



VIRAL HEPATITIS

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CONTENTS

EDITORIAL	1
MEETING NEWS	2-13
Israel implements universal hepatitis A immunization	2
Catalonia, Spain introduces mass hepatitis A vaccination programme	3-4
HA immunization recommended for children in 11 states in the US	5-6
Mass hepatitis A vaccination considered for Puglia, Italy	7
Cost of an outbreak in Puglia, Italy high to individuals and society	8
Selective childhood immunization considered in the Netherlands	9
Impact of media coverage on the uptake of hepatitis B vaccine ...	9-10
Risk-benefit analysis of HB vaccine	10-11
Current recommendations on HAV control in selected countries in Europe	12-13
• Belgium	12
• Germany	12
• Greece	12
• Italy	13
• Spain	13
• Switzerland	13
OVERVIEW OF PREVIOUS ISSUES OF VIRAL HEPATITIS	14-15
VHPB CONSENSUS STATEMENT	16

This edition of *Viral Hepatitis* is prepared from material presented at the Viral Hepatitis Prevention Board meeting held 25-27 March 1999 in Nice, France.

EDITORIAL

The epidemiology of hepatitis A is closely related to the level of economic development in a region; as living standards improve, disease incidence and prevalence decline. At the same time, the average age of exposure and subsequent infection increases. These changes in the epidemiological pattern have been taking place in all Western European countries in recent decades, first in Northern Europe and most recently in the countries of Southern Europe.

The implications of this epidemiological shift are important. Because the severity of clinical disease is directly related to the age of infection, the consequence of infection among older age groups is an increase in clinical illness and morbidity. In addition, natural immunity in the population is decreasing, particularly among children, adolescents and young adults, and the number susceptible individuals overall is on the rise, creating a situation in which outbreaks of hepatitis A can occur.

The Viral Hepatitis Prevention Board met March 25–27, 1999 in Nice, France to review the situation in Europe and to discuss whether hepatitis A vaccine should be included in universal vaccination programmes. Several countries are considering or have decided to begin mass vaccination against HAV, and these programmes and the rationale behind them are covered in this issue of *Viral Hepatitis*. We also revisit the subject of controlling outbreaks of hepatitis A in the community and have updated our general recommendations on controlling the spread of hepatitis A virus (see *Viral Hepatitis*, October 1997, Volume 6 – Number 1).

Another topic we have come back to here is the persistent concern in France over the safety of the hepatitis B vaccination and the possibility that it may be linked to new cases or flare-ups of multiple sclerosis. Although no scientific data support the idea that HB vaccine causes or exacerbates MS, the uptake of HB vaccine and of other vaccines as well has decreased significantly in France. Fortunately, the negative impact of the media coverage has been primarily limited to France and here we look at how other countries have addressed this sensitive issue and maintained the public's faith in universal immunization programmes.

It should be reiterated here that immunization is the most medically effective and cost-effective means of controlling hepatitis B, that the vaccine has been shown to be safe in clinical trials, and that the real risk of hepatitis B infection outweighs any claimed risk of MS.

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REPORT ON THE VHPB MEETING IN NICE, FRANCE, 25-27 MARCH, 1999.

Israel implements universal hepatitis A immunization

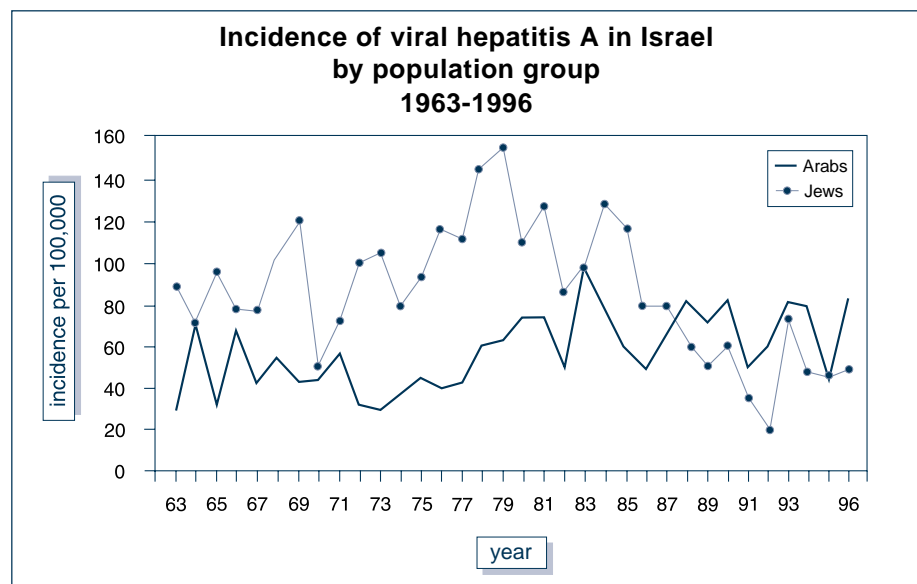
A universal hepatitis A immunization programme targeting 18-month-olds was implemented in Israel starting July 1, 1999. Israel has had a successful programme of universal hepatitis B immunization for eight years and as such very few cases of HB are reported there; currently hepatitis A accounts for 96% of all cases of viral hepatitis in the country.

Like other Mediterranean countries, Israel is witnessing a dramatic shift in hepatitis A epidemiology. Information from military recruits indicates a steady decline in seroprevalence; in 1977 64% of recruits showed markers of past infection; in 1996 that figure was 38%. In selected segments of the Arab population, the change has also come about recently, so that today the Jewish and Arab populations show similar epidemiological trends. Presently, the age group with the highest incidence rate is the 5-9 year olds, who show an incidence rate of 3/100,000.

