Strengthening immunization systems and introduction of hepatitis B vaccine in central and eastern Europe and the Newly Independent States.

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Strengthening immunization systems and introduction of hepatitis B vaccine in central and eastern Europe and the Newly Independent States.


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INTRODUCTION

It is now two decades since hepatitis B vaccine became available. Within 10 years of its introduction progress had been such that the World Health Assembly in 1992 called for the inclusion of hepatitis B immunization of infants in all national immunization programmes. Five years ago, in 1996, the Viral Hepatitis Prevention Board with the World Health Organization and the Centers for Disease Control and Prevention in the USA organized a conference on the prevention and control of hepatitis B in countries of central and eastern Europe and the newly independent states, held in Siofok, Hungary.1 2

Remarkable progress has been made since that landmark meeting in Siofok (see Table 1). At that time only 5 of the 25 countries in the region had implemented hepatitis B vaccination programmes, and that meeting identified the major constraints to the implementation of more programmes as financial, the lack of knowledge about burden of disease and the absence of medium-term plans of action. That lack of epidemiological data has been substantially overcome, and the information available demands to be translated into action. The St Petersburg meeting grew in part out of the interest in the progress made since 1996 as well as the lack of donor interest in supporting hepatitis B immunization programmes in the countries of the region where the disease burden had thus been shown to be patent. On the positive side, it aimed to promote action, such as the use of the powerful tool of education, to ensure political and community support as well as to secure funding for immunization programmes.

Table 1
A chronology of hepatitis B vaccine and immunization in central and eastern Europe, Turkey, and the Newly Independent States.

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981</td>
<td>Hepatitis B vaccine becomes available</td>
</tr>
<tr>
<td>1991</td>
<td>World Health Assembly resolution calls for the inclusion of hepatitis B immunization of infants in all national immunization programmes</td>
</tr>
<tr>
<td>1996</td>
<td>Conference on prevention and control of hepatitis B in countries of Eastern and Central Europe and the Newly Independent States, Siofok, Hungary</td>
</tr>
<tr>
<td>2000</td>
<td>Global Alliance for Vaccines and Immunization (GAVI) launched</td>
</tr>
<tr>
<td>2001</td>
<td>(June) GAVI Board decision on fourth round of proposals to its Vaccine Fund</td>
</tr>
<tr>
<td>2001</td>
<td>(June) Conference on strengthening immunization systems and introduction of hepatitis B vaccine in Central and Eastern Europe, St Petersburg</td>
</tr>
</tbody>
</table>

The breadth of co-sponsorship of this conference in St Petersburg in June 2001 indicates the commitment and range of international and nongovernmental organizations to the major public health challenge that viral hepatitis poses in the region. Furthermore, the broad participation reflected the measure of support at multiple levels within the different countries represented.

High prevalence rates demonstrate that hepatitis B continues to be a significant public health burden in the region, but they do not show the whole picture. The local epidemiological pictures are much more clearly delineated, allowing better decision making about prevention and control activities. That in turn facilitates more effective negotiation for vaccine procurement. At the same time it is becoming evident that hepatitis C is contributing comparably to morbidity and mortality in the region.


Training, provision of better equipment and increasing political attention to health issues are strengthening epidemiology and surveillance in the countries of the region. Better epidemiology and surveillance not only define the burden of disease and help to monitor the impact of immunization campaigns but will also lay the ground for the introduction of newer or less used vaccines to prevent and control infections due to *Haemophilus influenzae* type b and other communicable pathogens.

The cost of hepatitis B vaccine has decreased substantially since its launch. The increased political attention being paid to public health, the presence on the scene of organizations such as the Global Alliance for Vaccines and Immunization\(^3\) and the priority being accorded to childhood immunization programmes by charitable organizations such as the Bill & Melinda Gates Foundation through the Gates Children’s Vaccine Program, implemented by the Program for Appropriate Technologies in Health (PATH), have accelerated and facilitated the process of implementing affordable and sustainable programmes. Now 21 countries in central and eastern Europe and the newly independent states, including five categorized as highly endemic and six with intermediate endemicity, are implementing hepatitis B vaccine programmes. High rates of coverage are being achieved in many countries and incidence rates of new cases of hepatitis B are declining rapidly in some areas. There is the full expectation that hepatitis B vaccination will soon be part of the routine infant immunization programmes in all the countries of the region (see Figure).

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**Figure:** universal hepatitis B immunization programmes in the European Region of the World Health Organization, 2001 (including programmes planned until 2003).

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\(^3\) GAVI web site: [www.vaccinealliance.org](http://www.vaccinealliance.org)
OBJECTIVES OF THE MEETING

The meeting drew some 150 people mainly from the countries of central and eastern Europe and the newly independent states as well as from the intergovernmental, international and nongovernmental cosponsors. The aims of the meeting were as follows:

- to present an overview of the epidemiology of viral hepatitis, in particular in the countries of central and eastern Europe and the newly independent states, and to describe the activities of the Global Alliance for Vaccines and Immunization (GAVI) and its Vaccine Fund relevant to these countries;
- to review the status of hepatitis B vaccination;
- to provide a forum for discussion and to share experiences of hepatitis B prevention strategies in the context of prevention and control of viral hepatitis generally;
- to help to prepare for and facilitate programme planning and to formulate a broad plan of action, including mechanisms for strengthening national immunization systems, thereby contributing to efforts to reduce the prevalence of and morbidity and mortality due to viral hepatitis.

Significant steps had been taken to facilitate communication. Not only was there simultaneous translation into English and Russian, but all the background documentation was provided in both English and Russian, and many presentations included materials in both languages.

GLOBAL ALLIANCE FOR VACCINES AND IMMUNIZATION (GAVI)

GAVI was formed in 1999 with the mission of ensuring that every child in the world will be protected against vaccine-preventable diseases. It provides a mechanism for coordinating and revitalizing immunization programmes at international, regional and national levels, bringing together traditional and new partners, from both the private and public sectors, including countries, United Nations agencies (such as WHO and UNICEF), development banks, industry, technical agencies (such as the Centers for Disease Control and Prevention in the USA), foundations (e.g. the Bill & Melinda Gates, Rockefeller and Mérieux Foundations), nongovernmental organizations (e.g. the Gates Children's Vaccine Program at PATH) and academe.

These partners share a vision and a set of strategic objectives against a common background: immunization coverage rates are stagnating and even declining in certain countries and regional discrepancies are evident. Newly developed or under-used vaccines against diseases that are major causes of childhood deaths simply are not being introduced. There is only limited investment in research on vaccines for diseases that place a heavy burden on developing countries.

GAVI’s mission to save lives and protect health through the widespread use of vaccines translates into five strategic objectives:

- to improve access to sustainable immunization services
- to expand the use of all existing infant vaccines
- to hasten the introduction of new vaccines
- to accelerate research and development of vaccines for developing countries, such as against HIV/AIDS, malaria and tuberculosis, and
- to make high immunization coverage a centrepiece of international development efforts.
Within the next six years the related measurable outputs are the following:

- by 2002, 80% of countries with adequate delivery systems for immunization will introduce hepatitis B immunization and by 2007 all countries will have done so
- by 2005, 80% of developing countries will have routine immunization coverage of at least 80% in all districts
- by the same year, 50% of the poorest countries with heavy burden of disease due to *H. influenzae* type b infection will have introduced Hib immunization, and
- also by 2005, the vaccine efficacy and burden of disease will have been established in all regions for rotaviral and pneumococcal infections, and mechanisms will have been identified to make the relevant vaccines available to the poorest countries.

GAVI operates through a 15-member Board (with secured institutional commitment for its members) and a 10-member Working Group that helps to formulate joint policies and work plans. The meetings and activities are coordinated by a small secretariat, funded by partners’ fees. It works through Task Forces, focusing on advocacy, country coordination, financing, and research and development, and five Regional Working Groups (see p.19 for a description of the work of the European Regional Working Group).

GAVI established its Vaccine Fund in order to strengthen immunization services and to deliver vaccines in countries. The Board of GAVI established the Fund’s principles, including a separate board for fund-raising and management. The Fund has a working capital account and three sub-accounts: immunization services, vaccines and safe injection materials, and research and development (although this last sub-account is not yet active). Applications are invited at least twice a year and the Board makes recommendations about allocations. To be eligible for support from the Vaccine Fund, countries must have a gross national product of less than US$ 1000 per capita and a population of less than 150 million, although special arrangements exist for large countries (China, India and Indonesia). They must also have a functioning high-level collaborative mechanism such as an Interagency Coordinating Committee, have had an assessment of infant immunization within the past three years, and have drawn up a multi-year plan for immunization that includes proposals for financial sustainability.

At present countries with DTP3 coverage of 80% can apply for support for immunization services. Those with DTP3 coverage of 50% or higher can apply for support for new and under-used vaccines. By new and under-used vaccines, GAVI refers to hepatitis B vaccine (globally), Hib vaccine for countries in Africa, Latin America, the Middle East and where evidence of a sufficient burden of disease exists, and yellow fever where recommended in Africa and South America (even where DTP3 coverage is <50%). Safe injection equipment, with auto-disable syringes and safe sharps disposal boxes, will be packaged with vaccines as they are delivered to countries.

The immunization services sub-account extends the pool of existing funding and channels funds from disparate donors into one source, avoiding multiple monitoring and conditions. It provides an investment in advance but later makes “reward” payments according to performance. Progress is monitored, with standard indicators and annual review.

In the WHO’s European Region 11 countries are eligible to apply for support from the Vaccine Fund (see Table 2). Before 1999, while all had immunization plans and most had had assessment of the EPI programme and the cold chain, only two had looked at the burden of Hib disease and just Kyrgyzstan had a functioning Interagency Coordinating Committee. In 2001, four countries applied for support from the immunization services sub-account and 10 countries for new and under-used vaccines. Of the former, the applications from three countries, Armenia, Azerbaijan and Tajikistan were approved and Georgia was invited to resubmit its application. The approved plans will mean that nearly 29 000 extra children will be covered by immunizations at a cost of US$ 313 000. Of the 10 countries that applied to introduce hepatitis B immunization the applications of four were approved, a further five were approved with requests for clarification or conditions attached, and one country was invited to resubmit (see p.19 for more details). The proposals included applications from Uzbekistan for nearly 3.6 million doses and from Kyrgyzstan and Turkmenistan each for nearly 500 000 doses. One of five countries that applied for Hib vaccine had its application approved (Kyrgyzstan).
HEPATITIS B EPIDEMIOLOGY AND VACCINATION PROGRAMMES

Epidemiology
Globally, among the 2000 million or so people who have markers of current or past infection with hepatitis B virus, 350 million are chronically infected, of whom 15-25% will die from liver cancer or cirrhosis – some 750 000 deaths a year. The outcome of hepatitis B viral infection depends on age: the younger the age at infection the greater the likelihood of that infection becoming chronic, and about 25% of infected young children will die from chronic liver disease compared with <10% of infected adults.

About 45% of the world’s population lives in areas of high endemicity for hepatitis B (where the prevalence rate of hepatitis B surface antigen, HBsAg, equals or exceeds 8%, the lifetime risk of infection exceeds 60% and early childhood infections are common) and a further 43% lives in areas of intermediate endemicity (with a 2-7% HBsAg prevalence rate, lifetime risk of infection of 20-60% and all age groups at risk for infection). Between a half and three-quarters of chronic infections are acquired in childhood in areas of medium and high endemicity. Mother-to-child, child-to-child and unsafe injections are the main routes of transmission of the virus in both these areas, whereas for adolescents and adults in low endemicity areas and to a lesser extent in intermediate endemicity areas sexual contact and injecting drug use account for most infections. Most chronic infections in children are unrecognized.

Immunization programmes
Hepatitis B immunization programmes have as their objective the prevention of chronic hepatitis B infections, thereby preventing chronic liver disease and reducing the reservoir for the transmission of new infections. In addition they will prevent nosocomial infections. The strategies for preventing transmission comprise universal infant immunization, prevention of perinatal transmission and catch-up immunization in addition to protection of at-risk individuals.

The goals set out in the resolution adopted by the Forty-fifth World Health Assembly in 1992 (resolution WHA45.17) called for integration of hepatitis B immunization into national childhood vaccination programmes by 1995 in countries with an HBsAg prevalence of ≥8% and in all countries by 1997. By January 2001, 129 countries had implemented that policy; these countries represent about half the global birth cohort. Most of the remaining 85 countries are among the least developed and are home to about one third of all chronically infected people.

The advent of GAVI, with its particular focus on developing countries, opened new opportunities for the 74 poorest countries that are eligible for support from the Vaccine Fund. At the end of the first 18 months of GAVI’s operation, 24 countries had had their proposals approved for hepatitis B vaccine funding to implement routine infant immunization programmes.

Introduction of hepatitis B immunization programmes rapidly reduces the prevalence of chronic hepatitis B viral infections, to <1% in areas with a low rate of perinatal transmission and <2% where that rate is high. Examples from several countries show reductions of the order of 10-fold, one of the most striking illustrations being the lowering of the rate of chronic infection from 16% to zero in a group of 268 children aged 1-10 years in Alaska in 1995. The programmes have an additional impact, by reducing “infection pressure”. Unimmunized people with chronic infection become less infectious (losing HBsAg over time) with the consequence that the immunization programme has a greater impact on transmission than expected. The long-term outcome will be a reduction in liver disease.

