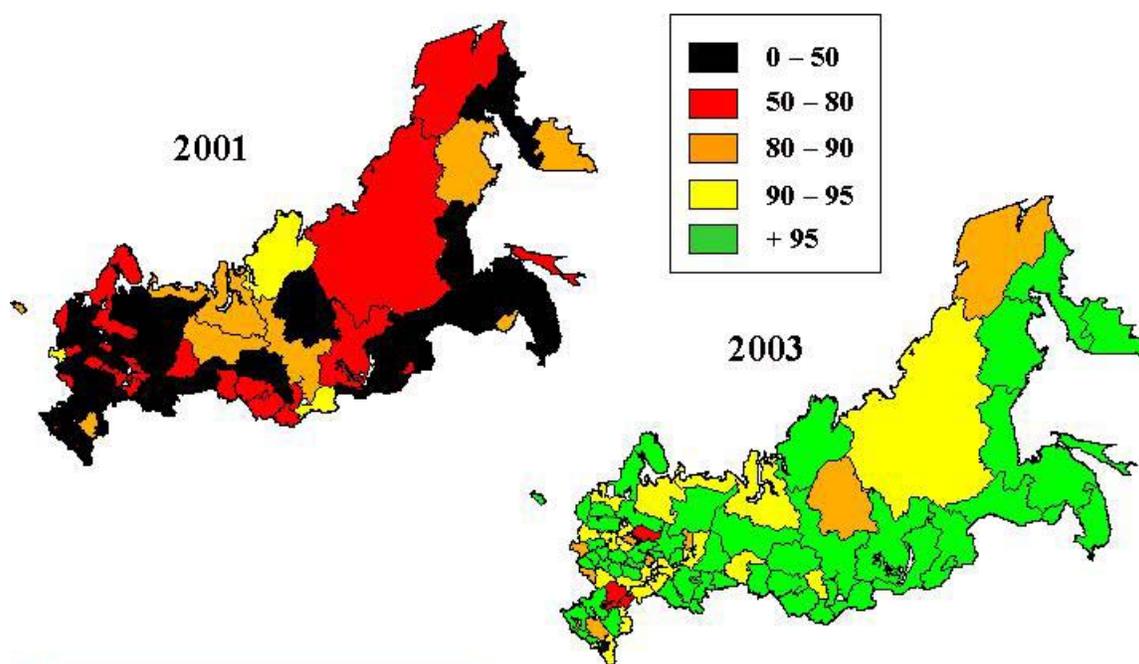
Although the Russian Federation as a whole has a low burden of hepatitis B infection, the incidence of disease is high in some sub-regions. The introduction of universal neonatal (cfr. Table 1) immunisation for hepatitis B in 2000 has reduced disease incidence throughout the country. The total number of infant hepatitis B immunisations rose from a few hundred thousands in 1999 to more than 3.4 million in 2003, with improved coverage in nearly all sub-regions (Figure 6).

The Russian Federation produces most of the vaccines used in its national immunisation programme. At the present time, three domestic and three foreign manufacturers (from India, France, and the United States) are licensed to manufacture and sell hepatitis B vaccine in the Russian Federation.

In 2000, with support from the Vishnevskaya-Rastropovich Foundation, the Russian Federation expanded hepatitis B vaccine coverage to include older children and adolescents in high-endemicity areas, including 6 oblasts and the Komi Republic. Significant decreases in HBV-related morbidity have been documented in each of these locations.

Current efforts continue to focus on improving universal coverage for infants and completing "catch-up" vaccination among adolescents and young adults in high-endemicity areas.

**Figure 6 Hepatitis B3 coverage in Russia by 12 months of age, 2003 compared with 2001**



WHO Regional Office for Europe

#### **D. KYRGYZSTAN**

Kyrgyzstan, a high endemicity country, introduced universal neonatal immunization against hepatitis B in 1998-99. During the following year, Kyrgyzstan instituted population-based surveillance for acute cases of viral hepatitis, as part of a regional project that also involved Kazakhstan, Tajikistan, Turkmenistan, and Uzbekistan (Box 3).