In addition, outbreak control has proved problematic. In a 1996 outbreak in an Arab village an estimated 10% of the population were affected. Immune globulin was ineffective in stopping the outbreak, although later intervention with vaccine aborted the outbreak. During the epidemic, the majority of children infected were under six, although adults are also affected during these periods. The disruption to individual lives caused by infection and the rise in cases of fulminant hepatitis A influenced the decision to implement universal hepatitis A vaccination.

The vaccination schedule for the universal vaccination programme will be as follows: the first dose of vaccine will be delivered at 18 months of age and a booster dose will be given six months later. The rationale behind this schedule is one of practicality: children of this age are still under the care of the national health system and are scheduled for routine visits. Cost savings is another factor; the cost of delivering the vaccine is often greater than the cost of the vaccine itself and simultaneous scheduling of routine visits and vaccine delivery can significantly reduce the cost of a vaccination programme, although currently, HAV vaccines are still relatively expensive.

As presented by Prof Daniel Shouval, Hadassah University Hospital, Jerusalem, Israel.



Catalonia, Spain introduces mass hepatitis A vaccination programme

One of the first to do so, Catalonia, Spain began a programme of universal hepatitis A immunization, delivered in conjunction with its long-standing and successful hepatitis B immunization programme. The school-based immunization programme targets 12-year-olds.

Catalonia is one of 19 autonomous regions within Spain. When choosing to institute a mass hepatitis A vaccination programme, to be implemented along with the mass hepatitis B programme already in place in the region, the public health authorities of the region took a number of factors into consideration:

- the characteristics of the vaccine;
- the epidemiology of the infection;
- the cost-benefit of immunization;
- the feasibility of the programme;
- the level of public acceptance of vaccination.

The immunogenicity, safety and protective efficacy of the hepatitis A vaccine are well documented in clinical trials. Additionally, the vaccine appears to provide long-term immunity against infection.

In the past, hepatitis A was considered a benign, self-limiting disease which rarely gave rise to complications. This picture is generally true in infections in early childhood, where few cases are clinically apparent and infection is usually benign; among adults, however, the picture is very different. In children under five years of age, 80–95% of hepatitis A infections are subclinical, while in adults the pattern is reversed, with 75–90% of infections being clinical. Infection can lead to fulminant hepatitis and death, with case fatality rates found to be 0.1% among those under 14 years of age, 0.3% in the 15–39 year age group, and 2.1% in the over 40 age group.

In Catalonia, hepatitis A affects mainly children and young adults, and its incidence in the region is greater than all other types of viral hepatitis combined. Over 50% of cases of viral hepatitis reported through the compulsory notification system are due to hepatitis A virus. In recent years, reported morbidity has been around 360 cases per year, or approximately 6/100,000 population. It is estimated, however, that the true rate of morbidity is between 5 and 10 times greater than the reported cases. Additionally, there is no specific treatment for hepatitis A infection.

Hepatitis A virus is transmitted via the faecal-oral route and the incidence and age of infection are closely related to the levels of hygiene and sanitation. Regions are characterized

as having high, intermediate or low endemicity. In areas of high endemicity, the majority of cases occur in infancy and are asymptomatic, with the result that the majority of the population above 10 years of age possess protective antibodies.

In areas of low endemicity the incidence of infection among infants and children is low, and the proportion of susceptible, young adults is higher.

Catalonia, like many other regions in the Mediterranean, is an area of intermediate endemicity. Rapid improvements in sanitation have drastically reduced the level of HAV circulation among children. In these regions, the prevalence of anti-HAV antibodies is low in childhood but increases rapidly during adolescence and young adulthood.

Infection in childhood is very low in the region (less than 5% of those under 15 show markers of infection) but increases rapidly among adolescents and young adults, to such an extent that the majority of the population over 45 show evidence of antibodies. Hepatitis A infection among adolescents and adults is associated with higher morbidity and mortality than childhood infections.

Seroepidemiological surveys show a clear reduction in the prevalence of infection in those under 45 years of age. It can be predicted that this trend will continue, as has been the case in Northern Europe, the United States and Japan. It is likely that in the future Catalonia will be a region of low endemicity, giving rise to an increase in the proportion of susceptible people followed by an increase in clinical infections and case fatality rates.

In Catalonia, risk factors associated with a positive HAV serology include: personal contact (31%); a connection with a day-care centre (8.7%); consumption of raw fish or contaminated water (4.5%); travel to an endemic area (4.3%); homosexual activity (3.7%). In 47.8% of cases, however, the risk factor is unknown.

In 1995, when the hepatitis A vaccines became available in Spain, the Vaccination Advisory Committee of Catalonia initially recommended vaccination of high-risk groups, including international travellers, homosexual men, IV drug users, sewage workers, people exposed to non-human primates, day-care workers, food handlers, individuals with an increased risk of fulminant hepatitis, and those living or working in institutions.

In 1998, the Committee revised its policy, adopting a strategy of universal vaccination of 12-year-olds in a school-based programme while continuing to vaccinate risk groups. The programme was introduced in the 1998–1999 school year.

The decision to implement universal immunization was supported by a number of factors:

- The impact of selective vaccination policies is limited.
- The impact of universal vaccination programmes of pre-adolescents on clinical case incidence is immediate.
- Mass vaccination affords the potential for elimination of the disease.
- The combined hepatitis A+B vaccine is now available.
- The school-based hepatitis B vaccination programme of adolescents is highly effective, with high coverage rates.
- The programme offers the potential for reducing the cost of delivering HA vaccine to high-risk age cohorts.