Clearly routine infant or childhood immunization is the cornerstone of preventive strategy against chronic infection. In addition, strategies need to be implemented to prevent perinatal transmission. One such strategy comprises selective immunoprophylaxis: screening pregnant women for HBsAg and giving prophylaxis to newborns of HBsAg-positive mothers. This approach has the advantages that prophylaxis is targeted to newborns that need it and that vaccine and, if available, hepatitis B immunoglobulin (HBIG) can be administered. However, such programmes need extensive resources for screening pregnant women and tracking newborns of HBsAg-positive mothers, and sadly there are few examples of successful programmes. A second strategy to prevent perinatal transmission is to immunize all newborns beginning at birth, by integrating hepatitis B vaccine into routine infant
immunization programmes. This approach does not entail screening pregnant women and is practicable when a high proportion of infants are born in health-care facilities, but only if effective delivery of hepatitis B vaccine can be assured for all infants. In prioritizing approaches, several issues need careful consideration. For giving a birth dose information is needed about the contribution of perinatal transmission to the overall burden of hepatitis B and the feasibility of administering the first dose at birth must be determined. Currently such immunization is most feasible in hospitals, but the availability of self-contained unit-dose administration systems (e.g. Unijet™) to deliver monovalent hepatitis B vaccine may facilitate immunization of newborns delivered at home. Perinatal prevention is a priority in areas such as South-East Asia where a high proportion of chronic infections are acquired perinatally. In these areas, the first dose of hepatitis B vaccine should be given at birth (within 12 hours) in the health facility where the baby is born, and efforts should also be made to reach and immunize those infants delivered at home. In regions where perinatal transmission accounts for a lower proportion of chronic infections, such as in some African countries, a birth dose may be considered when disease burden, cost-effectiveness and feasibility have been evaluated.

Catch-up immunization of older children and adults who have not been immunized becomes a priority where hepatitis B virus infection is not highly endemic and where infections acquired in older age groups contribute substantially to the disease burden. There, because immunization of infants may not greatly lower disease incidence for decades, catch-up immunization of single-age cohorts (for instance, routine adolescent immunization) and people at high risk (such as men who have sex with men, injecting drug users and people with sexually transmitted infections) may be appropriate. The latter group can be immunized at locations such as sexually transmitted infection (STI) clinics, correctional facilities and drug treatment centres. Where hepatitis B virus is endemic, most chronic infections are acquired before 5 years of age and immunization of infants will rapidly reduce transmission, vitiating the need for catch-up immunization.

Finally, the prevention of transmission of blood-borne pathogens such as hepatitis B virus in health-care settings needs to focus on preventing transmission from patient to patient – contrary to popular perception this route is much more common than that from patient to health-care provider or vice versa (and the recent reports from China and Russia of hundreds of thousands of people infected with HIV through unsafe practices in blood donation and collection underlines this point). Here the emphasis should be on safe injection practices, use of sterile equipment and the screening of the blood supply (not just for markers of hepatitis B virus but also HCV and HIV). Health-care workers need to apply standard (universal) precautions in their routine practices, but immunization against hepatitis B is an obvious preventive measure.

Epidemiology: Moscow

The pattern of risk factors for viral hepatitides is changing significantly in eastern Europe and the newly independent states, but, up until the present, epidemiological studies of such factors in the region have been largely descriptive. Several years ago a study in the Republic of Moldova had shown that nosocomial transmission was a major risk factor for hepatitis B infection and a study in Kazakhstan in 1998 confirmed this, showing that 52% of acute hepatitis B infections were associated with medical injections.

A case-control study in Moscow compared some 430 adult patients (mean age 24 years) in Moscow with jaundice and raised liver enzyme activities with a reference group of 311 volunteers from medical school and participants in pre-recruitment medical examinations (mean age 19 years). (The limitation

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inherent in the selection of the control group was recognized.) Nearly two thirds of cases of hepatitis were hepatitis B and 14% were hepatitis C. In the patients significant associations compared with the control group were found for both hepatitis B and C with invasive manipulations during the previous 6 months and illicit drug use. The population attributable risk for acute hepatitis B from injections, excluding those for drug use, was 41%; overall, outpatient treatment was highly associated with acquiring both hepatitis B and C – the attributable risk for non-drug users was 39% among hepatitis B patients and 34% among hepatitis C patients. Injection drug use with unsafe injection practices was strongly associated with acquiring acute hepatitis B and C. For non-drug users, admission to hospital, tattooing, and multiple sexual partners carried an attributable risk of between 3% and 12%.

Three main recommendations emerged: first, to promote the use of single-use (auto-disable) syringes and needles; secondly, to promote infection-control practices among drug users in Moscow; and thirdly, to educate members of drug-using communities and health-care workers about the risks associated with re-usable injection equipment.

Prevention and control of hepatitis B in countries of central and eastern Europe and the newly independent states

At the time of the Siofok meeting in 1996, more than one million people acquired acute hepatitis B infections annually in the 51 countries of the WHO European Region (1,2). In about 90 000 cases, these infections became chronic. Only five countries in central and eastern Europe and the Newly Independent States had implemented hepatitis B immunization programmes. The meeting at Siofok recommended that all countries in the region should plan to integrate hepatitis B immunization into their national immunization programmes as soon as possible and that each should formulate a national plan for the control of hepatitis B. Such plans should summarize the current disease burden, include a strategy for routine immunization of all infants and high-risk groups and specify a time-table and the resources needed to implement the control programme. Separate recommendations to partners and WHO included support for neediest countries to obtain vaccine and the preparation and dissemination of guidelines for control plans.

By 2001, the overall epidemiological picture had changed little in the countries of the WHO European Region, with low prevalence rates of HBsAg positivity in northern and western Europe and highest rates in the south and east, in particular the Central Asian republics. (In most countries notification of acute hepatitis B is mandatory.) The estimated number of cases of clinical hepatitis B was stable at around 110 000 a year. Although surveillance is not everywhere well established, methods vary and some countries have comprehensive data (but with an unknown degree of underestimation). By the end of the decade the highest reported rates in the countries of central and eastern Europe, about 20 per 100 000, were in Bulgaria (1998), Estonia and Latvia. Higher rates than that were reported from Kazakhstan, Kyrgyzstan, Moldova, the Russian Federation and Uzbekistan. In western Europe, in contrast, incidence rates of less than 6 per 100 000 were reported from all countries of the European Union apart from France (9 per 100 000) and Luxembourg (13 per 100 000).

By 2001, some 22 out of 28 countries in central and eastern Europe and the Newly Independent States had implemented a programme of hepatitis B immunization. Data collected at the meeting, see Table 2, indicate the range of programmes; only Yugoslavia (not present at the meeting) appears to have no programmes planned. The Russian Federation, where the incidence of new cases of hepatitis B had stabilized at about 55 000 a year, and the former Yugoslav Republic of Macedonia, are expecting progress in 2002-2003. Among the highly endemic countries, Albania, Armenia, Kazakhstan, Kyrgyzstan, Moldova and Uzbekistan, all eligible for support from GAVI, had immunization programmes, as did seven countries with intermediate endemicity. Among the highly endemic countries, Azerbaijan, Bosnia and Herzegovina, Tajikistan and Turkmenistan (also all eligible for support from GAVI) had plans for immunization programmes to be implemented between 2001 and 2003.

Information available to WHO’s European Regional Office from surveys in 51 member countries and other sources shows that universal screening of pregnant women for HBsAg is recommended in 21 countries, mostly in the west, and 4 operated a selective screening policy, while seven countries made no recommendation because a birth dose was given. Information was lacking for a further 19 countries. The schedules used for hepatitis B immunization of neonates and infants vary considerably between
countries. Many programmes contain an element of targeting people at risk in addition to universal immunization.

Most countries throughout the Region have hepatitis B immunization coverage rates of more than 90%, and surveillance is vital to monitor the impact of immunization programmes. Data from Moldova provide an excellent example of the close correlation of a rapid increase in coverage rates to more than 90% with a marked fall in the number of new cases of hepatitis B. In other countries such as Kazakhstan and Kyrgyzstan where immunization rates have only recently reached good levels or are still rising, it is too early to detect the impact on new cases. In Turkey, where an immunization programme was introduced in 1998, coverage had reached only the sub-optimal level of about 65% in 2000 and only a limited impact in terms of caseload was evident.

Feedback from countries pinpointed the critical elements needed for decisions to be taken about hepatitis B immunization programmes. Good data are needed on incidence and prevalence rates of HBsAg carriers, cases of liver cirrhosis and cancer, and deaths from chronic or fulminant hepatitis (all with their respective age distributions). Cost-effectiveness analyses are vital, and the final element is a financing plan. These elements have enabled hepatitis B to be given high priority with firm political commitment and have laid the basis for recognition that it is one of the leading causes of death among vaccine-preventable diseases and immunization against it is one of the most cost-effective health interventions.

Countries are facing the same major challenges to successful immunization programmes. Immunization services generally need to be sustained, and coverage rates for hepatitis B immunization need to be raised in some countries. The logistics of vaccine delivery and the cold chain are problematic and need to be strengthened. Safety of injections must be improved, through education and provision of appropriate equipment and training. Performance needs to be continually monitored and assessed, and surveillance is necessary to evaluate the impact of such programmes.

Table 2
Universal hepatitis B immunization programmes in central and eastern Europe, Turkey, and the Newly Independent States (as of June 2001)

<table>
<thead>
<tr>
<th>Country</th>
<th>Eligible for GAVI</th>
<th>Immunization status and programmes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1996¹</td>
</tr>
<tr>
<td>Albania</td>
<td>Yes</td>
<td>Universal, newborn</td>
</tr>
<tr>
<td>Armenia</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Azerbaijan</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Belarus</td>
<td>No</td>
<td>-</td>
</tr>
<tr>
<td>Bosnia &amp; Herzegovina</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>No</td>
<td>Universal, newborn</td>
</tr>
<tr>
<td>Croatia</td>
<td>No</td>
<td>-</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>No</td>
<td>-</td>
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<tr>
<td>Estonia</td>
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<td>Georgia</td>
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<td>-</td>
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<tr>
<td>Country</td>
<td>Program Status</td>
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</tr>
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<td>---------------------------------</td>
<td>----------------</td>
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</tr>
<tr>
<td>Hungary</td>
<td>No</td>
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</tr>
<tr>
<td>Kazakhstan</td>
<td>No</td>
<td>1997</td>
</tr>
<tr>
<td>Kyrgyzstan</td>
<td>Yes</td>
<td>1999</td>
</tr>
<tr>
<td>Latvia</td>
<td>No</td>
<td>1997</td>
</tr>
<tr>
<td>Lithuania</td>
<td>No</td>
<td>1998</td>
</tr>
<tr>
<td>Moldova (Republic of)</td>
<td>Yes Universal</td>
<td>1995</td>
</tr>
<tr>
<td>Poland</td>
<td>No</td>
<td>1994-96; Adolescent, 2000</td>
</tr>
<tr>
<td>Romania</td>
<td>No</td>
<td>1995</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>No</td>
<td>1996; Planned 2002</td>
</tr>
<tr>
<td>Slovakia</td>
<td>No</td>
<td>1998</td>
</tr>
<tr>
<td>Slovenia</td>
<td>No</td>
<td>1998</td>
</tr>
<tr>
<td>Tajikistan</td>
<td>Yes</td>
<td>Planned 2002</td>
</tr>
<tr>
<td>The former Yugoslav Republic of Macedonia</td>
<td>No</td>
<td>Planned 2002-2003</td>
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<td>Turkmenistan</td>
<td>Yes</td>
<td>Planned 2001-2002</td>
</tr>
<tr>
<td>Ukraine</td>
<td>Yes</td>
<td>1996</td>
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<tr>
<td>Uzbekistan</td>
<td>Yes</td>
<td>1998, in some regions; 2001, in all regions</td>
</tr>
<tr>
<td>Yugoslavia</td>
<td>No</td>
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Notes
1Countries represented at the Siofok conference in 1996 reporting hepatitis B immunization programmes. Bosnia-Herzegovina and Yugoslavia were not present.
2Newborn: immunization of all newborns with three doses at specified intervals (w, weeks; m, months; yr, years).
3Children or adolescent hepatitis B immunization programmes according to a 0, 1, 6 month vaccination schedule.
QUALITY, SAFETY AND SAFE IMMUNIZATION PRACTICES

Safety and side effects
Extensive investigations have failed to confirm any causal link with hepatitis B immunization with any of several adverse events, ranging from hair loss and diabetes to multiple sclerosis, that have been linked with hepatitis B vaccines. A thorough review of all the evidence compellingly showed that hepatitis B vaccine is one of the safest vaccines ever developed. There is no link between hepatitis B vaccination and multiple sclerosis, all the data demonstrating a complete lack of causality. WHO maintains its recommendation that all countries should have universal infant and/or adolescent immunization programmes and should continue to immunize adults at increased risk of hepatitis B infection as appropriate.

The most publicized allegation was a link with multiple sclerosis. In France, after more than 25 million people had been immunized, several case reports raised concerns that hepatitis B immunization might be linked to new cases or relapse of multiple sclerosis. After both media and professional concern, the French authorities suspended their school-based adolescent immunization programme in 1998, contrary to advice from WHO. At the same time, they maintained the recommendations for universal infant immunization and for immunization of adults at risk, and they reiterated continued support for immunization of adolescents through primary care physicians; however, these decisions were given much less attention in the media than the suspension of the school programme.