The legal basis for the Kyrgyzstan Acute Hepatitis Sentinel Surveillance System (KAHSS) is a 1999 Ministry of Health document that established sentinel sites in the cities of Bishkek, Nryn, and Jalal-Abad. KAHSS includes three institutional components: hospitals, the Regional Center of State Sanitary Epidemiologic Surveillance, and the Republican Reference Laboratory. Hospitals report acute cases of hepatitis to their Regional Centers, collect blood samples, conduct interviews with patients, and fill in epidemiological questionnaires. The Regional Centers process blood samples, ship samples and questionnaires to the Republic Reference Laboratory, and are responsible for quality assurance of collection, storage, and transport procedures. Microbiologists at the Republican Reference Laboratory set standards for diagnostic testing and quality control, test blood samples for markers of hepatitis A, B, C, and D, and analyze the questionnaire data and test results using a software program developed by CDC for the region.

Healthcare workers who participate in KAHSS - including microbiologists and laboratory technicians, infectious disease physicians, epidemiologists, and nurses - have received training in hepatitis surveillance, infection control, and laboratory procedures. Quality control back-up for blood testing is provided by a CDC reference laboratory in Atlanta.

As illustrated in Box 3, KAHSS data is being used to define etiologies of viral hepatitis, evaluate the national hepatitis B vaccination program, gather information on viral hepatitis risk factors and routes of transmission, and plan for the future.

## E. KAZAKHSTAN

Kazakhstan - a high endemicity country - introduced routine neonatal immunisation against hepatitis B infection in 1998-99. Vaccines were purchased from four companies in three countries (Cuba, Belgium, and South Korea) and technical assistance was provided by WHO/EURO, CDC, and GAVI. Infants were immunised at birth, at 2 months, and at four months. Based on sentinel surveillance data (Box 3), the incidence of acute cases of hepatitis B was cut in half by 2003, decreasing from 25.3 to 13.2 cases per 100, 000 people. Three-dose hepatitis B coverage rates among infants rose to 97-98 percent.

“Catch-up” vaccination for older children and adolescents began in January, 2004, along with vaccination of medical workers and medical students. For older children and adults, the second and third doses are given one month and 6 months after the first dose. Overall, more than 3.8 million people were vaccinated between 1998 and 2003, leading to substantial reductions in the incidence of acute hepatitis B in all age groups.

Future objectives include sustaining routine vaccination of newborns, maintaining high coverage rates among adolescents and adults in high risk groups, and conducting ongoing sentinel surveillance of viral hepatitis.

## VI. WORKSHOP REPORTS

Once a country has established a national hepatitis B immunisation programme, the next steps are:

- To evaluate progress through the collection of public health surveillance data
- To improve technical aspects of the immunisation programme
- To improve capacity to manage a vaccine safety crisis
- To ensure financial sustainability that newborns and infants will continue to be vaccinated each year

Workshops on each of these topics were conducted at the Kyiv meeting.

### **WORKSHOP A: EVALUATION OF INFANT HEPATITIS IMMUNISATION PROGRAMMES**

Disease surveillance data can help public health authorities demonstrate the benefits of hepatitis B immunisation. It can also help identify programme areas that may need improvement.

**Workshop A** considered the advantages and disadvantage of four different types of disease surveillance:

- 1) ***Immunisation coverage surveys.*** Most immunisation coverage surveys are based on data that are routinely collected during immunisations, making these an inexpensive way to gather information. Coverage surveys can provide data on how many people initiate hepatitis B vaccination; how many complete all three doses; and how many babies receive the birth dose. It can also allow comparisons of hepatitis B immunisation coverage rates with those of more established vaccines such as DTP. Coverage surveys may also be used to monitor vaccination rates in populations of special concern, such as newborns or school age children.

Coverage surveys do not provide a direct measure of the impact of vaccination on disease burden. Although high vaccine coverage often correlates with decreased disease burden, it is possible to have high coverage and low vaccine efficiency (e.g., if frozen vaccine is used, the vaccine is not administered properly, or the vaccine is administered after infection occurs [i.e., perinatal infection]).

- 2) ***Serologic surveys.*** Serologic surveys can provide a more direct measure of the impact of an immunisation programme by comparing the prevalence of infection before and after the programme is implemented. Serologic surveys typically measure HBsAg (present in those with chronic infection) and antibody to hepatitis B core antigen (anti-HBc) (present in those who have been infected in the past or are chronically infected).