As was the case with the hepatitis B vaccine, the potential impact of a strategy of immunizing risk groups has limited impact. Only a strategy of universal vaccination can significantly reduce the number of HAV infections in Catalonia. Using available data on seroepidemiology of hepatitis A in Catalonia, it is possible to predict that universal vaccination of 12-year-olds will lead in the short- and medium-term to a significant reduction in the incidence of disease in the population.

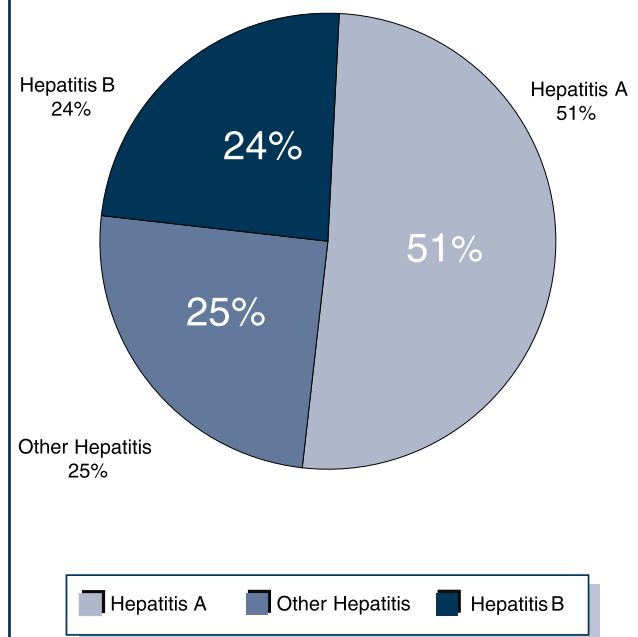
Furthermore, as there is no non-human reservoir and because hepatitis A infection does not become chronic, universal vaccination has the potential to eliminate the disease from a community or country, or even eradicate it from the world as was the case with smallpox.

Universal adolescent hepatitis B vaccination has been a success in Catalonia. The programme has been in effect since 1991 and is now well established, with coverage rates reaching about 90%. Since the programme was implemented, the impact on the incidence of infection has been considerable; in the 10–19 year-old age group incidence rates have decreased by 80%. Similar reduction rates are expected for hepatitis A. Furthermore, because the infrastructure for the HB immunization programme is already in place and the combined HA+HB vaccine is now available, the cost of the new initiative is very low, the only differential being in the price of the combined vaccine, versus the price of the monovalent HB vaccine. The pilot programme was started in 1998–1999 and a programme evaluation is planned in three years.

Reported hepatitis A morbidity by age in Catalonia, 1991-1997 (reported cases)

Age group	Number of cases	Percent
<10	703	23.54
10-19	726	24.31
20-29	870	29.14
30-39	413	13.83
40-49	97	3.25
>50	97	3.25
Total	2,986	100.00

Distribution of reported viral hepatitis cases in Catalonia (1990-1997)



As presented by Prof Lluís Salleras, Department of Health and Social Security, Barcelona, Spain.

References:

1. Salleras L, Bruguera M, Vidal J, Taberner JL, Plans P, Jiménez de Anta MT, Rodés J. Cambio en el patrón epidemiológico de la hepatitis A en Cataluña (España). *Med Clin (Barc)* 1992; 99:87-89.
2. Bruguera M, Salleras L, Plans P, Vidal J, Navas E, Domínguez A, Batalla J, Taberner JL, Espuñes J. Cambios en la seroepidemiología de la infección por el virus de la hepatitis A en Cataluña en el período 1989-1996. Implicaciones para una nueva estrategia vacunal. *Med Clin (Barc)* 1999; 112:406-408.
3. Salleras L, Bruguera M, Buti M, Domínguez A, Vidal J, Navas E, Batalla J, Garrido P, Taberner JL, Esteban R. Hepatitis A vaccination policy in Catalonia (Spain). *Vac Invest Pract* 1999 (in press).

HA immunization recommended for children in 11 states in the US

The Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) recommended in February 1999 that children living in states, counties and communities with consistently elevated hepatitis A incidence should be routinely vaccinated. This includes areas where the average annual hepatitis A incidence rate during 1987-1997 was at $\geq 20/100,000$ population (approximately twice the national average).¹

The 11 states covered under the recommendation are Arizona, Alaska, California, Idaho, Nevada, New Mexico, Oklahoma, Oregon, South Dakota, Utah and Washington. The ACIP advises routine vaccination of children living in these states, and in other areas with similar incidence rates.

These areas were selected for routine vaccination because they had consistently elevated rates of hepatitis A, even between outbreaks. The eleven states included in the recommendation represent only 22% of the US population, but approximately half of all cases reported yearly during 1987-97 occurred among residents of these states.

The ACIP is also recommending consideration of routine vaccination of children living in states, counties, and communities where the average rate of hepatitis A during 1987-97 was $\geq 10/100,000$ but $< 20/100,000$. These states include Missouri, Texas, Colorado, Arkansas, Montana and Wyoming.

In areas where routine vaccination is recommended, various implementation strategies can be considered. These include vaccinating one or more single age cohorts of children or adolescents, vaccination of children and adolescents in selected settings (e.g., day care) or vaccination of children and adolescents over a wide range of ages in a variety of settings, such as when they seek healthcare for other purposes.

The ACIP came to its recommendation after evaluating the impact of the previous HA control strategy on overall hepatitis A incidence.² This strategy involved routine vaccination of persons at increased risk of hepatitis A, or its adverse consequences, and of children living in communities with the highest hepatitis A rates.

In communities with intermediate rates, from which the majority of hepatitis A cases are reported, vaccination was to be considered to control communitywide outbreaks, with subsequent ongoing routine vaccination of children.