None of eight subsequent epidemiological studies, involving more than 2500 people with multiple sclerosis and cohort studies on several hundred thousand children and nurses in several countries, showed any statistically significantly raised risk for multiple sclerosis after hepatitis B immunization. Moreover, no experimental data support a link: there is no biological plausibility for a causal link. The most plausible explanation is a coincidental association, especially given that France reports the vast majority of cases of multiple sclerosis in the world. While a weak risk or the existence of sub-populations with specific sensitivities cannot be rejected, it should be remembered that it is impossible to demonstrate the absence of a correlation.

Subsequent meetings and reviews have confirmed that there is no need to change public health policies on hepatitis B immunization. WHO recommendations that all countries should have universal infant and/or adolescent hepatitis B immunization programmes and should continue to immunize adults at increased risk of hepatitis B infection as appropriate remain valid.

A continuing sub-theme illustrated by this example is the important contribution of the media, both lay and technical, in conveying messages, not always accurate. In allowing questionable reports of adverse effects of the vaccine to be published, the scientific world was guilty of a failure of the peer-review process. For the general public, press reports, fuelled by legal actions and court decisions, painted a very misleading picture, in particular misquoting the French decision or at least only partially reporting it.

The consequences could have been disastrous. Several countries considered stopping hepatitis B immunization and several others contemplated cancelling its introduction. Overall, the impact on immunization coverage appears now to have been limited, but the effect is hard to measure. Certainly there has been a long-term negative impact on both hepatitis B vaccine and immunization in general.

Medical settings
Another misperception that persists is that with regard to infections in medical settings the main risk of transmission of hepatitis B (and HIV) is from patient to health-care worker. In fact, epidemiological studies in the region underlined the importance of unsafe injections and the transmission between patients. On the positive side, a report from the Russian Federation noted the value of public education in preparing the way for the introduction of a hepatitis B vaccination programme.
Efficacy and effectiveness

The first generations of hepatitis B vaccines were prepared from HBsAg obtained from the plasma of people with chronic hepatitis B infection. Given to recipients, this surface antigen elicits the development of neutralizing antibodies that confer protection against infection. The vaccines are purified by biophysical and biochemical methods with heat or chemical inactivation steps. They are safe: there is no transmission of blood-borne pathogens. With the next generation of vaccines, preparation has shifted from the use of human plasma to recombinant HBsAg expressed in yeast or mammalian cells. The antigen can be produced in large quantities and production does not depend on a constant supply of plasma.

Typically hepatitis B vaccine is administered in three doses, although four-dose schedules were used in the 1980s. Current schedules vary, but that with doses given a birth, 1-2 months and 6 months is most common, especially in industrialized countries. This schedule and the lack of incompatibility of the vaccine with other vaccines make it easy to incorporate hepatitis B immunization into existing schedules.

The latest development is delivery of the vaccine in combination. Both hepatitis B vaccine and Hib vaccine have been formulated in DTP-based combinations, and others that include antigens such as inactivated poliovirus and hepatitis A virus are being developed. However, the advantages of using combined vaccines are offset by disadvantages. On the one hand, combined vaccines decrease the number of immunizations and visits needed to health centres for immunization; the likelihood that children will be fully immunized is increased; the demands on the cold chain, for storage, transport and waste disposal are reduced; and their use will simplify management, training and record keeping. On the other hand, they cost significantly more than single vaccines; they cannot be given at birth because pertussis and Hib vaccines cannot be given before 6 weeks of age owing to their decreased immunogenicity, and their content of DTP precludes the possibility of DTP vaccine being manufactured in the country buying in the new combined vaccine. The choice of monovalent or combination vaccine prompts lively debate because of the numerous, varied parameters to be considered. One country, Armenia, found that the need for a birth dose of hepatitis B vaccine and the resulting total of five doses of the vaccine (because of the four doses of DTP administered in its EPI schedule) would have meant a three-fold higher cost for the combined vaccine compared with the monovalent option.

Immunogenicity

Both plasma-derived and recombinant hepatitis B vaccines result in seroconversion rates of >95% after three doses, with protection titres of ≥10 mIU/ml of anti-HBs antibody. The immunogenicity of the vaccine decreases with older age (over 40 years) at immunization and the presence of immunosuppressive conditions, such as HIV infection, chronic liver disease, chronic renal failure and diabetes. To a lesser extent obesity and smoking weaken its immunogenicity. Hepatitis B vaccines are equally immunogenic when administered in monovalent or combination form.

Efficacy

Hepatitis B vaccine is about 95% effective in preventing hepatitis B viral infection when it is given before exposure. The rate is similar in preventing perinatal infection if the infant is immunized within 12 hours of birth. Addition of hepatitis B immunoglobulin has only a limited additional effect on the rate (2-6%). Cumulating evidence proves the long-term protection afforded by the vaccine, with immunity persisting despite loss of anti-HBs antibody. Protection has been documented for up to 15 years and based on the current scientific evidence protection is expected to last lifelong. At present, booster doses of hepatitis B vaccine are not recommended for universal newborn, infant or adolescent programmes.

Effectiveness of routine infant hepatitis B immunization programmes

Well documented studies in Alaska (USA) and Taiwan have clearly shown the effectiveness of hepatitis B immunization. Such programmes have decreased the incidence of acute hepatitis B, the prevalence of chronic hepatitis B viral infection and the incidence of hepatocellular carcinoma. In Alaska, the incidence of acute hepatitis B had dropped more than 10-fold in the two years after immunization was introduced in 1982, first as a demonstration project before routine immunization with three doses. By 1993 the prevalence of HBsAg among children under 5 years of age was zero,
compared with 3% in 1973. Similarly, routine immunization of children in Taiwan effectively halved the incidence of hepatocellular carcinoma between 1984 and 1994. This latter study underlined the fact that this cancer does occur in children but that its detection and monitoring needs a good surveillance programme. (A similar point about the lack of recognition of hepatitis B in children emerged in discussion. Transmission of hepatitis B virus does occur between children and in households where a chronically infected person lives; often the paediatric illness passes unrecognized – “kids don’t get sick”.)

**Safe immunization practice**

A safe injection, by definition, does no harm to the recipient, does not expose the provider to any avoidable risks and does not result in any waste that is dangerous to other people. To achieve that objective, the obstacles of overuse of injections, unsafe practices such as re-use or lack of sterilization, and unsafe disposal of injection materials have to be overcome. In many countries where hepatitis B and hepatitis C are highly endemic, unsafe injection practices account for a large proportion of infections; for example the proportion of new cases of hepatitis B that were attributable to unsafe injections was 52% in the Republic of Moldova in 1994. In the USA, data from CDC show that the proportion of new cases of hepatitis C that are attributable to injecting drug use exceeded 60%. Overall, each year an estimated 8-16 million hepatitis B infections, 2.3-4.7 million hepatitis C infections and 80000-160000 HIV infections world-wide are attributable to excessive use of injections or unsafe injection practices.

Bringing together intergovernmental, governmental and nongovernmental organizations as well as the private sector and civil society WHO has created the Safe Injection Global Network (SIGN)\(^5\) to design and support strategies for safe immunization. One of its activities has been to identify the determinants of unsafe injection practices in immunization services. Immunization programmes all have an incentive to achieve high vaccination coverage, but while the vaccine itself is usually provided by or through funding from donors, there is no system incentive to ensure safety of injections. The equipment needed to implement safe injection strategies, such as the use of auto-disable syringes, is not costed, budgeted or funded. Injection safety is not considered within the overall policy of immunization delivery.

However, injection safety is more than just a problem of logistics, more than simply the use of new, disposable injection equipment. Clearly the use of sterile syringes and needles would reduce the risk of transmission of blood-borne pathogens. Yet it is known that hepatitis B virus can persist in the environment and that both it and hepatitis C virus can be transmitted between injecting drug users despite the supply of clean needles. Experience from dialysis units indicates the high risk of transmission of hepatitis B in some health-care settings, and in Romania in 1998 transmission of hepatitis B virus was seen even when equipment was not re-used. The risk of transmission in health-care settings depends on factors such as the prevalence of infection in the community, exposure to blood, percutaneous exposures, and the prevalence of patients with high viraemia.

Thus a strategy for safe and appropriate use of injections will comprise:

- **behavioural change among patients and health-care workers to decrease injection overuse and make injection practices safe** (two examples being reduction in the demand for injections and introduction of complete barrier nursing in for instance dialysis units);
- **availability of necessary equipment and supplies; and**
- **the management of sharps waste.**

Support and assistance can cover areas such as policy formulation, sharing of best practices, rapid assessment and response guides, planning, implementation and monitoring of impact. Best practices, for instance, apply not only to provision and use of sterile equipment but to prevention of risks due to contamination and needlestick injuries and access to used needles and syringes. Tools for rapid assessment and response have been developed, for example a template for epidemiological studies and methods for surveys of injection frequency. For planning, an aide-memoire for a national strategy for the safe and appropriate use of injections has been drafted which looks at assessment, national coalitions, and a three-element strategy comprising behavioural change, equipment and supplies, and management of sharps waste (see above). With regard to implementation, other tools have been

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\(^5\) SIGN web site: [www.injectionsafety.org](http://www.injectionsafety.org)
developed for changing behaviour, especially among health-care workers, and steps to improve provision of supplies include guidelines to ensure quality and safety and the inclusion of injection equipment in essential drugs lists. Waste management can be improved through integrated policies and training of staff and supervision.

Challenges remain. Past efforts to improve injection safety have not been very successful. Previous approaches have a history of being narrow and technologically oriented. New initiatives will incur costs. The aim of maximizing immunization coverage may conflict with safety goals, and the Expanded Programme of Immunization cannot be responsible for the safety of all injections. Nevertheless, several opportunities present themselves. Comprehensive approaches have proven to be successful and there is increasing recognition of the value of a holistic strategy. Routine immunization programmes have a track record of responsible budgeting and implementation, and immunization coverage with safe practices has been well documented. Finally, EPI can spearhead and catalyse injection safety efforts. Despite the long-standing complacency, the public health consequences of poor injection practices and the resulting widespread transmission of pathogens are now being recognized together with the fact that prevention initiatives exist and can be successful.
HEPATITIS B PREVENTION STRATEGIES AND PROGRAMME EVALUATION

Prevention: the broader context

There are good arguments for combining prevention strategies for viral hepatitis (B and C) with those for HIV. All three infections pose major public health problems. The routes of viral transmission are similar and overlap. Effective prevention tools exist, namely immunization against hepatitis B, blood screening, universal (standard) precautions, risk reduction and treatment. Such prevention programmes are well established for HIV/AIDS. The lack of integrated prevention activities allows the continued transmission of these infections, especially the viral hepatitides. As the burden and impact of hepatitis C become more evident, it may be that that disease provides a turning point for new approaches to prevention.

In 1998, when the estimated number of people living with HIV globally was 33.4 million, the comparable figures for chronic hepatitis B and C viral infections were 371.6 million and 176.9 million, of which respectively 10.9 million and 21.8 million were in Europe - all three viruses are endemic in the newly independent states of the former USSR.

With the existence of hepatitis B vaccine, the first priority should be prevention of hepatitis B viral infection in newborns, infants and young children, by means of immunization of newborns or infants. A hepatitis B prevention programme will comprise three components. The first is immunization – for newborns or infants; for older children through catch-up programmes, with ages defined by local epidemiological patterns; for health-care workers; and for other adults at high risk, again with local epidemiology defining the categories. The second component will be assessment of the effectiveness of hepatitis B immunization in terms of age-specific vaccine coverage and population-based serological studies. The third is surveillance for acute disease among all age groups, with serological confirmation and data on risk factors, immunization status and source of infection.

Considering the risk factors for transmission, a model hepatitis B prevention programme would feature the following:

- immunization (newborns or infants, older children, health-care workers and other adults at high risk)
- safe blood supply and blood products (with screening for HBsAg, good manufacturing practices for blood products, and viral inactivation procedures for pooled products)
- safe injection practices in all settings
- infection-control practices
- surveillance to assess effectiveness of prevention.

Control of viral hepatitis: more than just hepatitis B

Screening of blood donors allows countries to be categorized in terms of prevalence of markers of hepatitis C infection: high (>5%), intermediate (1.1-5%) and low (0.2-1.0%). For instance, Romania has a high rate and the Central Asian Republics have intermediate rates. Across the world, distinct patterns of transmission and risk factors emerge depending on the endemicity of hepatitis C virus. Case-control studies have identified unsafe injections as a major route of infection in countries with high or intermediate prevalence of hepatitis C virus, followed by transfusion of unsafe blood or blood products. In developing countries and those with economies in transition, some 44% of the estimated total of 4.8 million hepatitis C viral infections are attributable to unsafe injections. This proportion is comparable to that for hepatitis B viral infections but much greater than the attributable fraction of 2% for HIV infections. Post-transfusion hepatitis (due to hepatitis B or C) is a significant problem in countries where blood and blood products are inappropriately used, where transfusions services are not well organized and most transfused units are not tested for either virus, and where donors are paid. Prevention strategies thus should focus on securing the safety of the blood supply and assuring safe injections as well as imposing infection-control measures.