Serologic surveys require extensive laboratory diagnostic capacity and are therefore expensive. When planning a survey, it is also necessary to consider whether the population sample to be surveyed is representative of the population as a whole.

WHO/HQ is preparing a protocol for serologic surveys of hepatitis B for use as an immunisation programme assessment tool. This protocol was pilot-tested in 3 countries in 2004 and will be further tested and refined in 2005.

- 3) ***Surveillance for acute cases of hepatitis B.*** This type of disease surveillance is useful in countries in which there is a high incidence of acute hepatitis B cases (Table 2, Table 5). Acute disease surveillance provides a direct measure of the disease burden of different types of acute hepatitis among children and adults. It can also be used to collect demographic, geographic, and risk factor data.

Acute disease surveillance requires a standardised case definition that includes clinical and laboratory components, and a strategy for identifying ill persons. In countries where most persons with acute viral hepatitis are hospitalized, hospital-based surveillance can be used. Like serologic surveillance, it requires sufficient laboratory diagnostic capacity to distinguish among types of viral hepatitis. Among NIS and CEE countries, acute disease surveillance is currently being conducted in Romania, Moldova, Albania, and the Central Asian Republics of Kazakhstan, Turkmenistan, Uzbekistan, and Kyrgyzstan (see Box 3).

- 4) ***Surveillance for hepatitis B-related mortality.*** This type of disease surveillance is performed by identifying deaths from the chronic sequelae of HBV infection, cirrhosis and hepatocellular carcinoma (HCC) (liver cancer). Since these outcomes are rare among children (i.e., cirrhosis and HCC are usually not clinically apparent until the third decade of life) except in countries of very high HBV endemicity, this type of surveillance is best suited for evaluations of the long-term impact of infant vaccination programmes.

Surveillance for hepatitis B-related mortality may be accomplished through the collection of data from municipal death records, hospital death records, or cancer registries. When interpreting the data, it is necessary to consider the completeness and accuracy of each data source.

## **Conclusion**

**Workshop A** concluded that the choice of a programme assessment method depends on what information is needed and what resources are available. A summary of the advantages and disadvantages of coverage surveys, serologic surveys, acute disease surveillance, and mortality-related disease surveillance is provided in Table 5.

**Table 5 Comparison of methods to evaluate hepatitis B immunisation programmes**

	<b>Coverage Survey</b>	<b>Serosurvey</b>	<b>Acute Disease Surveillance</b>	<b>Morbidity &amp; Mortality</b>
<b>Feasibility</b>	+	+++	+++	+++
<b>Expense</b>	+	+++	+++	++
<b>Frequency of evaluation</b>	I*	I	I or C*	I or C
<b>Program effectiveness</b>				
<b>short-term</b>	-	+++	+	+
<b>long-term</b>	-	+++	+++	+++
<b>Information collected</b>	<b>Coverage data</b>	<b>Prevalence of infection</b>	<b>Incidence new infection</b>	<b>Incidence chronic sequelae</b>
			<b>Risk factor information</b>	

\* I=intermittent; C=continuous

Courtesy of CDC

## **WORKSHOP B: TECHNICAL ASPECTS OF HEPATITIS B VACCINES**

**Workshop B** covered a wide range of technical questions on vaccine use, including:

**Wastage monitoring.** Vaccine wastage should be tracked at all levels and its causes should be identified (e.g., cold chain problems or inefficient use of multi-dose vials).

As a rule of thumb:

- If vaccine coverage and wastage remain stable: Improve wastage management.
- If vaccine coverage decreases and wastage increases: There may be a problem with the cold chain.
- If vaccine doses/coverage increase and wastage increases proportionately: All is well.

**Vaccine Preparations.** Hepatitis B has an excellent safety profile (Box 5). All vaccine preparations available on the market are safe and effective and may be used interchangeably<sup>13</sup>, with dosages provided according to each manufacturer's instructions. This is true for both inactivated plasma-derived vaccines and recombinant vaccines. The overwhelming majority of hepatitis B vaccine manufactured is now recombinant. All WHO-pre-qualified vaccine and therefore, all vaccine purchased by UNICEF is recombinant.