It was determined that continued implementation of this strategy would not result in vaccination of persons in most areas with consistently elevated hepatitis A rates, and therefore would have only a limited impact on the incidence of hepatitis A in the United States.

Implementation of routine childhood vaccination in communities with high hepatitis A rates has been largely successful in controlling and preventing hepatitis A in these communities when relatively high first-dose vaccination coverage of preschool and school-age children is achieved and routine vaccination of young children is sustained.

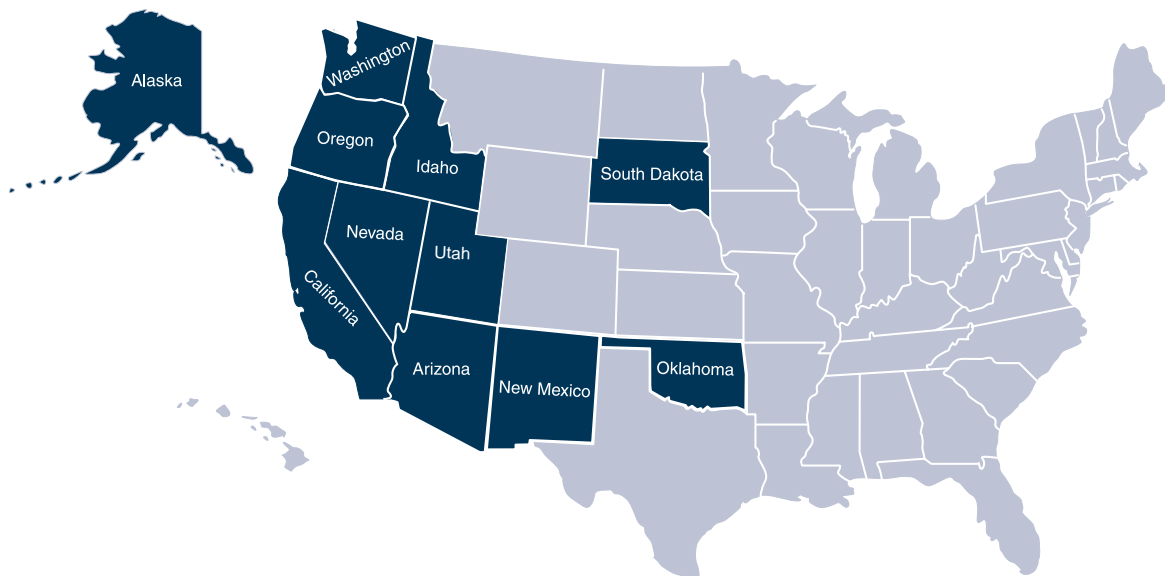
However, in communities with intermediate hepatitis A rates, results of vaccination programmes to control outbreaks have been variable for a number of reasons. First, first-dose vaccination coverage of children has been generally low. Second, the vaccination programmes often have not been implemented until the outbreak is well underway. Finally, routine vaccination of children has usually not been sustained after the outbreak subsides. In general, the impact of these programmes has been modest, and often limited to reducing incidence in the vaccinated age groups, which may not represent the majority of cases.

Average hepatitis A incidence rates, percent reported cases, percent population, and birth cohort size: states with average rate $\geq 20/100,000$ population, 1987-1997*				
State	Rate (<i>per 100,000</i>)	Cumulative % cases	Cumulative % population**	Cumulative birth cohort***
Arizona	48	7	2	70,846
Alaska	47	8	2	81,524
Oregon	40	12	3	123,361
New Mexico	38	14	4	150,952
Utah	32	16	5	189,231
Washington	30	21	7	266,589
Oklahoma	24	24	8	312,292
South Dakota	24	25	8	322,799
Nevada	21	26	9	346,710
California	21	49	21	914,640
Idaho	20	50	22	932,166

* The overall US rate during 1987-1997 was 10.8/100,000 population - ** 1997 Estimate, US Census - *** 1994; National Center for Health Statistics

The ACIP recommendation states:

Routine childhood hepatitis A vaccination is the most effective way to reduce hepatitis A incidence nationwide over time. Since licensure of hepatitis A vaccine in 1995, this strategy has been implemented incrementally, starting with the recommendation of the ACIP in 1996 to vaccinate children living in communities with the highest rates of infection and disease. The updated recommendations represent the next phase of this hepatitis A immunization strategy. Vaccination of children living in states and communities with consistently elevated rates of hepatitis A will provide protection from disease and is expected to reduce the overall incidence of hepatitis A.

The implementation of routine vaccination in these 11 states represents a further step towards universal childhood immunization for hepatitis A.

As presented by Dr Beth Bell, CDC, Atlanta, GA, USA.

Reference:

1. CDC. Prevention of hepatitis A through active or passive immunization: recommendations of the advisory committee on immunization practices (ACIP). *MMWR* 1999; 48 (No. RR-12):1 – 37.
2. CDC. Prevention of hepatitis A through active or passive immunization: recommendations of the advisory committee on immunization practices (ACIP). *MMWR* 1996; 45 (No. RR-15):1 – 30.

Mass hepatitis A vaccination considered for Puglia, Italy

Mass vaccination against hepatitis A is being considered for a particular region in Italy that continues to have elevated rates of hepatitis A and experiences periodic outbreaks of infection due mainly to contaminated sea food.

The epidemiology of hepatitis A has shifted in Italy in recent years, with incidence rates decreasing from 10/100,000 in 1985 to 5/100,000 in 1993. Seroepidemiological studies confirm that the reduction in notified cases corresponds to a reduction in the number of infections. At the same time, the age of first infection is increasing.