In countries of low endemicity, that is most of the countries of central and eastern Europe and the newly independent states, the predominant risk (about 75% of cases) is injecting drug use, followed by sexual transmission. Injecting drug use is a highly efficient route of transmission of both hepatitis B and C viruses. Studies in the USA showed that within one year of starting injecting 80% of drug users...
were infected with hepatitis C virus compared with about 60% with hepatitis B virus and less than 20% with HIV. Injecting drug use is emerging as a risk factor also in countries with intermediate prevalence, and the occurrence of cases of acute hepatitis B and hepatitis C in young adults may be considered as a sentinel marker for the emergence of injecting drug use in a country. Thus, for instance, the highest incidence of hepatitis C is being observed in young adults in some countries such as Italy and Japan, and about half the people presenting with acute hepatitis C in Italy and the Russian Federation report a history of injecting drug use as do about 40% of people seropositive for hepatitis C viral markers under the age of 40 years.

Thus, in countries of low endemicity, prevention strategies need to concentrate on risk reduction as well as testing and counselling services. These strategies parallel those for hepatitis B in countries with low and high or intermediate endemicity, except that a vaccine against hepatitis B exists. They make a compelling case for integrating strategies for preventing hepatitis C with those for hepatitis B; prevention and control of viral hepatitis concern more than just hepatitis B viral infection.

**Evaluating outcome and assessing impact of hepatitis B immunization programmes**

Most childhood infections result in immediate disease and the effects of immunization programmes can be monitored by surveillance for acute disease, for example acute flaccid paralysis in the case of poliomyelitis and meningitis in the case of *H. influenzae* type b infection. Infection with hepatitis B virus is different: it is rarely symptomatic in young children, making it hard to identify infected children, and morbidity, in the form of hepatocellular carcinoma, usually occurs much later, in the third, fourth and fifth decades of life. In such circumstances, evaluation of a hepatitis B immunization programme will depend on surveys of coverage of immunization and serological surveys as well as surveillance for any acute cases of disease and for chronic consequences. Parameters to be covered in any such assessment will include the markers (e.g. HBsAg or anti-HBc (core) antibodies) that should be monitored, the age at which vaccinees are investigated, the frequency and criteria of assessments, and whether operative targets have been met. Questions will need to be asked about the acceptability and validation of data sources, and confidentiality. Information technology should be applied to the collection and management of data.

**Immunization coverage surveys.** Immunization coverage is the proportion of vaccinees in the target population to the size of that population. There are no standard coverage indicators for hepatitis B. Coverage surveys should include review of immunization certificates and, at national level, of data collected at school entry. Other sources of data include child health registries, vaccine sales figures, prescriptions for vaccine, numbers of doses of vaccine imported or licensed and number of doses of distributed vaccine. Useful data would be the percentage of newborn given a birth dose of vaccine, the percentage of infants who received a first dose and the percentage who completed three doses (the last two pieces of information giving the drop-out rate).

Limitations include the fact that such surveys do not directly measure impact. Even if coverage is high, that does not necessarily guarantee effectiveness: for example, there may be weaknesses in the cold chain or the vaccine may not be optimally administered. The recording of data on doses delivered, to give a measure of administrative coverage of vaccine, will mean separate surveys.

**Serological surveillance.** Serological surveys compare the prevalence of HBsAg and other markers of hepatitis B viral infection in target populations as well as other parts of the general population before and after the introduction of an immunization programme. Prevalence rates may differ widely – for example, with age, sex, ethnicity, place of residence (urban or rural), socio-economic status, and risk behaviour. Historical data may be obtained from published articles, unpublished reports such as theses, blood banks and special studies conducted by ministries of health or academe, for instance. Data collection should commence at the same time as the immunization programme, and the programme should not be delayed to collect data. For relevant data, the screening programmes need to look at representative populations, with similar populations for follow-up, and to be supported by adequate laboratory capacity.

Screening programmes may target blood donors, pregnant women and military personnel. These three populations are easy to screen, without great cost, and the last two are reasonably representative of the general population. Hospital-based populations, easy and cheap to screen, are not representative;
increasingly representative are outpatient clinic groups, schools and community and households (the most representative) but the difficulty in reaching them and the cost increases proportionately. Laboratory capacity needs to be able to detect reliably anti-HBc antibodies as well as HBsAg (to detect chronic infections).

**Acute hepatitis B surveillance.** Such surveillance needs a sufficient number of cases, careful clinical examination and history taking to identify risk factors, an agreed case definition, reporting mechanisms and good laboratory capacity. Reporting may depend on mandatory notification, supported by laboratory notification; sentinel systems may be in place, and other reports may come from hospitals and death registries.

Clinical examination alone cannot distinguish between different viral hepatitides; for that laboratory confirmation is necessary. Definitions were put forward at the meeting to facilitate reporting:

- A clinical case of acute viral hepatitis is an acute illness that includes the discrete onset of symptoms and jaundice or raised serum aminotransferase activities (>2.5 times the upper limit of normal)
- A confirmed case of hepatitis B is a clinical case that is laboratory confirmed to be anti-HBc-positive and IgM anti-HAV negative
- Patients who are not tested for IgM anti-HBc but who are positive for HBsAg and negative for IgM anti-HAV are suspected cases of acute hepatitis B.

The surveillance system in Romania was cited as an example. Since 1997 surveillance for acute viral hepatitis in under-5 year olds has been hospital based, as most children with jaundice are admitted to hospital. Demographic data and a vaccine history are obtained for each child and laboratory tests determine the IgM anti-HAV, anti-HBc and HBsAg status. For passive surveillance, weekly reports are made first to the regional level and then to the Ministry of Health. In 1997-1999 a total of 1931 cases were reported. Hepatitis A was diagnosed in 77%, hepatitis A and B in 2%, and hepatitis B alone in 4% (71 cases), with no serology done in a further 8% of cases. Possible risk factors in these 71 cases were injections (36%), admission to hospital (29%), contact with a chronic hepatitis B carrier (27%) and contact with somebody with acute hepatitis B (15%), there being more than one risk factor in some instances. Another example was cited from the Republic of Moldova. As immunization coverage increased between 1994 and 1997 to about 80%, surveillance showed that cases of acute infection in children under 2 years of age plummeted to about 2 or 3 a year in 2000.

One of the considerations for a surveillance system is whether it should be national or sentinel. Clearly costs will be higher with a national programme. Sentinel surveillance is practical, provided that the population being studied is representative. Other issues include whether children or other groups should be studied, whether there are other programmes such as for health-care workers and whether risk-factor information is being sought, in which case adults need to be surveyed.

Data on mortality related to hepatitis B is also important, especially in areas where the prevalence of HBsAg and HBeAg are high and hepatitis D is present, such as in the Central Asian Republics. Information of deaths from acute illness, chronic disease (including hepatocellular carcinoma) and the proportions due to hepatitis B virus, hepatitis C virus and hepatitis D superinfection are important, and well suited for long-term evaluation.

Evaluation of hepatitis B immunization programmes is vital for three reasons. The first is to show that immunization actually does decrease morbidity and mortality in individual regions and countries. The second is to provide information to boost confidence in the practice of immunization generally. And the final reason is to obtain the evidence needed to argue convincingly for sustainable programmes.
COUNTRY EXPERIENCES

Kazakhstan
The country is endemic for hepatitis B, with an average seropositivity for HBsAg of 5%, but with wide variations, and a high rate of hepatocellular carcinoma. Most viral hepatitis is due to hepatitis A and only low rates of hepatitis C have been reported. In 1997 a hepatitis B immunization programme was introduced, with vaccine bought with national funds, aimed at protecting newborns and infants.

The immunization programme has greatly reduced hepatitis B rates in children and young people, except students. Highest seropositivity rates in 2000 were found in the unemployed and in people aged 20-29 years. A persisting risk factor is associated with unsafe injections, in outpatient clinics and dental surgeries, but a growing new risk factor is injecting drug use, which accounted for a substantial proportion of new cases in 2000.

With support from CDC in the USA health staff were trained in preparation for the new programme. Surveillance has been based on the existing epidemiological and laboratory network, which is functioning well. With the evident impact on children, the policy will be adjusted to focus on injecting drug users, catch up in older children and adults at risk and incorporated into a five-year plan aiming at total coverage.

Kyrgyzstan
With its 4.5 million people Kyrgyzstan has a high rate of viral hepatitis. Seropositivity rates of 7-11% for HBsAg and 40-62% for anti-HBs have been recorded across the country, and rates of 5-8% for anti-hepatitis D viral antibody have also been found. Among blood donors in Bishkek in 2000 positive for viral hepatitis markers, these were for hepatitis B in 26%, hepatitis C in 31% and hepatitis D in 13%.

As part of a prevention and control system, the government launched a sentinel surveillance system. In 1999 the Ministry of Health established a national reference laboratory for viral hepatitis, set case definitions and undertook training seminars for health workers. A national programme on hepatitis A, B, C, D and non-A, non-C was initiated at the beginning of 2000. Results for the first year (2000) underlined the importance of serological testing: in about 30% of cases the initial clinical diagnosis of hepatitis A or B had been wrong. Overall hepatitis A accounted for 67% of cases and hepatitis B alone for 13.6%. Highest rates for hepatitis B and C were seen in the 15-29 year age group. In terms of risk factors for transmission, contact with patients with viral hepatitis was reported in 20% of hepatitis A and 10% of hepatitis B cases, family contacts in 50-60% of both illnesses and all cases of hepatitis C, and admission to hospital in half the cases of hepatitis C but only small percentages for hepatitis A and B. Blood transfusion was mentioned in about 20% of cases of hepatitis B and C, but the proportion varied across the country. Unsafe injection was a common route of infection.

Immunization of newborns against hepatitis B began in 1999 and has rapidly proven to be an effective control method. Mortality in acute cases of hepatitis dropped from 14.6% in children under one year of age in 1999 to 0.7% in 2000 and only one case of acute hepatitis B was reported. The aim is to achieve 100% vaccine coverage with hepatitis B vaccine in the newborn immunization programme in 2001.

Poland
In the early 1980s Poland faced a dire situation with hepatitis B, with incidence and prevalence rates among the highest in Europe. Once infection control measures improved with the advent of the HIV/AIDS epidemic incidence rates dropped from about 45/100 000 in 1985 and further with the introduction in 1989-90 of obligatory immunization of newborns and infants born to HBsAg-positive mothers, of health-care workers and of medical students. In the early 1990s incidence rates in women aged 20-40 were nearly twice as high as in men in the same age group while that in health-care workers was five times higher than in the general population.

The main risk factor in hospitals and medical institutions was the use of hot dry air rather than autoclaves to sterilize medical equipment and materials. An intensive control programme was introduced in 1993 that included replacement of hot-air sterilization by the use of autoclaves and
extension of obligatory immunization to further risk groups. Between 1994 and 1996 such immunization was extended to all newborns and infants, and in 2000 immunization of adolescents (at age 14 years) was made obligatory. From 2000, some two million people are being immunized against hepatitis B each year.

The results have been impressive. Between 1993 and 2000 the annual number of cases of hepatitis B fell by nearly 80% to about 2800 and the incidence rate was cut five-fold to 7.3/100 000, an average figure for central European countries. The imbalance in rate between young men and women was eliminated.

The target is that by 2010 95% of the population under the age of 25 will be immunized against hepatitis B as will be 5-10% of those over that age. In addition, sterilization procedures for materials and equipment in medical institutions will be satisfactory.

Republic of Moldova

Moldova, with its population of 4.3 million (23% aged less than 14 years), has long recognized hepatitis B as a major public health problem. Very high incidence rates of up to 50/100 000 population were recorded in the 1980s (e.g. 53.3/100 000 in 1987 with a peak incidence of 57.3/100 000 in 1987) and serological evidence showed the spread of hepatitis C and D from 1991 onwards. In the early 1990s HBsAg was present in about 10% of the population, with rates of 17% in children under 5 and 3-8% in pregnant women. With high infection rates in children and high incidences in hospitals an immunization programme for children was planned but shelved because of lack of supplies. However, in 1995 a programme of obligatory immunization of newborns was introduced, with the first dose at birth. A national prevention programme against hepatitis B, C and D was implemented in 1997, with measures to protect the rights of patients.

Good progress has been made. Testing of donated blood has secured the blood supply. Re-use of injecting equipment was forbidden and now most medical institutions use disposable material. Training of health-care workers has been continuous. Starting in 1995, all newborns are being immunized and some 10 000 health-care workers were vaccinated in 1999-2000. Although the Government faced economic constraints, with support from UNICEF and Japan it was able to obtain supplies of hepatitis B vaccine. Incidence rates of hepatitis B have fallen by nearly 75%, to 17 per 100 000 in 2000, especially among children under 5 years of age.

The goal is now broader, aiming at all the populations at risk, so that by 2006 some 35-40% of the population, about 1.6 million people, should be immunized. Some problems remain. Discussion of sexual transmission poses difficulties and the use of condoms is low. Occupational risks are still present. More case-control studies are needed to lay a solid foundation for immunization programme goals and objectives.

Russian Federation

Since the early 1990s the epidemiological picture for hepatitis B and C has worsened significantly in the Russian Federation. In the past 10 years incidence rates for hepatitis B have doubled, to 42 per 100 000, although they seem to have plateaued recently at that level. The rate for hepatitis C has increased monotonously since 1994, reaching nearly 21 per 100,000 in 2000. In particular, infections in young people in the 15-19 year and 20-29 year age groups have contributed to these startling increases, especially in 1998. Between 1994 and 1999, the growing epidemic was fed mainly by transmission of infection in hospitals and medical centres, but since then it has been fuelled by injecting drug use, which now far and away exceeds other routes of transmission, of both viruses.