WHO procedures for quality control of vaccines administered by UNICEF are described in the section on *Safety Issues*.

***Use of Thiomersal as a Preservative.*** There is no evidence of adverse health effects linked to the use of thiomersal in vaccines (see Box 6). Thiomersal-containing and thiomersal-free vaccines are both acceptable for use in national immunisation programmes, also when starting at birth.

***Thermostability.*** Hepatitis B vaccine **must not be frozen!** It should be shipped and stored at 2-8<sup>0</sup>C. Freezing dissociates the antigen from the adjuvant, leading to changes in the antigen's three-dimensional structure. .

***Birth Dose.*** WHO has designated the prevention of perinatal transmission as a high priority for hepatitis B immunisation programmes (Box 1). Providing a birth dose to all newborns is substantially less expensive than identifying infected mothers and providing immunoprophylaxis to their newborns. It is also less difficult logistically and ensures that all children are protected from birth.

The birth dose of hepatitis B vaccine **must** be given as a monovalent vaccine. If possible, it should be provided within 12 to 24 hours of birth, because its efficacy decreases if given later<sup>32</sup>. The added value of providing newborns with hepatitis B immunoglobulin (HBIG)—which is very expensive and not available in all countries—is small (a 2-3% increase in protective efficacy<sup>33</sup>). Offering combined hepatitis B vaccines at birth is wasting some of the non-hepatitis B antigens due to the low immune response they induce in newborns less than 6 weeks old.

***Vaccine Schedules.*** The three intramuscular doses of hepatitis B vaccine may be provided with a diversity of schedules. Hepatitis B vaccine is usually provided in a 0, 1, and 6 month or 0, 1, 2, and 12 month schedule.

As a general rule, hepatitis B vaccination schedule is composed of two parts, a priming and a completion part. The priming is composed of at least two doses. Countries should respect a minimum interval of 4 weeks between consecutive doses of the priming part. The completion part is the final dose of a 3 or 4 doses series. Countries are recommended to respect at least four months between the completing dose and the first dose of the priming. For infants, however, it is recommended that the third dose not be given before 6 months of age. NOTE: in many countries of Africa and Asia, for reasons of convenience and ease, hep B is given at 6-8, 10-12, 14- 16 weeks with DTP, according to the EPI schedule.

If a child or adult misses a dose, it is not necessary to restart the three-dose sequence. Instead, the next dose may be provided at the next visit, whenever that may be. Moreover, hepatitis B vaccine may be administered simultaneously with BCG or other live, inactivated or attenuated vaccines. (see Box 4)<sup>34,35,36</sup>. This flexibility allows integration of hepatitis B vaccination into each country's existing infant vaccination programme. Most commonly the three doses of hepatitis B are provided at the same time as the three doses of DTP. As a result, many countries have been able to implement hepatitis B vaccination without hiring additional personnel or purchasing additional equipment, except for syringes. In some countries, the combination vaccines containing hepatitis B antigen (e.g. DTP-Hep B) may be used for the second and third dose of hepatitis B vaccine (though not for the first dose if given at birth), reducing the total number of injections children must receive. Extra doses of hepatitis B vaccine (i.e., 4 doses, one monovalent at birth and three combo doses) are not harmful.

***Duration of Protection.*** Hepatitis B vaccine causes the immune system to create immune memory cells (HBsAg-specific T cells and B cells) that persist in most individuals for at least fifteen years<sup>37,38</sup>. When stimulated by hepatitis B virus, these cells produce a rapid immunologic response that prevents both acute and chronic infection. Therefore, there is **no need for booster doses** of hepatitis B vaccine in fully vaccinated neonates, infants or adolescents and in immunocompetent individuals who have responded to a primary course of vaccination.<sup>39,40</sup>

**Pre- and Post-Vaccination Testing.** Hepatitis B vaccine can be safely administered to people who have already been infected with HBV. Therefore routine pre-vaccination testing for hepatitis B virus markers (evidence of previous infection or vaccination) is not recommended. In areas where the prevalence of infection is sufficiently high to make the procedure cost-effective, pre-vaccination testing for anti-HBc may be used. HBsAg testing should be done among anti-HBc positives to identify chronically infected people who require referral for counselling and treatment.