In Puglia, a region in the south east of Italy with a population of four million, the epidemiological pattern is completely different. Despite an improvement in socio-economic conditions, Puglia remains an area of intermediate endemicity for hepatitis A. The region experiences periodic outbreaks of hepatitis A and even during interepidemic periods reported incidence rates are high (as high as 30/100,000).

In February 1996, an outbreak of hepatitis A began in Bari city and subsequently spread throughout the region. This was the largest and most persistent epidemic of hepatitis A reported from Puglia since the disease became notifiable in 1989. In February 1996, the incidence of notified cases rose to 5.6/100,000, versus 1/100,000 the previous year. The epidemic reached its peak in August, with more than 1,600 cases notified in that month. In all, the infectious disease surveillance system (Sistema Informatizzato delle Malattie Infettive or SIMI) reported 5,620 cases of hepatitis A for 1996. The province of Bari had the highest incidence rate at 230/100,000, followed by Brindisi (124/100,000) and Taranto (118/100,000).

In the past, epidemics occurred every few years, however, in 1997, the epidemic curve repeated itself, with a first peak noted in February followed by an increase in cases notified in the summer and a quick decrease thereafter. More than 1,400 cases were notified in July and 883 in August; the total of cases notified in 1997 was 5,000. Again, Bari province was the most affected; there incidence rates were 208/100,000. In 1998, infection rates returned to the normal level of interepidemic periods.

For both the 1996 and 1997 epidemics, the average age of infection was 19, with those between 15 and 29 accounting for over 50% of notified cases. People aged 5 to 34 years of age accounted for 96% of all notified cases.

Outbreak investigations have shown that the transmission of hepatitis A in the region can be attributed largely to the consumption of raw seafood and the storage of seafood in sea water at the place of sale. Person-to-person contact also accounts for a substantial proportion of cases, particularly among children, and may be instrumental in maintaining the outbreaks between peaks.

Recommendations on the handling and consumption of seafood have had little impact on disease incidence. Mass vaccination is therefore being considered and looks likely to be the most effective method for controlling hepatitis A infection in the region. The goal of the programme would be the complete interruption of virus transmission in the area and the avoidance of a shift in incidence towards adulthood.

Vaccination of risk groups alone has been shown to be unsuccessful in reducing the spread of the virus in the general population. However, neither is it necessary to vaccinate the entire population to stop the spread of the virus. This goal can be obtained by reducing below a critical level the number of individuals susceptible to infection.

Currently, a 'two cohort' strategy is being investigated. The cohorts being considered are children 15-18 months of age and 12-year-olds. The vaccination programme would be combined with a school-based health education campaign.

Young children play an important role in the transmission of the virus, and protecting this group is fundamental in the elimination of HAV infection. Twelve-year-olds would be included in the programme because: they are easily accessible through school-based vaccination programmes; they are nearing the age where they are most at risk of infection; and there is low natural immunity in this group. Furthermore, as hepatitis B vaccination is already mandatory for this group, the combined hepatitis A+B vaccine could be delivered at little additional cost.

The decision to vaccinate would also be based on economic considerations. The cost of treatment and hospitalisation are high. For instance, in the recent epidemics, 87% of the notified cases were admitted to hospital. The cost to individuals and to society in terms of work days lost is also considerable. In addition, the epidemics have a negative impact on the economy and on tourism in the region.

Based on information provided by Dr C Germinario and Dr PL Lopalco, Institute of Hygiene, University of Bari, Italy.

Cost of an outbreak in Puglia, Italy high to individuals and society

Economic data provide important information when evaluating preventative strategies for hepatitis A, whether these be public education, sanitation or immunization. Understanding the cost to society and to the individual of HAV infection and the economic evaluation of prevention can help in choosing the strategy which makes the best use of local health resources.

After the 1996 hepatitis A epidemic in Puglia, a study was carried out to assess the economic impact of the outbreak. Some patient data was available from the SIMI database and a detailed questionnaire was also sent to 250 randomly chosen individuals who provided a representative sample of the patients infected with clinical HAV. The majority of patients (87.6%) were 11 to 30 years of age, reflecting the increasing susceptibility of young adults to hepatitis A infection.

The questionnaire was designed to collect information on:

- occupational status and income;
- number of working or school days lost due to illness;
- extra hospital costs such as visits to a GP or specialist, diagnostic examinations, prescription or over-the-counter drugs, dietary supplements, and travel time;
- duration of hospitalization;
- time of home help, whether voluntary or paid;
- additional costs sustained by the patient;
- perceived subjective evaluation, including the degree of disruption to life.

The purpose of the questionnaire was to identify the direct and indirect costs of the outbreak from the perspective of the individual, the National Health Service (NHS), and society.

After calculating the costs incurred from the Puglia outbreak it was concluded that the cost borne by each patient (662 USD) amounted to about 6.6% of the mean annual income for the employed patients in the sample.

The total cost of the outbreak to the NHS (15.6 million USD) was equivalent to 0.4% of the public health expense in Puglia in 1996. About 99% of this cost was due to hospitalization, required by 90% of patients.

The total cost of the outbreak to society (24.4 million USD) was equivalent to 0.04% of gross domestic product for Puglia in 1996. The mean cost per patient from a societal perspective was 4,150 USD. The degree of disturbance caused by the illness was graded as nil (9%), mild (17%), moderate (38%) or severe (36%).

Certain costs, such as the negative impact on tourism, could not be calculated so the overall calculated cost of the outbreak was conservative. Even so, the figures illustrate how costly epidemics of hepatitis A can be to the individual, the health service and to society, and that financially as well as clinically, hepatitis A is not a benign disease with little impact.

As presented by Prof Paolo Bonanni, Public Health Department, University of Florence, Italy.