The recognition of HIV/AIDS led to the reconstruction of the whole medical system and the introduction of preventive and control measures, such as screening blood for HBsAg and the use of disposable equipment. But controlling the real and serious epidemic among drug users lies beyond such measures; immunization with vaccine is the most efficient way of controlling hepatitis B and other measures including safe injection are needed to prevent and control hepatitis C.
In the late 1980s only few people were immunized with hepatitis B vaccine and in 1988 legislation was enacted introducing hepatitis B vaccine into the immunization schedule of the USSR. The cost of vaccine was to be borne by the state. However, the financial restraints allowed only 1 million doses to be bought. By the year 2000 the Government of the Russian Federation was buying 4 million doses for immunization of newborns, and for 2001 the plan was to immunize all children aged 0-12 months. Vaccination of adolescents depends on decisions at regional as opposed to federal level, but preventive measures are proving inadequate. Only in Sverdlovsk and Moscow are effective programmes under way, and the first effects are evident in the capital: since 1998 incidence rates have been falling. Moscow City’s council is setting a rare example by purchasing vaccine.

**Federal steps** There are steps to standardize legislation, and at the beginning of 2001 a new national immunization calendar was introduced which included catch-up vaccination of adolescents at state expense and regional prevention programmes, a new decree valid from January 2002 recommends hepatitis B immunization of all newborns and adolescents. Investments in upgrading the cold chain have paid off, with an effective system. Further investments have been made to educate and mobilize public opinion. Videos have been made and pamphlets advocating hepatitis B immunization distributed widely.

Besides federal programmes some local and nongovernmental initiatives have been launched, such as the Rostropovitch-Vishnevskaya Foundation’s support for an oblast-wide immunization programme, and needle-exchange programmes.

**Russian Federation: Nizhnyi Novgorod**

Hepatitis B accounts for about half of all cases of viral hepatitis in this oblast of the Russian Federation. After a decline in morbidity rates from a peak of 40.3 per 100 000 population in 1995, the number of cases of acute hepatitis B and of HBsAg carriers began to increase again in 1998. This rise is mainly attributable to cases in young people, especially those aged 15-19 among whom the rate nearly trebled in 1998-2000 to 182 per 100 000. This trend reflected the spread of injecting drug use and was mirrored in the growing morbidity due to hepatitis C. Besides injecting drug use, sexual transmission accounts for many cases of hepatitis B.

A pilot project to immunize children was developed by local authorities with the support of a nongovernmental organization (the Rostropovitch-Vishnevskaya Foundation). A social mobilization campaign to raise awareness about the value and efficacy of hepatitis B vaccine preceded the pilot project in which 96.7% of children aged up to 17 years in one district were immunized. As a result, a plan for the whole province was developed on the basis of known epidemiology with the active support of the public health authorities and other parts of the administration, with the aim of immunizing newborn children not covered by vaccine procured with federal support, undergraduate and medical students, children and adolescents in detention centres, and, progressively, schoolchildren in different grades – a total of more than 500 000 children and adolescents to be immunized in the period 2000-2003. The media have been enlisted to raise awareness and to advocate the programme; educational activities for parents have been organized; and health workers throughout the province have been targeted with information through special meetings, workshops and seminars. The plan included a calendar for vaccine procurement and detailed scheme for vaccine delivery, supported by measures to strengthen the cold chain.

The programme has been implemented with funds from federal as well as local (compulsory) medical insurance sources as well as from the Foundation. So far more than 200 000 adolescents have been immunized, more than 92% of the target population.

**Turkey**

With its young population, a third of the 64 million people being below the age of 15 years, Turkey has an intermediate endemicity for hepatitis B. Since 1990 hepatitis A and hepatitis B have been reported separately and in the four years 1997-2000 hepatitis B has accounted for 20-25% of all reported viral hepatitis cases, the total being reported to the Ministry of Health in 2000 being about 15 000. Because of under-reporting, and allowing for asymptomatic cases, the actual figure is thought to be at least 10
times higher. About 5% of the population are positive for HBsAg and 25-30% positive for anti-HBs, in other words about 21 million people have been infected with hepatitis B virus and at least 3.5 million are chronically infected carriers.

Blood has been screened since the 1970s. Data show high rates among military personnel (8.7%), more than twice the rate in first-time blood donors in Ankara (3.9%) for instance. The high overall seropositivity rates reported may be due to blood being drawn from professional donors and prisoners as well as soldiers. Substantial variations in HBsAg seropositivity are seen across the country, ranging from 3.5% in the west to 8.9% in the eastern regions, where families live traditional life-styles in crowded conditions, socio-economic status and infrastructure are poor, and little or no access to good health services.

The age structure of infection (both antigen and antibody prevalence rates) shows an increase after 10 years of age with a peak between 21 and 25 years. High rates of infection are found in people with known risks, such as haemophiliacs, haemodialysis patients, patients with chronic liver disease and female sex workers. The seropositivity rate in health workers is no different from that in blood donors, although the frequency of anti-HBs is significantly higher, probably owing to more frequent exposure. Investigation of possible routes of transmission in people with viral hepatitis generally revealed accepted modes in 55% of cases, indicating that the somewhat nebulous concept of horizontal transmission may be an important route in 45% of cases in Turkey.

A nongovernmental organization, the Viral Hepatitis Prevention Society, conducted a cost-effectiveness study of three strategies for the 1.5 million children born in 1997: no vaccination, screening mothers and immunizing infants born to HBsAg-positive mothers, and universal immunization. The results were categorical in showing the savings of a universal programme. The Ministry of Health introduced in 1998 such a universal immunization programme for newborns into its routine immunization programme (EPI) and enlisted the aid of the nongovernmental organization to mobilize community opinion in the health sector through communication networks targeting health-care workers. To cope with different situations, such as children being born outside health facilities (35% of births), the ministry allowed three different schedules for immunization. By April 2001, the hepatitis B immunization coverage rate for three doses of vaccine had reached 74%, for which the ministry had planned the purchase of 11 million doses of vaccine in 2000. For the first time the ministry extended immunization to those with high risks who previously were immunized in the private sector, with an expensive reimbursement scheme. (A further 900,000 doses were still imported by the private sector in 2000.)

Despite the major advances of the past three years, two main obstacles remain. One of the immunization schedules includes the first dose of vaccine at three months of age, in circumstances where immunization at birth is not practicable. The second problem is the lack of a catch-up immunization programme for adolescents.

**Regional summary**

As vaccination programmes are implemented together with the necessary supporting laboratory networks, other types of viral hepatitis are increasingly recognized. The particular unreliability of clinical diagnosis, strikingly demonstrated in one study, pointed to the need for serological testing. Sentinel surveillance was a very effective mechanism for monitoring the epidemics, especially where resources are limited.

Country examples show the value of building on existing epidemiological and surveillance systems, with appropriate training, technical and financial support, and national capacity building. Dramatic success stories were provided from several countries. In Kazakhstan, capacity building and training helped to secure political commitment and legislative responses to introduce a vaccination programme with national resources to buy the vaccine. Sound epidemiology revealed a shift in the disease pattern, revealing the transfer of disease burden to injecting drug users.

Kyrgyzstan’s experience of using sentinel surveillance showed that, given the high endemicity and large number of cases, this approach provided a useful method of demonstrating the efficiency of the
vaccine programme. Its programme of training and national capacity building, building on existing surveillance systems and a national reference laboratory, supported by the United States Agency for International Development, paid dividends.

A further general observation to emerge from several sessions was the recognition of nosocomial transmission of hepatitis B virus and unsafe injections as major routes of transmission. Safe immunization together with safe injection practices are crucial to cutting and preventing that route of transmission of hepatitis B and C viruses. They are the responsibility of all health workers. The tools, ranging from the application of standard precautions to the introduction and use of disposable equipment, are available.

The risks of transmission within medical settings can be reduced. Poland showed how a programme of vaccination plus the introduction of autoclaves in hospitals rapidly reduced the levels of infection.

The diversity of local responses was striking, reflecting the local conditions and the varied local epidemiology, but common features were the growing problem of injecting drug use as a route of transmission of hepatitis B and C, and the contribution of hepatitis A to the disease burden.

Hepatitis B prevention programmes can be integrated into national and regional health programmes and with other prevention programmes such as those for HIV. When they are integrated, their impact needs to be monitored and evaluated, but the methods needed differ from those for other vaccine programmes, with monitoring of the seroprevalence of hepatitis B viral infection in children being vital. Model prevention programmes were presented and described, showing the core elements of immunization, safe blood and blood products, safe injection procedures, infection control practices and surveillance to assess effectiveness.
STRENGTHENING IMMUNIZATION SYSTEMS AND INTRODUCTION OF NEW VACCINES

GAVI Regional Working Groups
The GAVI Vaccine Fund presents an opportunity to revitalize the EPI and to develop EPI plans in a more comprehensive way, with review of the EPI status of GAVI-eligible countries and the identification of countries’ needs. With knowledge of disease burdens, it provides a tremendous boost for the introduction of hepatitis B and other vaccines such as that against Hib disease. It also allows for emphasis on injection safety at the same time as provision of vaccines. Its working groups provide a means of establishing and maintaining immunization programmes at regional level.

GAVI set up one such Working Group for the WHO European region in order to optimize the support given by partners (see p.4 above) to countries in central and eastern Europe and the newly independent states. Eleven countries are eligible for support from the Vaccine Fund (see Table 1). Before the latest (fourth) round of applications to that Fund, all countries had immunization plans, some had introduced limited vaccine programmes, and six had conducted assessments of their cold chains. Only one (Kyrgyzstan) had an Interagency Coordinating Committee (ICC) and two (Albania and Kyrgyzstan) had estimated the burden of disease due to *H. influenzae* type b.

For the fourth round, four countries applied for support under the immunization services sub-account, and in June 2001 applications from Armenia, Azerbaijan and Tajikistan were approved. Georgia was invited to resubmit. The three approved programmes will enable a further 29 000 children to be immunized at an investment cost of some $313 000. Ten countries submitted applications for support for introduction of hepatitis B immunization: four applications (from Armenia, Azerbaijan, Kyrgyzstan and Uzbekistan) were approved directly and three more (from Albania, Tajikistan and Turkmenistan) subject to clarifications. These programmes include a major programme in Uzbekistan, aiming to provide some 3.6 million doses at a cost of more than $1.5 million. Overall, support to these seven countries will enable coverage of 1.47 million children, with 5.5 million doses of hepatitis B vaccine at a cost of $2.85 million (i.e. $1.94/child).

In order to coordinate support to countries the European Working Group, based in WHO’s Regional Office for Europe, will focus on EPI and cold-chain assessments, the development and finalization of multi-year national plans of action, preparation of funding proposals and specific plans for hepatitis B immunization. In addition it will assist with finalization of documentation of applications, strengthening national ICCs, and the monitoring and evaluation of the whole implementation process.

Feedback from the review committee at the end of June 2001 indicated that more substantial information was needed for, in particular, financial sustainability, with evidence of commitment from governments and partners and details of financing schemes. Further, information was needed on plans to improve injection safety, for the introduction and integration of hepatitis B immunization (including training and logistics), and on vaccine handling and securing the cold chain. Data were also needed on the burden of Hib disease and plans for introducing the Hib vaccine. Finally more evidence should be provided on progress in implementation of plans.

The European Working Group plans support in several areas. It will help Bosnia and Herzegovina, Georgia and Moldova to complete or commence their applications to the Fund for introduction of hepatitis B immunization in 2002. With regard to Hib disease estimations of burden are currently under way or planned in six countries (Albania, Armenia, Bosnia and Herzegovina, Kyrgyzstan, Moldova and Ukraine), in preparation for introduction of Hib vaccine in 2002 or 2003. The Working Group will strengthen national ICCs and will work to ensure that for all EPI activities plans are implemented. Future areas will extend activities to cover other vaccine-preventable diseases, monitoring of performance through quality assurance, and safety of immunization – including safe injections, vaccine handling, storage and transport with adequately maintained cold chains, and waste disposal.

Introducing Hib vaccine
The existence of an effective vaccine does not necessarily guarantee its use. For many countries in the developing world, immunization programmes are limited to the same vaccines as a couple of decades
Three main obstacles have prevented the introduction of newer vaccines such as those against hepatitis B and Hib: the lack of data on disease burden; the high cost of vaccines; and the insufficiency of national capacity or expertise to introduce the new vaccines. To counter the increasing gap between protection against infectious diseases in rich and poor countries, GAVI is working through its partners to accelerate the introduction of new vaccines.

In the case of illness due to *H. influenzae* type b (Hib) infection, the bacterium causes about 400,000-500,000 deaths a year in children aged under 5 years worldwide, that is about 20-25% of all deaths each year due to respiratory infections in that age group. It accounts for 30-50% of all cases of bacterial meningitis and 20-25% of severe bacterial pneumonia in children. Yet safe, immunogenic and highly effective polysaccharide-protein conjugate vaccines have been available for more than a decade. In developed countries, Hib meningitis and other invasive Hib diseases have been almost eliminated through the use of the vaccines, but routine immunization programmes elsewhere fail to include them.