Because more than 95% of adults - and 98% of newborns, children and adolescents - develop protective levels of antibody to hepatitis B vaccine, routine post-vaccination testing is not required. In areas where the prevalence of infection is high, post-vaccination testing may be considered for adults in high risk groups or for infants born to infected mothers.

**Management of Adult Non-Responders.** For certain groups such as health care workers, post-vaccination testing may be indicated. For persons who do not respond to the 3-dose vaccination series, re-administration of hepatitis B vaccine is 30% effective after the first dose and 50% effective after the second dose. In individual cases, non-responding adults exposed to infection may be given HBIG or a second course of immunisation.

## **WORKSHOP C: HOW TO MANAGE A VACCINE SAFETY CRISIS**

Vaccines are one of public health's greatest successes, and one of its least heralded. In many countries immunisation is taken for granted by a complacent majority and attacked and questioned by a vocal minority. Thus, it is more important than ever to improve public communication about the value, effectiveness, and safety of vaccines.

**Workshop C** focused on public health communication during a real or rumored vaccine safety crisis. The participants shared experiences and resources materials and considered how best to prepare for and respond to a crisis.

**Communication Challenges.** Modern developments that make health communication on vaccines more difficult include:

- The decreased visibility of some diseases due to universal vaccination
- A new generation of vaccines that use new antigens, adjuvants, and molecular technologies
- Modern telecommunications, which allow local rumors and isolated events to become the topics of national and international news stories

Another significant problem is the loss of public trust. Publicly available information on vaccines is confusing, and this can exacerbate safety concerns. Moreover, politically, economically, or socially marginalized groups may distrust government-provided and promoted commodities and services.

**Crisis Management.** Improved public health communication is essential to build public confidence in national health authorities. Public health officials must be ready to provide documentation of vaccine quality, including data on adverse events following immunisation (AEFI). When a vaccine safety issue arises, health authorities must promptly mount an investigation to determine if the event is a coincidence, a programme error, or a real vaccine safety issue. At the same time, health authorities must maintain clear, accurate, and continuous communication with the public via the newsmedia. Scientists and public health authorities must not treat fear and reservation as ignorance, trying to destroy them with a blunt "rational" instrument.<sup>41</sup> Neither should they keep silent, allowing rumors and misinformation to flourish.

Public health staff must be prepared to work with members of the news media, with political leaders, and with the medical community. They must quickly address rumors and misinformation, based on an understanding of the sources of mistrust.

**Training in Media Relations.** Media training should emphasize that media relations are part of preparation for any immunisation activity. Public health officials should develop ongoing partnerships with journalists who can report on vaccination campaigns and public health achievements—as well as on safety crises.

Public health officials must understand the needs and attitudes of reporters and journalists, who typically look for controversies and high profile events that their readers will find interesting. It is important to be pro-active, providing information that emphasizes public health concerns and reassures the public that health authorities are doing what must be done to address the situation.

In dealing with the news media, it is important to respond quickly, with accuracy and simplicity. Information should be given in context, and statistics should be provided with an explanation of their implications. It is best to identify a single spokesperson who will answer questions, keep on message, and explain the scientific evidence - or lack of evidence - on the safety issue in question. The spokesperson should provide information from the highest national and international public health authorities.

**Resources.** When a vaccine safety issues arises, it is important to give press conferences and provide press releases at each stage of an investigation. Assistance with media relations is available from WHO, UNICEF, and other international groups. Media resources include:

- WHO Global Training Network on AEFI Monitoring (<http://www.who.int/vaccines-access/quality/gtn/aefi.htm>)
- The UNICEF Media Guide for Health Workers (under development)
- WHO check list for ensuring the safety and efficiency of mass campaigns (under development)

## **Conclusion**

**Workshop C** made these suggestions for managing a vaccine safety crisis:

- Ensure that public health staff are trained to work effectively with the newsmedia
- Ensure that there is a functioning and effective system for monitoring AEFI
- Investigate promptly to determine if the event is a coincidence, a programme error, or a real vaccine safety issue
- Think twice before blaming the vaccine or stopping immunisation
- Identify a spokesperson who provides accurate and consistent messages
- Communicate with political leaders and with the medical community
- Involve professional organisations and global partners, such as WHO and UNICEF