Mean cost to society per patient (USD) with clinical HAV infection according to age				
Age group	Frequency	Direct costs	Indirect costs	Total
0-10 years	8.4%	2,435	354	2,789
11-20 years	50.4%	3,261	686	3,947
21-30 years	37.2%	3,104	1,550	4,654
>30 years	4.0%	3,338	1,531	4,869
Overall	100%	3,157	995	4,152

Reference:

Lucioni C, Cipriani V, Mazzi S, Panunzio M. Cost of an outbreak of hepatitis A in Puglia, Italy. Pharmacoeconomics 1998 Feb;13 (2): 257-266.

Selective childhood immunization currently considered in the Netherlands

A recent study of the four major cities in the Netherlands showed that children who spent the summer holidays in endemic countries appeared to be the main importers of hepatitis A in these cities. Routine vaccination of children from ethnic minority groups early in life is suggested; the vaccine would be incorporated into the current vaccination programme delivered through mother and child clinics so that vaccination coverage greater than 80% could be achieved. It is estimated that with the HAV vaccination programme a 50% reduction in HAV incidence could be achieved within three years.

With the improvements in hygiene over the past fifty years, the epidemiology of hepatitis A in the Netherlands has changed. It is no longer an endemic childhood disease and the seroprevalence of antibodies in those born after 1970 is less than 20%. Currently, the Netherlands witnesses small outbreaks in schools, day-care centres and healthcare institutions, with 80% of notified epidemics in primary schools.

Hepatitis A is a notifiable disease; between 700 and 1,100 cases per year have been notified over the past 10 years, for an incidence rate of 5-7/100,000, although considerable underreporting is suspected. Of the notified cases, 25% are infections which occurred while the person was abroad and the number of cases among children remains the highest.

Data from the study in Amsterdam, Utrecht, Rotterdam and The Hague showed a seasonal pattern in HA incidence which can be explained by importation of the virus by children travelling to endemic areas and subsequently transmitting the virus to siblings and schoolmates. Peaks

in incidence occur in the autumn when the number of notified cases among non-Dutch children increases. This is followed by an increase in incidence among children and adults who acquired their infection in the Netherlands. Until 1997, the incidence of hepatitis A decreased in the winter, although in recent years this decline has not been noted. This could indicate ongoing transmission in the population.

At present, all parents travelling to endemic countries are advised to bring children for immunization, however, coverage rates estimated by vaccine sales appear to be very low. During outbreaks, all family members and classmates are given immune globulin or HA immunization by the public health service. In individual cases of hepatitis A infection, all family members are given immune globulin.

Incorporating vaccination of children from ethnic minorities into routine childhood immunization programmes is suggested by the National Bureau for the Prevention of Infectious Diseases. A feasibility study is in the works to see whether the selective vaccination programme would be effective, cost-effective and politically attainable.

As presented by Jim Van Steenberghe, Epidemiologist at the Bureau of the Coordination Structure for Communicable Disease Control, The Hague, the Netherlands.

Reference:

van Gorkom LJC, Leentvaar-Kuijpers A, Kool JL, Coutinho RA. Association between the yearly hepatitis A epidemic and travel behaviour of children of immigrants in the four major cities of the Netherlands. Ned Tijdschr Geneesk 22 August 1998; 142: 34.

Impact of media coverage on the uptake of hepatitis B vaccine

The French Ministry of Health announced in October 1998 that it would temporarily suspend routine HB immunization of adolescents in French schools, while continuing the immunization of infants and high-risk adults. This decision followed concerns, despite lack of scientific evidence establishing a causal relationship, that hepatitis B immunization might be linked to the development or flare-up of multiple sclerosis (MS) and other demyelinating diseases. The decision comes in the wake of pressure from anti-vaccine groups and follows over two years of negative coverage in the French media. Even before the decision, there had been a reduction in the uptake of HB vaccine in France.

Information from Pasteur Merieux MSD indicates a steady decline in hepatitis B vaccine sales to the private market

in France, starting in 1996. In addition, sales of other vaccines have been negatively affected, even though there has been no negative press coverage of other vaccines. Market research conducted by SmithKline Beecham indicates a similar trend, although according to the seven-country study this trend is by far most important in France. A clear decline in HB vaccine uptake has also been noted in the French-speaking region of Belgium.

Seeking to avoid a similar situation to that in France, several health authorities in Europe have issued statements to assuage the fears of the public and maintain their faith in the safety and effectiveness of the HB vaccine. For instance, the National Committee on Immunization in Spain issued a statement that 'the committee finds no scientific reasons to modify the current policy on HB

immunization in Spain, including the universal immunization of adolescents'. In Italy, the National Vaccination Board met to discuss the issue and concluded that there is no evidence of a connection between HB vaccination and MS. The preliminary results of a study conducted by the Italian Association for Multiple Sclerosis also found no evidence of an association.

After careful review of the scientific evidence, WHO issued a statement that the scientific data does not demonstrate a causal association between HB immunization and MS. WHO has expressed concern that the decision taken in France could lead to a loss of public confidence in the HB vaccine and influence other countries to suspend or delay introduction of the HB

vaccine. Stopping or delaying immunization could see an increase in the number of HB infections worldwide. This has been the case in the past when unsubstantiated anti-vaccine information lead to a loss of public confidence in the diphtheria, tetanus, pertussis vaccine. Millions of cases and hundreds of deaths followed the reduced use of the DTP vaccine in several countries.

Over 1 billion doses of the HB vaccines have been used with an outstanding record of safety and efficacy. Hepatitis B vaccines are more than 95% effective in preventing the development of the chronic carrier state of hepatitis B, and while any risk of MS following HB immunization is hypothetical, the risk of HB infection and disease in non-immunized individuals is real.