There is limited, equivocal data for central and eastern Europe and the newly independent states indicating that the burden of Hib disease. If, unlike in Western Europe, there is little Hib disease, then these countries are in a fortunate position and do not need the vaccine. But some data from hospitals in the Russian Federation and Ukraine have suggested that the disease is a problem. Despite this, there have been few national epidemiological studies on Hib disease burden. Those that have failed to find much Hib disease may have suffered from poor culture techniques and no laboratory confirmation. Patients with suspected disease may not undergo lumbar puncture or there may be difficulties in the collection and transport of cerebrospinal fluid. Sometimes antibiotic treatment vitiates attempts at culture; and even the culture itself of *H. influenzae* needs care and good conditions.

Studies to define the burden of Hib disease are needed, with both retrospective and prospective epidemiological investigations used to define if and how the vaccine should be used (for example, in routine immunization programmes or, if it is not a nation-wide issue, in special situations such as day-care centres and special paediatric units). For several years, a generic protocol for population-based surveillance of Hib disease has been available. In addition, a Hib Rapid Assessment Tool has been developed to allow a quick determination of disease burden based on retrospective analysis of laboratory data. Management guidelines, which also contain information for health workers and parents, have been prepared for those (many) countries that are already using the vaccine.6

**Health information systems: the Ukrainian infectious disease programme**

The need for good epidemiological surveillance was a clear lesson that grew out of the outbreak of diphtheria in the newly independent states in the 1990s, and in Ukraine that epidemic illustrated the weaknesses of existing health information systems. These included lack of reliable data on vaccine distribution and use, confusion about definition of target populations, non-standardized statistical methods, and inconsistent data collection and reporting. A programme to reform health information systems and management was designed to improve public health management and the prevention and control of infectious diseases. It aimed to raise the quality of information and to ensure better use of information by and for management. The programme, supported by the US Agency for International Development, began in 1997.

The first step was to assess the current state of data collection and to identify deficiencies in the system. Improvements and changes were recommended and prioritized. Initially implemented in a single oblast, the progress of reform was monitored. An oblast working group was set up to oversee the introduction of reforms and training of staff, followed by the holding of first oblast-wide meetings and then a national conference on the management of information. The reform programme was then expanded to two additional oblasts and a national working group was established to advise on and coordinate the nation-wide adoption of the programme reforms. Similar steps were taken to ensure the success of parallel management and public health surveillance reforms, culminating in regional training seminars for epidemiologists, and national adoption of reforms in 2000.

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6 See, for example, [http://www.who.int/vaccines-documents/DocsPDF/www9723.pdf](http://www.who.int/vaccines-documents/DocsPDF/www9723.pdf) for a generic protocol for population-based surveillance of Hib.
The information software facilitates the flow of data and highlights deficiencies or weaknesses such as suboptimal performance and presents information in such a way as to alert users to inconsistencies. The data can be archived and require only 2-3 hours a month every month for entry. Outputs include the number of type of immunizations, monthly reports on immunization, contraindications, timeliness, coverage, vaccine supply, consumption and wastage patterns.

The system works well. The information and its presentation allow managers to respond, for example, to wastage or difficulties in transport. Reported long-term contraindications to DTP dropped from 4% to 2.6% in a year. Immunization coverage (for all vaccines) has risen, with areas where rates were low being highlighted automatically. As a result of the improved and reformed information system, immunization programme managers are able to monitor supplies and usage (low stocks or high rates of usage can be graphically displayed), at all levels, from town to oblast, and thus investigate anomalies.

The public health system can now forecast its vaccine needs accurately. A direct consequence of this was the re-establishment of centralized vaccine procurement in the country in 2001. The public health result is more children being immunized and in a more timely manner.

In-country coordination and strengthening national Interagency Coordinating Committees

Coordination at national level is relevant to all countries, not just those eligible for GAVI support, in particular where immunization programmes were previously unstructured. Interagency Coordinating Committees (ICCs) were introduced to strengthen coordination mechanisms, and in many countries globally they have contributed towards sustainable immunization programmes. Since 1994 the Regional ICC based in the WHO European Regional Office has supported polio eradication and diphtheria control.

All countries have acknowledged the need for such a mechanism, in particular in finding additional support for immunization programmes, and a functioning ICC or equivalent at national level is a prerequisite for eligibility for support from GAVI. Such a committee endorses country proposals and national immunization plans as well as conducting annual, mid-term and final reviews of the supported immunization programmes. The rationale for ICCs is to provide a facilitative tool for promoting effective and efficient immunization programmes, but not to replace current funding, and for support in the acceleration of development and introduction of new vaccines.

Several roles can be ascribed to the national ICCs. These include advocacy to increase national commitment, identification of needs and resources required, optimizing use of resources through coordination of existing partners, identification and integration of new partners into national plans, contribution to the formulation and implementation of strategies and projects, and the monitoring of performance and progress.

Conceptual framework

An ICC will need to adapt and build on existing coordination mechanisms. It will need flexibility to make the most of local conditions, needs and circumstances. It should unite government entities and partners to ensure that immunization activities are given high priority and are sustainable, yet leadership and ownership of the ICC should belong to the ministry of health, with the government being the driving force. An ICC can use the national immunization plan of action as a tool for coordination and monitoring. It should establish a forum for information and mobilization of resources, and can serve as an advisory board or clearinghouse for information on immunization services.

The main partners of an ICC, while obviously varying with country, will include public and private sector parties. National governments, through ministries of health, will take the lead role but will be supported by other ministries (such as those concerned with planning and finance). Other partners will include intergovernmental agencies and organizations such as WHO, the World Bank and UNICEF, bilateral and multilateral agencies and nongovernmental organizations as well as the private sector and international institutions.
In its actions, an ICC should be transparent and accountable, with formal meetings with clear agendas and records circulated to all members. It will need to work with other relevant coordinating bodies at national level where they exist. Indeed an ICC should have a broader vision than just immunization, looking at health sector reforms, decentralization of health services and other political processes, with the result of building national capacity. Thus, no one formula, mechanism or model exists; rather each national ICC will be country specific and reflect national priorities.

Functions
The functions of a national ICC fall into four categories: technical, political, financial and capacity building. Technical functions include support of implementation of plans of actions for immunization, monitoring and evaluation of performance, delivery and even specific disease-control initiatives. Further, they should include application of quality control mechanisms and observance of accepted international standards. Financial functions include ensuring efficient and effective use of available resources, and helping the national immunization programme enhance transparency and accountability, for instance by reviewing the use of funds and other resources. At the political level, functions include advocacy and increasing the commitment to immunization programmes and activities, social mobilization to raise public awareness, and providing a feedback mechanism both within and outside the country. The capacity building function will be seen in the ability of governments to take ownership of the administration and delivery of national immunization services.

Multi-year plans
Strategies, actions and resources are needed to reach all target groups with high-quality immunization services and to meet national targets for prevention and control of vaccine-preventable diseases. A good multi-year plan, another pre-requisite for eligibility for support from GAVI, covers these three elements. The format of such a plan may differ by country according to health system, local needs and tradition, but, with a planning period of usually 3-5 years, medium-term strategic priorities and resource needs must be clearly defined.

Plans will need to address the five interlocking operational components of immunization systems – vaccine supply and quality, logistics, advocacy and communication, surveillance and service delivery – as well as the underlying health systems functions of financing, management and strong human and institutional resources. Besides the objectives of the immunization programme, the plan must define the steps, responsibilities and costs of implementation. These will include training, introduction of new vaccines, increased or accelerated disease-control activities and social mobilization. Indicators such as coverage and those relating to priority areas and targets will have to be specified. Other essential elements of the plan will be budget, financing and a time-line. The plan will be complemented by national and sub-national plans for each year covered by the medium-term plan.

Critical to the success of the plan will be the monitoring of its implementation. The national immunization programme will have specified and published a set of indicators, whose collection and analysis will form the basis of monitoring. National data will also be reported to WHO and UNICEF regularly each year. When donors provide financing or vaccine, the national ICC will have the responsibility for monitoring progress. So far, implementation of multi-year plans has not always been completely successful. Reasons for this include an imbalance between the needs assessment and the plan, with often the latter not dealing with the main problems. Sometimes planning is unrealistic, with inadequate estimates for financing and limitations in human resources, management and priority setting not being recognized or properly allowed for. In other cases, responsibilities for implementation of specific activities has not been clearly defined.

The importance of the multi-year plan lies in its function in defining national strategic priorities and resource needs for the medium term in a framework that allows actions of donors to be coordinated. Through monitoring of its implementation, feedback will be obtained to allow essential fine-tuning or revision of strategies and activities.
Financing

No matter how excellent are the multi-year plans, they still have to be financed. To focus on this crucial aspect, GAVI set up a Financing Task Force, comprising a core group of partners from WHO, UNICEF, industry, developing countries, a development bank, the Children’s Vaccine Program, the Vaccine Fund and an outside expert. Consulting frequently and meeting quarterly, this group examines issues such as financial sustainability of immunization programmes and alternative financing arrangements, capacity building, strategies for vaccine development, and forecasting demand for and procurement of vaccine.

International immunization programmes have been successful, but their progress needs to be maintained. Through its task force GAVI aims to help to stimulate the improvement and expansion of existing immunization programmes. Some existing vaccines, such as those against hepatitis B, Hib disease and yellow fever, are underused, and new vaccines are being developed. As their use increases and as new antigens are introduced into vaccines, the overall costs of immunization programmes will increase, and newly introduced vaccines are generally much more expensive than later when production capacity and demand are high. The Task Force has created a “framework document” that lays out issues and options for sustainable financing with the aim of helping countries to identify adequate approaches. Self-sufficiency is, of course, the ultimate goal, but in the meantime countries need to be able to mobilize and use efficiently both domestic and supplementary external resources on a reliable basis in order to attain their performance targets for immunization programmes.

Three major steps needs to be taken: understand and specify the financial requirements, improve efficiency, and ensure reliable and adequate resources. The financial requirements will be predicated on the objectives set out in the multi-year plan, the budget originally drawn up, and funds expended during implementation and will need to be reconciled with costs inherent in the health system (e.g. personnel and logistics). Resources will be used most effectively when demand is optimized, the procurement of vaccine is most cost-effective (consider the 10-fold range in prices of hepatitis B vaccine – see Table 3), the efficiency of immunization services is maximized (for example through appropriate vial size, reduction of wastage and better delivery strategies), and health systems’ performances (including staffing issues) are improved. Not all countries need external support, and funding sources need to be assured in the public, private, domestic and, when appropriate, international sectors; in addition, the funds from these sources need to be available where and when needed. Ensuring resources will depend essentially on political commitment.

The Task Force is finalizing a set of fact sheets and briefing documents to facilitate financial decision making. These cover subjects such as social health insurance, cross-subsidies, loans (or mixed grants and loans) to purchase vaccines, mechanisms of funding such as revolving funds (such as that operated by the Pan-American Health Organization), UNICEF’s Vaccine Independence Initiative, user fees, the economics of vaccine production and sources of funding for immunization programmes (given that countries have a long history of successful acquisition of funds for vaccines).

Countries need to consider various priority areas. Can ways to increase the efficiency of programmes be identified? Can a greater part of the national budget be allocated to immunization programmes and a legislative basis for funding established? Can long-term financial commitments need to be negotiated? Should international procurement mechanisms for some vaccines, with all the attached complications, be considered? Should agreements to procure vaccine be long-term? Finally, have performance targets at sub-national levels been established (possibly with incentives as in the GAVI scheme)?

Table 3: Cost (in euro) per dose of hepatitis B vaccine for countries of the European Region of the World Health Organization for public market for 2001 (unless otherwise indicated) and for private market for 1999.