## **WORKSHOP D: FINANCIAL STABILITY PLANNING**

The subject of **Workshop D** was financial sustainability planning for immunisation programmes. Workshop participants included representatives of:

- Countries who plan to submit Financial Sustainability Plans (FSP) to GAVI in January 2005: Bosnia & Herzegovina, Moldova, and the Ukraine
- Countries who are refining or implementing FSPs prepared between January 2001 and January 2004: Armenia, Azerbaijan, Kyrgyzstan, and Uzbekistan
- International partners: WHO/EURO, UNICEF, CVP/PATH, and CDC

The Workshop focused on the process of developing an FSP and included a presentation on FSP implementation in Kyrgyzstan (Box 11).

**FSP Workshop.** The process began with training at the FSP Workshop held in Moscow in 2003 and the Workshop on Health Reform and Financial Sustainability Planning in Budapest in 2004. In preparation for these workshops, each Ministry of Health is requested to establish a multi-sector team that includes experts in vaccine issues, public health policy, and financial planning. During the Workshop, this team prepares an FSP document.

**Plan development.** After the Workshop, the World Bank and WHO consultants visit participating countries to provide technical assistance for data collection and FSP development. Once the initial data are gathered and analyzed, the consultants assist in pre-reviews data on the past and projected costs of the country's immunisation programme.

The 2004 workshop is planned for August, the team visited countries in early fall, and the pre-review of financial data in November. The FSP document is to be submitted in January 2005.

The FSP includes programme goals and financial strategies to support them. Strategy development requires ongoing dialogue and negotiation among members of the ministry of health, the ministry of finance, and the Interagency Immunisation Coordination Committee established in each GAVI-funded country. The FSP planning team may also consult donors, lenders, and international partners such as UNICEF, WHO and CVP/PATH.

**Implementation and evaluation.** Each year, health authorities can use the FSP to compare the past year's financing projections with actual costs and revise the immunisation-programme budget accordingly. The implementation process may involve resolving both short-term issues (e.g., ensuring that committed funds are released) and long-term issues (e.g., negotiating loans to replace vaccine procurement funds when the years of GAVI support are over). Yearly evaluations based on FSPs are the basis of national progress reports that help GAVI monitor successes and challenges.

## **Conclusions**

For many GAVI countries, the long-term financial planning required to prepare an FSP represents a new way of doing business. Representatives of countries who have completed FSPs agreed that the workplans prepared during the FSP Workshop were valuable in moving the process along. They made the following suggestions to countries who are in the process of FSP development and implementation:

- Ensure that the FSP team includes representatives from the Ministry of Finance or other relevant bodies as well as the Ministry of Health
- Leave the Workshop with a plan of action in which all team members have well defined roles and commitments
- Ensure that discussions of health reform include public health and immunisation issues, as well as healthcare delivery
- Always describe immunisation costs together with benefits
- Emphasize to financial planners that financial sustainability is not synonymous with complete self-sufficiency, but may lead the way to decreased dependency on donors.

## VIII. CONCLUSION

The WHO European Region, that includes the NIS and CEE countries is one of the most successful in progressing towards the WHO goal of 90% immunisation coverage with the three-dose regimen of hepatitis B. These countries have built a solid foundation for continued public health progress over the long-term.

### A. TAKING STOCK

The NIS and CEE countries have made rapid progress since the first regional conference was held in 1996 in Siofok, Hungary. Today, hepatitis B infection is recognised as a major health priority throughout the region. All 29 NIS and CEE countries have implemented hepatitis B immunisation programmes; of these, 26 target infants or infants and newborns (Table 2). At the current rate of progress, childhood coverage with hepatitis B vaccine will soon approach that of other EPI vaccines.

Country experiences suggest that major reasons for success include solid political support, extensive infrastructure development, and long-standing collaborations and partnerships. Continuing challenges include vaccine costs, management issues, difficulties in reaching newborns in some populations, difficulties in achieving a high three-dose coverage in infants in some populations/areas and public concerns about vaccine safety.