Risk-benefit analysis of hepatitis B vaccine does not support change in policy

In light of the recent negative publicity surrounding the hepatitis B vaccine and the questions in the media about the safety of the vaccine, the National Institute of Public Health Surveillance in France conducted a risk benefit analysis, weighing the risk of adverse side effects of the vaccine against the benefit of being protected against hepatitis B infection. The results were firmly in favour of vaccination and the conclusions were that:

- The available data do not support any modification of vaccination strategies for infants or high-risk populations.
- Under all scenarios considered, the risk of serious adverse events after HB vaccination, if real, appears very low, and less than 1/100,000 vaccinated.
- The balance for immunization of pre-teenagers, even in the worst-case scenario, is in favour of maintaining this strategy.

France has had some policy of hepatitis B immunization since 1982, when selective immunization of high-risk groups was implemented. In 1994-1995 universal HB immunization was implemented in the infant immunization schedule and a catch-up, school-based vaccination campaign aimed at 11-year-olds was instituted. These programmes were not mandatory, however, and vaccination was only obligatory for healthcare workers.

From 1994-1998, immunization coverage was varied. A coverage rate of 30% was reached among infants, whereas nearly 90% of pre-teens were vaccinated. Vaccination of high-risk groups was well beyond the target population. In total, more than 75 million doses were sold in France by 1997, 84% of these since 1994. It was estimated that over 1/3 of the French population was immunized.

Initially, the vaccine was received largely without incident. By end March 1998, 249 notifications of acute

Incidence rates (per 100,000 vaccinated) of adverse events assumed to be attributable to vaccination, according to age at vaccination, notification rate and time of onset **Relative risk: 1.8 - France, 1990-1997**

Time since vaccination	0-2 months		0-6 months		All intervals	
Notification rate	100%	50%	100%	50%	100%	50%
Age at vaccination						
0-6 years	0.00	0.00	0.00	0.00	0.00	0.00
7-9 years	0.14	0.28	0.35	0.70	0.42	0.84
10-12 years	0.10	0.21	0.12	0.24	0.14	0.27
13-15 years	0.26	0.51	0.29	0.58	0.38	0.77
16 years and more	0.30	0.60	0.38	0.77	0.46	0.91
Total	0.24	0.48	0.31	0.62	0.37	0.74

central demyelinating episodes following immunization had been made to the French Agence du Médicament. This included 131 episodes of multiple sclerosis, including 74 first episodes; 46 cases of ophthalmic diseases; 23 cases of myelitis; and 49 other demyelinating disorders. None of these episodes were notified in infants or children up to six years of age. Taking into account the number of doses sold, the number of persons vaccinated and the number of adverse events notified according to age of vaccination and time since vaccination, no significant difference was found in adults between the number of notifications observed and the number expected.

After the claim of a relationship between hepatitis B immunization and MS, case control studies were performed in adults. These included a hospital pilot study, a multi-centre study in France, and a GP database study in the UK. These studies neither confirmed nor disproved a small increase in risk.

Due to the absence of evidence of risk in infancy and the important risk of infection by the hepatitis B virus for adults targeted for vaccination, the risk-benefit analysis focused on pre-teens, a target group for which the balance between potential risks and benefits of vaccination was not straightforward. In the analysis, a theoretical cohort of 800,000 pre-teens immunized at 11 years was used. The analysis looked at the number

of adverse events due to HB immunization, assuming a causal relationship, and the number of prevented severe complications of HB infection. The approach was conservative, as the values of relative risk were estimated from case control studies conducted in adults.

Incidence rates of adverse events attributable to HB vaccination were computed, according to age, notification rate and time interval between immunization and onset of disease. The analysis assumed a relative risk of either 1.4 or 1.8 and adverse events notification of either 50 or 100%.

The number of cases of fulminating hepatitis B and future cirrhosis or liver cancers avoided by preventing infection were computed. The data used for the computation included information on: the natural history of infection, epidemiological data on HBV infection in France, vaccine effectiveness and duration of protection.

The analysis concluded that even taking a conservative approach and even under the worst case scenario, that the risk of hepatitis B infection and subsequent disease outweighs the risk, if real, of adverse events after HB vaccination. These data do not support modification of vaccination strategies for infants, high-risk populations or pre-teens. This preliminary analysis require confirmation with updated notification data when such data becomes available.

Estimated risk of adverse events assuming a causal relationship with HB vaccination and benefits of vaccination for a cohort of 800,000 pre-teenagers followed up until 30 years of age				
	Incidence of acute symptomatic infections: 7,800 (1994)		Incidence of acute symptomatic infections: 3,100 (1996)	
	Best case scenario for incidence of complications	Worst case scenario for incidence of complications	Best case scenario for incidence of complications	Worst case scenario for incidence of complications
Number of acute fulminating hepatitis prevented	29	7	12	3
Number of cirrhosis and primary liver cancer prevented	147	29	58	12
Number of adverse events assumed to be attributable to vaccination	0 to 2*			

*Low estimate: 0 for a relative risk of 1 (no association). Medium estimate: 0.56 adverse events for a relative risk of 1.4; only onset of disease within 2 months of vaccination included and notification rate of 100%. High estimate: 2.2 adverse events for a relative risk of 1.8; all notifications included and notification rate of 100%.