<table>
<thead>
<tr>
<th>Country</th>
<th>Cost per vaccine in euro - public market (2001) -</th>
<th>Cost per vaccine in euro - private market (1999) -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albania</td>
<td>0.64</td>
<td>3.18</td>
</tr>
<tr>
<td>Belarus</td>
<td>2.23 (2000)</td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>5.02</td>
<td>17.84</td>
</tr>
<tr>
<td>Bosnia and Herzegovina</td>
<td></td>
<td>27.89</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>1.79 - 1.62</td>
<td>30.72-38.6</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>3.68</td>
<td>10.25</td>
</tr>
<tr>
<td>Denmark</td>
<td>16.78 (1999)</td>
<td>23.36</td>
</tr>
<tr>
<td>Estonia</td>
<td>4.55</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td></td>
<td>10.21-10.67</td>
</tr>
<tr>
<td>Georgia</td>
<td>0.9/dose (10-dose vial)</td>
<td>0.96-2.56</td>
</tr>
<tr>
<td>Germany</td>
<td>27.55 (1999)</td>
<td>42.3</td>
</tr>
<tr>
<td>Italy</td>
<td>11.16 (1999)</td>
<td>18.97</td>
</tr>
<tr>
<td>Kazakhstan</td>
<td>1.39</td>
<td></td>
</tr>
<tr>
<td>Kyrgyzstan</td>
<td>0.84/monodose or 0.36/dose (10-dose vial)</td>
<td></td>
</tr>
<tr>
<td>Latvia</td>
<td>2.52</td>
<td></td>
</tr>
<tr>
<td>Lithuania</td>
<td>2.4</td>
<td>10.04</td>
</tr>
<tr>
<td>Moldova, Republic of</td>
<td>0.78/dose (10-dose vial)</td>
<td>11.15</td>
</tr>
<tr>
<td>Poland</td>
<td>8.22-9.04 (1999)</td>
<td>11.32</td>
</tr>
<tr>
<td>Romania</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>San Marino</td>
<td>7 (1999)</td>
<td>18</td>
</tr>
<tr>
<td>Slovakia</td>
<td>3.5</td>
<td>10.9</td>
</tr>
<tr>
<td>Slovenia</td>
<td>8.03</td>
<td>13.5</td>
</tr>
<tr>
<td>Spain</td>
<td>5.41 (1999)</td>
<td>9.84</td>
</tr>
<tr>
<td>Switzerland</td>
<td>13.61 (1999)</td>
<td>27.9</td>
</tr>
<tr>
<td>The Former Yugoslav Republic of Macedonia</td>
<td>12.78 for 300 doses</td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td>0.65/dose (20-dose vial)</td>
<td>16.51</td>
</tr>
<tr>
<td>Ukraine</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Uzbekistan</td>
<td>1.78/monodose or 1.09/dose (10-dose vial)</td>
<td></td>
</tr>
</tbody>
</table>

Note
1 At the moment of publication no information received from Andorra, Armenia, Austria, Azerbaijan, Federal Republic of Yugoslavia, Finland, Greece, Hungary, Iceland, Ireland, Israel, Liechtenstein, Luxembourg, Malta, Monaco, Netherlands, Portugal, Russian Federation, Sweden, Tajikistan, and Turkmenistan.
BREAK-OUT GROUPS: REPORTS

Group 1 – Albania, Bosnia and Herzegovina, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan and Uzbekistan

All the countries in this group, except Kazakhstan, are eligible for funding from the Vaccine Fund. All have good infrastructures enabling coverage with traditional EPI vaccines of 95% or more, indicating the feasibility of introducing new antigens into their immunization programmes. Five have introduced hepatitis B into their programmes, the exceptions being Tajikistan and Turkmenistan which plan to do so in 2002 and 2001/2002 respectively. Kyrgyzstan plans to introduce MMR in 2002 and Hib vaccine in 2003 and Albania is planning to introduce MMR in 2004, but otherwise new vaccines are not likely to be introduced soon, the exception for MMR being Bosnia and Herzegovina which introduced it in 1981.

Finance

Only Kazakhstan provides funds for all vaccines from its state budget. Although four countries (Albania, Bosnia and Herzegovina, Turkmenistan and Uzbekistan) provide funding for traditional EPI vaccines, they need extra support for new vaccines, and Kyrgyzstan, while seeking vaccine independence, also needs support. Tajikistan relies completely on donors for vaccine provision.

Training and technology

Training and technology were two areas identified as needing support. Short, clear educational materials were needed for training health-care workers including doctors, managers and other staff in institutions where immunizations are done. Vaccine wastage was a serious problem, with figures of doses lost ranging from 10% to 32%. Improved techniques and better equipment are called for. Weaknesses in the cold chain were identified; improvement would follow through evaluation of existing systems, upgrading of resources and monitoring. There should be a shift to auto-disable syringes but there was a general lack of modern equipment and weaknesses in sharps disposal. These problems should not, however, be obstacles to the implementation of policy.

Social mobilization

Advocacy for immunization was still needed at the level of the general population, including parents and families. More difficult would be to reach vulnerable groups and hard-to-reach populations such as migrants (whether forced or not, displaced populations or others).

Surveillance

General surveillance of hepatitis B needed to be improved, with better monitoring and evaluation of immunization coverage and impact. Systematic seroepidemiology would identify epidemic trends. Acute cases of hepatitis B should be verified by laboratory tests but such diagnoses should be subject to quality assurance; in other words there was a need for strong and well equipped laboratories with good management practices. Laboratory staff should have a manual for epidemiological surveillance of hepatitis B.

Group 2 – Armenia, Azerbaijan, Belarus, Georgia, Republic of Moldova, Russian Federation and Ukraine

Although numerically small, this group represented the largest total population in the region. Only Belarus and the Russian Federation are not eligible for funding from the Vaccine Fund, and because of their per capita gross national product their governments are expected to have the possibility of purchasing vaccine. Most of the other countries receive support for immunization programmes from donors.

Besides finance, the countries face several other challenges. These include the negative attitudes and perceptions of paediatricians and some other medical staff in some countries such as Armenia, a position that does not favour public acceptance of immunization programmes. The need was clearly identified for effective education and awareness programmes for both the general public and physicians. Some countries experienced problems with the cold chain, especially in its final links, through difficulties with transport and storage, especially where electricity supplies are fragile. As elsewhere, there was no single approach to disposal of sharps and waste management. Solutions
include provision of vaccine with safe injection equipment and single-use (auto-disable) syringes, but these remain to be introduced.

With regard to monitoring and data collection, the Russian Federation has instituted a method of gathering data from the private sector about immunization activities. Private physicians are not issued with licences to carry out immunizations if they do not undertake to submit data on those activities. Weaknesses in the diagnosis of viral hepatitis undermine the ability to monitor vaccine efficiency, although Moldova is an exception with its high rate of coverage supported by laboratory diagnosis, and in addition it was stated that all cases in the Russian Federation are confirmed by serological tests. Ukraine stressed that it had a good system of monitoring and evaluation.

Good vaccine coverage for routine immunizations in all seven countries bodes well for the introduction of new vaccines and epidemiological surveillance systems are in place. The overall conclusion for the countries in the group is that hepatitis B immunization needs to be made a strategic priority.

**Group 3 – Central Europe: Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Slovakia and Slovenia**

All countries have introduced hepatitis B and MMR immunization, while some have already introduced Hib vaccine into their programmes. All have a strong infrastructure, with resulting high immunization coverage rates. The most common structure is a national advisory expert committee and, in the absence of donor involvement, there are no Interagency Coordinating Committees as such. In all, the cold chain is strong and there is a high level of injection safety. No country has received external assistance in expanding its immunization programme and most find that they are paying a high price for hepatitis B vaccine compared with larger countries or those receiving vaccine through external agencies such as UNICEF.

**Major threats**

Apart from the universal problem of financial resources, the major threats to continued progress are two-fold. The first comes from the anti-vaccine movement. Recommended responses to its campaigns and advocacy against immunization included the need for WHO to concentrate efforts on countering this trend and for support to be given to health-care workers, including physicians. In this regard, both the media and the Internet can be used effectively. Information, documents and other resources need to be available in local languages. Other professionals should be engaged in developing strategies for promoting immunization. The second threat comes from the policy shift from mandatory to recommended (or voluntary) immunization, especially as generations grow up with no familiarity or knowledge of the dangers of vaccine-preventable diseases. Again, advocacy and information play a major role.

**Financing**

The introduction of new vaccines needs policy decisions which require multilateral support (including that from WHO). These include the need for catch-up immunization against hepatitis B of adolescents and teenagers on a large scale in the face of growing epidemics in these groups, as well as the switch to new formulations, for instance from oral to inactivated polio vaccine and from cellular to acellular pertussis in DTP, and the question of whether to introduce new antigens into immunization programmes. Although Hib vaccine is available, countries may not have the epidemiological evidence to support the introduction of Hib immunization and to monitor its impact. Similarly, the introduction of pneumococcal and other antigens (such as tick-borne encephalitis virus) needs full consideration.

Some of the countries face regulatory or licensing barriers to the global market. The small size of national markets places limits on a country’s negotiating powers over price of vaccines. Some countries have legislation requiring open procurement policies, thereby closing such approaches as procurement through UNICEF. Others have strict licensing requirements. Any new procurement model would need careful consideration.

**Monitoring and evaluation**

In some of the countries lack of outcome and operational targets impedes monitoring and evaluation of immunization programmes. All rely on routine EPI health information systems, supported by serological surveys. Some countries such as Estonia have legislation mandating reporting from both the
public and private sectors. Serological testing for hepatitis A and hepatitis B viral markers is universal in the countries of the group, but diagnosis of hepatitis C is still made by exclusion in some countries (although some do test serologically). Laboratory testing capability is not a problem, in principle.

The cold chains are secure and injection safety is strong, with all countries using disposable syringes.

**Sustainability**

No donor support is expected, meaning that national funds have to be used. The publication of the ranges of prices for vaccines would help with both planning and negotiation (Table 3).

A major hurdle is the enactment of legislation authorizing the introduction of new vaccines. Multilateral expert cooperation and advocacy are greatly needed to help to overcome this obstacle. Furthermore, it would be valuable for influencing policy if WHO were to publish benchmark health and economic data.

**Hepatitis C**

Screening and risk reduction are the two major elements for prevention and control of hepatitis C. Blood is screened for viral markers. Programmes to reduce risk include needle exchanges, promotion of safer sex, and the application of standard precautions in health-care settings. Screening is also applied to health-care workers and patients such as those with cirrhosis and transplant recipients.

**Advocacy**

Few groups outside government advocate for immunization. In Lithuania a special committee on hepatitis B was set up, but it has no budget. In Poland several nongovernmental organizations include hepatitis B on their agendas, but none has it as a specific focus. Slovenia has a scientific advisory board. In general there are no strong outside interest or advocacy groups.

**Conclusion**

Existing programmes are strong and economically secure. There is a need for increased intergovernmental (WHO) and international advocacy – to secure greater political commitment, to influence and shape policies on procurement and licensing, to gain technical support for the introduction of new antigens into immunization programmes and to counter the activities of anti-vaccine groups. (It was noted that WHO has developed extensive materials and a media pack for this purpose.)

**Group 4 – Bulgaria, Croatia, Romania, The former Yugoslav Republic of Macedonia and Turkey**

None of the five countries in this group is eligible for support from the Vaccine Fund and all are using their own resources to buy vaccines. All except The former Yugoslav Republic of Macedonia and Croatia have universal newborn or infant hepatitis B immunization programmes. The countries have infrastructures that ensure high coverage for routine immunizations (although in one country coverage was described as sub-optimal) and surveillance systems function well.

Hib vaccine has not yet been introduced by any of the five countries, although two are planning its introduction; finance is the main constraint. In 1997-99 Bulgaria conducted a population-based study of disease burden due to Hib infection which revealed prevalence rates of 6.1/100 000 among children under 5 years of age and 18.2/100 000 among infants aged 6-11 months.

**Challenges**

Although donors and international organizations played an initial role in introducing hepatitis B immunization in some countries, financing remains the main obstacle. Three countries use open-tender procurement for the vaccine but Romania obtains supplies through UNICEF and Croatia negotiates directly with the manufacturers. Croatia faces legal constraints as a consequence of the inflow of humanitarian aid. The price paid for vaccine differs 10-fold between the five countries, from $0.60 to $6.00 per dose, the lowest prices being explained by the large volume of doses being purchased: 11 million by Turkey. Its immunization programme includes about 4 million doses for universal childhood immunization and about 6 million for people considered to be at high risk, including health-care workers, medical students, dialysis patients and people with chronic liver disease, injecting drug users,
prostitutes, homosexual men and prisoners. The potential for savings was illustrated for the case of Bulgaria; for its 130 000 doses it pays $2.00, but if it paid the lowest price of $0.60 per dose it could save $182 000 in vaccine purchase costs.

For the past decade UNICEF had provided EPI vaccines to The former Yugoslav Republic of Macedonia, whose per capita gross national product lies above the cut-off for the Vaccine Fund and which receives no donor support for immunization. This year the government started buying those vaccines, but for the introduction of hepatitis B vaccine, which is supported by epidemiological evidence, it has appealed to UNICEF and donors for assistance.

**Monitoring and evaluation**

Although there is good laboratory and clinical surveillance for acute hepatitis B in the countries, programmes lacked outcome or operational targets. Good surveillance data will enable countries to measure the impact of immunization of childhood hepatitis B rates. Immunization coverage is monitored on the basis of administrative data and those derived from surveys. An obstacle to good monitoring and evaluation is the fact that case definitions and case-confirmation procedures are not standardized or well established in all the countries. Moreover, the purchase of diagnostic materials by governments adds to the cost of the programmes.

With all countries giving hepatitis C a high priority, the high technical laboratory capacity enables testing for hepatitis C viral markers. Blood is screened and identification of those people at high risk forms part of the control measures.

**Cold-chain capacity**

Croatia and Romania have enlarged their refrigeration capacity at various levels to accommodate the introduction of hepatitis B vaccine whereas that in Bulgaria and Turkey appears to be sufficient. Whereas the cold chain itself in The former Yugoslav Republic of Macedonia has the capacity to handle hepatitis B vaccine, that in Bulgaria needs updating.

**Injection safety and waste management**

Investigation of transmission of HIV in Romania’s early epidemic of AIDS revealed problems with injection safety, and donors responded by supporting appropriate programmes. These included injection safety packages, which proved to be very useful. All countries are now using disposable syringes but auto-disable syringes are not available. While the management of waste is improving and is being incorporated into national legislation, problems remain and the responses have been ad hoc.

**Advocacy**

Both nongovernmental and professional organizations are active in promoting awareness and support for hepatitis B immunization. For instance, the Croatian Medical Association is working to improve dialysis facilities and procedures. Turkey has a nongovernmental organization specifically devoted to the prevention of hepatitis B. In Bulgaria a nongovernmental organization is providing hepatitis B immunization to schoolchildren, and in Croatia a similar organization was recently formed with the aim of advocating for the prevention and control of hepatitis.