### B. SUMMARY OF RECOMMENDATIONS

The major themes of the Kyiv conference included the four workshop topics - programme evaluation; technical issues and policies; addressing vaccine safety concerns through improved public health communication; and financial sustainability planning. Other recurring themes included vaccine quality and safety, injection safety, and blood safety.

**Box 12** Recommendations on these topics are summarised in the box below:

**Recommendation on Disease Surveillance to Assess Immunisation Programmes**

Choose the disease surveillance method that is best suited to your needs. As described in Table 5, choices include:

- Immunisation coverage surveys
- Serologic surveys,
- Acute disease surveillance
- Mortality-related (cirrhosis and HCC) disease surveillance.

### **Recommendations on Technical Vaccination Issues**

- **Vaccine Preparations.** All vaccine preparations available on the market are safe and effective and may be used interchangeably, with dosages provided according to each manufacturer's instructions.
- **Thermostability.** Hepatitis B vaccine **must not be frozen!**
- **Use of Thiomersal as a Preservative.** There is no evidence of adverse health effects linked to the use of thiomersal in vaccines. Thiomersal-containing and thiomersal-free vaccines are both acceptable for use in national immunisation programmes.
- **Birth Dose.** The birth dose of hepatitis B vaccine should be given as a monovalent vaccine within 12 to 24 hours of birth
- **Vaccine Schedules.** The three intramuscular doses of hepatitis B vaccine may be provided with a diversity of schedules, and may be administered simultaneously with BCG or other live, inactivated or attenuated vaccines.
- **Duration of protection.** Hepatitis B vaccination confers, based on the current scientific evidence, long-term protection. Booster doses are not currently recommended.
- **Pre- and post-vaccine testing.** Pre-vaccination testing for immune status and post-vaccination testing for immune response to hepatitis B vaccination is not cost-effective and of little public health benefit. It is not recommended for routine use.
- **Waste Management.** Vaccine wastage should be tracked at all levels so that its causes can be identified and rectified.

### **Recommendations on How to Manage a Vaccine Safety Crisis**

- Ensure that public health staff are trained to work effectively with the newsmedia
- Ensure that there is a functioning and effective system for monitoring AEFI
- Investigate promptly to determine if the event is a coincidence, a programme error, or a real vaccine safety issue
- Think twice before blaming the vaccine or stopping immunisation
- Identify a spokesperson who provides accurate and consistent messages and has ongoing or frequent contacts with the public.
- Communicate with political leaders and with the medical community
- Involve professional organisations and global partners, such as WHO and UNICEF

### **Recommendations on Financial Sustainability Planning**

**Workshop C** made these suggestions for financial sustainability planning:

- Ensure that the participants in the WHO Workshop on Health Reform and Sustainability Planning include representatives from the ministry of finance as well as the ministry of health
- Leave the Workshop with a plan of action in which all team members have well defined roles and commitments
- Ensure that discussions of health reform include public health and immunisation issues, as well as healthcare delivery
- Always describe immunisation costs together with benefits
- Emphasize to financial planners that financial sustainability is not synonymous with complete self-sufficiency, but may lead the way to decreased dependency on donors

### **Recommendations on Vaccine Quality and Safety**

- Ensure that these essential elements are in place:
  - Good vaccine management
  - Complete and accurate AEFI surveillance
  - Readiness to mount prompt investigations of safety issues
  - Cold chain equipment that keeps hepatitis B vaccine cold but **NEVER** frozen!
- Make use of vaccine management training courses and self-assessment tools available at WHO

#### **Recommendations on Injection Safety**

- Assess injection safety practices (including risk to patients, providers, community)
- Encourage physicians to reduce the number of therapeutic injections
- Ensure proper sterilisation and disinfection of syringes and medical equipment
- Encourage the use of non-reusable syringes
- Establish infection control precautions in all healthcare settings to reduce the risk of exposure to contaminated blood
- Improve collection and disposal of sharps
- Incinerate or bury contaminated material
- Provide injection safety information to doctors, nurses, students and patients

#### **Recommendations for Blood Banks**

- Introduce transfusion services that always screen all blood units and discourage blood donation from people in high risk groups
- Standardise procedures for blood donor screening
- Ensure adequate supply of testing reagents
- Train staff in blood safety procedures
- Discourage blood donations from Blood Center Staff

### **C. PRIORITIES FOR FUTURE ACTION**

By 2007 - when a fourth regional conference is planned - it is hoped that all NIS and CEE countries will be able to report  $\geq 90\%$  coverage of the three-dose regimen of hepatitis B, as well as good coverage of adolescents and adults in high risk groups.