**Conclusions**

Inevitably, financing remains the biggest obstacle to introducing new vaccines, with little or no donor support, whereas on the other hand investigation of different purchasing mechanisms holds the prospect of considerable economic savings. High immunization coverage needs to be sustained, especially with the introduction of new vaccines. While hepatitis C is being recognized as needing attention, the burden of disease presented by Hib needs to be determined and possibilities for support for the introduction of Hib vaccine explored.
CONCLUDING REMARKS AND PROPOSED NEXT STEPS - A SUMMARY: Emerging themes and results

Progress since Siofok
With the objective of putting hepatitis B prevention on the political agenda of countries in central and eastern Europe and the Newly Independent States, the Viral Hepatitis Prevention Board, in collaboration with WHO and CDC, organized a meeting in Siofok, Hungary, in 1996 for national immunization managers, infectious disease control specialists and viral hepatitis experts from each of these countries (1,2). At that time, apart from the high levels of endemicity, the burden of disease and the local epidemiology were poorly known or understood, and only five of the 25 countries concerned had implemented universal hepatitis B immunization programmes: Albania, Bulgaria, Poland, Republic of Moldova and Romania. Economic constraints were widely cited as the reason for this low number.

Since then, extraordinary progress has been made towards the prevention and control of hepatitis B in these countries (Table 1). Five years after the Hungary conference, the Viral Hepatitis Prevention Board, in collaboration with CDC, the Children’s Vaccine Program at PATH, GAVI, WHO and UNICEF, reviewed the previous initiative and organized a conference on the strengthening of immunization systems and the introduction of hepatitis B vaccine in central and eastern Europe and the Newly Independent States, which was held in St Petersburg, Russian Federation, 24-27 June, 2001.

Compared to the situation in 1996, the country-specific epidemiology is much better understood. In addition, the cost of the vaccine has decreased, and the presence of partner agencies, such as GAVI and its members, has accelerated and facilitated the process of implementing affordable and sustainable programmes. The GAVI Regional Working Groups were established in each WHO region to provide technical assistance and a link to GAVI. The Alliance encouraged the countries of the regions to apply for support. In the WHO European Region 11 countries meet the criteria for application for support from GAVI/the Vaccine Fund: Albania, Armenia, Azerbaijan, Bosnia and Herzegovina, Georgia, Kyrgyzstan, Republic of Moldova, Tajikistan, Turkmenistan, Ukraine and Uzbekistan.

Just before the St Petersburg conference, the Board of GAVI announced the decision of its fourth round of applications to the Vaccine Fund. Of the four countries that applied for support for immunization services, three applications were approved and one country was invited to resubmit. Of the 10 applications for introduction of universal hepatitis B immunization, nine were approved – five with conditions or requests for clarifications – and one country was invited to resubmit. In the seven countries where programmes will start in 2001-2002, some 1.5 million children will be immunized against hepatitis B, with 5.5 million doses of vaccine at an overall cost of US$ 2.85 million.

This successful outcome resulted from countries drawing up a multi-year plan for immunization. Each of these countries has a functioning Interagency Coordinating Committee and underwent an assessment of infant immunization services.

At the beginning of 2001, a total of 22 countries, including five categorized as highly endemic and six with intermediate endemicity, were implementing universal hepatitis B immunization programmes. A further four countries with high endemicity but no universal hepatitis B immunization programmes will soon implement such programmes. Thus, by the end of the year 2002, 26 of the 28 countries in this part of the WHO region will have universal immunization programmes. Already, high rates of coverage for hepatitis B immunization are being achieved in many countries and incidence rates of new cases of hepatitis B are declining in some areas. There is the full expectation that hepatitis B vaccination will soon be part of routine infant immunization programmes in all countries of the region.

Emerging themes and results

Coordination and planning
Country experiences reported at the St Petersburg conference underline the value of the Interagency Coordinating Committees (ICC). These committees are not monolithic but flexibly respond to local conditions, needs and circumstances, bringing in appropriate partners, with the goal of making efficient and effective use of available resources. Every country in the region was encouraged to apply this concept as a public health tool. The reported experience from Kyrgyzstan and other countries showed that these committees were of great value not just for hepatitis B and other vaccine-preventable
diseases, but also for the overall strengthening of immunization services and more generally other areas of public health, even health system reform.

Tools exist for helping countries determine the financing of multi-year plans and to prepare for sustainable financing, that is mobilizing and efficiently using domestic funds and obtaining supplementary external funding on a reliable basis. Crucial questions were identified, for instance about real costs and the efficiency of programmes. The discussions at the conference highlighted the broad differences in cost of vaccine. The example of Turkey's negotiation and tender process for 11 million doses of hepatitis B vaccine showed how countries can reduce that cost.

A clear need emerged to investigate different mechanisms for procurement of hepatitis B vaccine, such as national or international cooperation, and models such as revolving funds. The example of the Pan-American Health Organization (PAHO) would be worth investigating (4).

Besides hepatitis B, hepatitis C is a serious epidemic problem. Further evidence of its links with injecting drug use was presented in a study from Moscow. Work in other countries in the region showed the high burden of disease due to hepatitis C and a higher attributable fraction of unsafe injections for hepatitis C than for hepatitis B or HIV infection. An associated need in such epidemiological studies is to standardize terminology (for instance "adolescents") and case definitions for viral hepatitis.

A report from Kyrgyzstan demonstrated the poor validity of clinical diagnosis: serological testing is needed. The substantial burden of hepatitis A was revealed when such testing was done. This national report also underlined the value of sentinel surveillance when resources are limited.

**Programmatic aspects**

For countries with high or intermediate endemicity, it was recommended that children should be immunized against hepatitis B at birth, with subsequent immunizations (monovalent or combination) given with DTP during the traditional EPI schedule (4). A clear issue needing further examination is the use of combined vaccines, which cannot be given at birth. There was general support at present for the Armenian decision to opt for the use of monovalent hepatitis B vaccines for newborns.

With implementation of prevention and control programmes, incidence rates of hepatitis B infection are falling and increasing numbers of children are protected, but programmes aimed at adolescents and young people at risk are indicated as well.

Different epidemiological and socioeconomic patterns demand different prevention and control strategies, but it was clearly shown that hepatitis B prevention programmes can be integrated with similar programmes – for example, those for HIV/AIDS.

The three elements of evaluation of a hepatitis B immunization programme are: continuous monitoring of immunization coverage - supplemented by coverage surveys when necessary; seroepidemiological surveys to identify the prevalence of carriers; and surveillance for acute hepatitis B. When hepatitis B programmes are integrated, the impact needs to be evaluated and the methods used will differ from those for other vaccine-preventable diseases. For instance, seroprevalence (of anti-HBc and/or HBsAg) in children is a crucial indicator.

There are epidemics of hepatitis B, hepatitis C and HIV among injecting drug users in many countries in the region. The epidemiological studies have resulted in an increasing recognition of nosocomial transmission and unsafe injections as major routes of hepatitis B viral infection as well as of hepatitis C virus and HIV. Much work remains to ensure the safety of medical settings, including those related to dentistry and outpatient clinics, the adoption and enforcement of standard precautions, and the provision and proper use of safe equipment. Romania reported its experience in designing and implementing a progressive programme to improve injection safety. A report from Poland exemplified the substantial reduction of the high risk previously associated with medical interventions there.

The World Health Organization reinforces the necessity of safe injections through its Safe Injection Global Network – SIGN – and provides support through, for instance, outlines of best practice and tools for rapid assessment and responses. Another emerging theme was the need for a transition to auto-disable syringes.
The management of medical waste, such as disposal of sharps, is another area to which much greater attention needs to be paid. In some countries, the need to assess and upgrade the cold chain came across as a clear message.

Surveillance, too, was a common theme. As a result of surveillance in Ukraine during the recent outbreak of diphtheria weaknesses in the existing health information system and management were identified. With support from the United States Agency for International Development the country radically reformed this system and its management. The new system offers a good model for monitoring performance, forecasting needs and identifying weaknesses; information systems need to and can become much more effective management tools. The result is that more children are being immunized and in a more timely manner. The process of procuring vaccines in the country has been re-centralized.

Overall, surveillance for hepatitis, with standardized definitions and procedures, needs strengthening. Laboratory support for diagnosis of hepatitis is lacking and also needs strengthening and capacity building. A huge need exists for training, with documentation and other information tools, at all levels in immunization programmes and for surveillance.

In considering underused or potential new vaccines, it was recognized that the burden of disease due to infection with *Haemophilus influenzae* type b is not well established.

**Cross-cutting themes**

Several cross-cutting themes emerged, such as the necessity of political commitment and the power of advocacy and education in preparing the ground – “social mobilization”. The power of the media, in both positive and negative ways, was apparent from several interventions. Whereas the media can be useful advocates for immunization programmes, in some countries the media have attacked hepatitis B vaccine with misreporting and misleading information, and anti-vaccine groups are becoming increasingly active. Failures of the scientific media were cited in the case of studies on the claimed adverse effects of hepatitis B vaccine. Compelling data from recent comprehensive studies were presented on the lack of a causal link between hepatitis B immunization and multiple sclerosis. The reassuring message is that hepatitis B is one of the safest vaccines ever produced.

Building on existing systems that work was another message, together with the need for national – or even regional – reference centres and networks (e.g. for hepatitis C).

Despite this progress in implementation of immunization programmes, some countries remain without universal infant immunization programmes or those aimed at adolescents and the strategies for use of hepatitis B vaccine are not always clear. It was abundantly clear that countries in the region are still experiencing severe resource constraints. These are compounded by ineffective procurement processes that lead to relatively high and inconsistent hepatitis B vaccine costs. Even when the immunization programmes are introduced, financial sustainability will not be simple and needs to be actively planned for.

Even though the burden of disease and the need for immunization are high, the countries of the region lack effective advocacy at the global level. Their voice needs to be heard by decision-makers, especially given the relatively small pool of donors who are interested in immunization and the spread of anti-vaccination propaganda. Although a functioning Interagency Coordinating Committee is a prerequisite for eligibility for application for support by GAVI through its Vaccine Fund, not all the countries in the region have such well-functioning committees at national level.

**Feedback from the country workshops**

The conference elicited a wealth of information in response to a pre-circulated questionnaire about progress in implementing hepatitis B programmes since Siofok (see Table 2). Some 22 universal programmes of immunization have been implemented, including one aimed at children aged 7 years (Slovenia) and two others at adolescents only (Croatia and Hungary). Azerbaijan, Russian Federation, Tajikistan, and Turkmenistan plan to implement programmes by the end of 2002. The former Yugoslav Republic of Macedonia plans to implement its universal programme in 2002-2003. Only Yugoslavia has no planned programme.
**Global health context**

The conference and the vaccine programme developments in the countries of the region come at a time of broadening partnerships and when health is rising up political agendas and increasing international and United Nations attention is being paid to strengthening health systems. Prevention and control of viral hepatitis – “more than just B” – need to be high on those agendas.

**Proposed next steps**

There should be another conference in two years’ time to ensure that in those countries receiving support from GAVI resources are being well used and plans for financial sustainability are progressing, as well as to monitor the situation in other countries. It should also consider the strategic planning process for prevention and control of not just hepatitis B but hepatitis C, *H. influenzae* type b disease and other vaccine-preventable diseases in the region.

The Regional GAVI Working Group should coordinate the provision of technical support to countries and should act as a liaison point for national Interagency Coordinating Committees for the mobilization of additional resources. All countries, even those that are not eligible for support from the Vaccine Fund, should go through a process of assessment of infant immunization services, preparation of a multi-year plan and establishment of such committees.

In terms of procurement of vaccines such as those against hepatitis B and Hib disease, options for more rational procedures should be explored, in particular for countries with small populations. One such approach could well be an innovative step for the countries of the region modelled on the regional mechanism of PAHO and its revolving fund. It was agreed at the conference that the Regional GAVI Working Group should be mandated to study the possibilities and implications of such a revolving fund in the region. The limited funding and partner support to countries in the region is an issue that should further be raised and discussed by the GAVI Board.

Financial sustainability of immunization programmes, including those for hepatitis B and Hib vaccines, should receive the highest priority in the region, with all countries and partners focusing their attention on the subject.

Safe injection is a major goal. All countries in the region should work with WHO and its Safe Injection Global Network (SIGN) and other partners to reduce nosocomial transmission of blood-borne pathogens. Next steps should include a move to auto-disable syringes, training and social mobilization.

Health information systems throughout the region need to be upgraded and used effectively as management tools, such applications including management of immunization programmes. Countries in the region should study the possibility of expanding or adapting the Ukrainian information management system. Within countries, transparent monitoring of immunization coverage at district level should be reviewed monthly and immediate action taken when reports are missing or data are inconsistent with those in previous reports. Similarly, surveillance data should also be used for active management of immunization programmes.

Regionally there should be support for countries to undertake assessments of the burden of Hib disease and to coordinate that work with the research and development group of GAVI.

Finally, as a cross-cutting activity, advocacy is needed. Countries need to engage in social mobilization in favour of immunization programmes, encouraging and supporting the media in that task if necessary. In particular, countries need to be supported in countering the activities of anti-vaccine groups; possible mechanisms include the holding of seminars and the provision of information on a web site.
References [Also appear as footnotes]


3. GAVI web site: [www.vaccinealliance.org](http://www.vaccinealliance.org)


5. SIGN web site: [www.injectionsafety.org](http://www.injectionsafety.org)


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