Major priorities for future action include augmenting or expanding activities and strategies that facilitates the successful introduction of hepatitis B vaccine into national immunisation programmes. These include:

- Advocacy to ensure political commitment and continued funding
- Technical support to sustain progress and improve implementation
- Improved programme evaluations and impact assessments
- Financial sustainability planning to ensure continued progress
- Improved management capacity for monitoring programme performance at all levels
- Strengthened disease surveillance systems to improve the quality of data
- Better communication and collaboration with all stakeholders
- Better integration between the private and public healthcare sectors

New public health priorities for some NIS and CEE countries may include:

- Introduction of *Haemophilus influenzae* type b vaccine
- Group procurement of vaccines
- Integrated programmes for sentinel surveillance and prevention of hepatitis B, hepatitis C, and HIV

## LIST OF ACRONYMS

**AD** – auto-disable (syringes)  
**AEFI** – adverse events following immunisation  
**AIDS** – acquired immunodeficiency syndrome  
**ALL** – acute lymphoblastic leukemia  
**ANAES** – Agence Nationale d’Accréditation et d’Evaluation en Santé  
**ATT** – Access To Technology  
**BCG** – bacillus Calmette-Guerin vaccine (tuberculosis vaccine)  
**CDC** – Centers for Disease Control and Prevention  
**CEE** – Central and Eastern Europe  
**CIS** – Commonwealth of Independent States  
**CVP/PATH** – Children’s Vaccine Programme at the Programme for Appropriate Technology in Health  
**DTP** – diphtheria, tetanus, and pertussis vaccine  
**DTaP** – diphtheria, tetanus, and acellular pertussis vaccine  
**DTwP** – diphtheria, tetanus, and whole cell pertussis vaccine  
**EASL** – European Association for the Study of the Liver  
**EPI** – Expanded Programme on Immunisation  
**ETAGE** – European Technical Group of Experts  
**EU-IBIS** – European Union Invasive Bacterial Infection Surveillance  
**EVSM** – Effective Vaccine Store Management  
**FSP** – financial sustainability plan  
**FSSAPS** – Agence Française de Sécurité Sanitaire des Produits Santé  
**GACVS** – Global Advisory Committee on Vaccine Safety  
**GAVI** – Global Alliance for Vaccines and Immunisation  
**GBS** – group B streptococcus  
**HBsAg** – hepatitis B surface antigen  
**HBIG** – hepatitis B immunoglobulin  
**HBV** – hepatitis B virus  
**Hib** – *Haemophilus influenzae* type B  
**HIV** – human immunodeficiency virus  
**HIV/AIDS** – human immunodeficiency virus/acquired immunodeficiency syndrome  
**ICBS** – International Consortium on Blood Safety  
**IOM** – Institute of Medicine  
**KAHSS** – Kyrgyzstan Acute Hepatitis Surveillance System  
**MMF** – macrophagic myofasciitis  
**MS** – multiple sclerosis  
**NIP** – National Immunisation Programme  
**NIS** – Newly Independent States  
**NRA** – national regulatory authority  
**OPV** – oral polio vaccine  
**PATH** – Programme for Appropriate Technology in Health  
**RAT** – rapid assessment tool  
**STI** – sexually transmitted infections  
**UNFPA** – United Nations Population Fund  
**UNICEF** – United Nations Children’s Fund  
**USAID** – United States Agency for International Development  
**VHPB** – Viral Hepatitis Prevention Board  
**VMTC** – Vaccine Management Training Clusters  
**WHO** – World Health Organisation  
**WHO/EURO** – World Health Organisation, European Regional Office  
**WHO/HQ** – World Health Organisation, Head Quarters

## **Tables, Figures, and Boxes**

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- B. List of Representatives from Supporting Organisations

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