Current recommendations on HAV control in selected countries in Europe

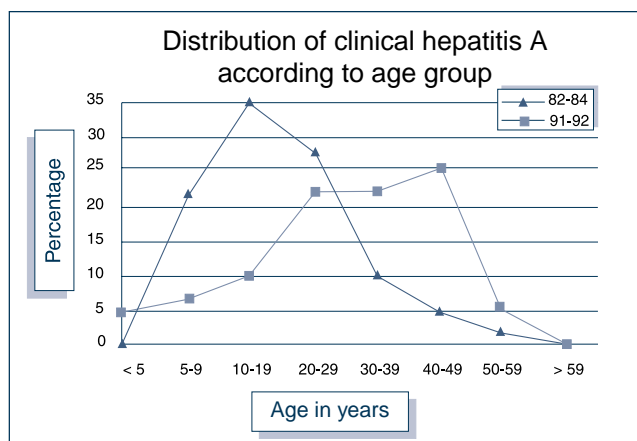
B

BELGIUM

Data from sentinel practices across Belgium indicate the overall incidence rate of clinical HA cases to be 23/100,000. The incidence is lower in the northern region of Flanders (20/100,000) than in the southern region of Wallonia (38/100,000). In 1991–1992, the highest number of cases (63%) occurred among 20–49-year-olds; 23% of cases were in those younger than 20. In 1982–1984, the 5–19-year-old age group accounted for 57% of cases. During that time the number of new cases per year fell from 7,129 to 2,326.

Known risk factors included direct contact with a case (41%), travel to high-endemic areas (19%), and contaminated food (19%). In the past 20 years there has been a substantial decrease in infection among children and the mean age of infection has risen, leaving young adults at risk of infection.

Currently there are no official recommendations for the use of hepatitis A vaccine in Belgium, although it is usually recommended to travellers to endemic regions and military personnel. During outbreaks, HA vaccine as well as immune globulin are used. In addition, it is generally perceived that the frequency of outbreaks does not warrant the systematic use of the vaccine.



As presented by Dr Pierre Van Damme, University of Antwerp, Belgium.

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D

GERMANY

Reporting of hepatitis A infection is mandatory in Germany. From 1991 to 1996, reported cases per year decreased from 8,587 to 4,905, although it is estimated that the true figures are between one and two times higher when corrections for underreporting are made. The incidence of fulminant cases is 0.2/100,000; in the past six years there have been 86 deaths from hepatitis A; 70 of those deaths were of persons over 50 years of age.

The epidemiology of hepatitis A in Germany is similar to that of other West European countries. A 1983 study conducted in Berlin found a much higher prevalence among non-German children than among German children; also, seropositivity increased with the number of children in the family and the number of trips to the parents' home country.

Vaccination is recommended for laboratory workers, workers in day-care centres, personnel of psychiatric institutions, sewage workers, travellers to high-endemic regions, homosexual men, persons with chronic liver disease, haemophiliacs and contacts of HAV cases. Vaccination rather than immune globulin is also indicated for outbreaks. Vaccination given because of travel-related risk is paid for by the individual.

To date, there is no recommendation for universal HA vaccination in Germany. The rationale being that the combined A+B vaccine would be used and would delay delivery of the hepatitis B vaccine because of licensing restrictions in Germany.

As presented by Dr Johannes Hallauer, Charity University Clinic, Berlin, Germany.

GR

GREECE

Improvements in living conditions and sanitation have caused a decrease in the incidence of hepatitis A infection in early childhood, and the epidemiological pattern is similar to that of other countries in the region.

It is difficult to gauge the incidence as reporting is not mandatory and serious underreporting takes place.

The health authorities in Greece recommend HA vaccination for travellers to high-endemic regions, day-care workers, persons living in institutions, immigrants from endemic regions, healthcare workers, sewage workers, IV drug users, homosexual men, prostitutes and patients with liver disease.

Vaccination for these groups is recommended but not obligatory and the vaccine is not supplied by the government. Most vaccinations in Greece are carried out in the private sector and paid for by the individual.

As presented by Dr Georges Papaevangelou, Athens School of Hygiene, Greece.

cases incidence rates are 8/100,000, although this estimate is considered low as underreporting is a problem.

Currently, HAV vaccination is recommended for travellers, sewage workers, workers in day-care centres, patients with chronic liver disease, haemophiliacs, homosexual men, healthcare workers and contacts of HAV cases. Vaccination of individuals working in the public healthcare system is covered by the state; in all other cases vaccination is paid for by the employer or by the individual. Catalonia is the only autonomous region to have instituted a pilot vaccination programme for HAV, the results of which will be reviewed in three years.

As presented by Dr José de la Torre, Ministry of Health and Consumer Affairs, Madrid, Spain.

I ITALY

Italy is a country of intermediate endemicity for hepatitis A; the average incidence of notified cases of HAV is 19/100,000. Like other countries in the Mediterranean, the epidemiological pattern of HAV infection is shifting. Overall incidence rates in Italy have risen because of the two recent outbreaks in Puglia.

The current vaccination strategy recommended by the health authorities in Italy is to vaccinate travellers to endemic regions, patients who have liver disease or who have undergone liver transplants, HAV-negative haemophiliacs, IV drug users, military personnel and sewage workers. At present, food handlers are not included in the recommendation as they represent 5-10% of the population and the cost of mass vaccination would be prohibitively expensive for the national health service. Healthcare workers are also excluded from the recommendation because they are deemed to be at no additional risk. The above control measures are recommended but are not mandatory and the local health authorities implement policy at their discretion.

As presented by Prof Paolo Bonanni, University of Florence, Italy.

E SPAIN

The epidemiological pattern for HAV in Spain is shifting, with infection occurring later and the number of susceptible individuals increasing. Epidemiological data is collected at the national level; based on notified

CH SWITZERLAND

Switzerland is a country of low endemicity for hepatitis A. Sporadic cases of HAV infection occur, but no major outbreaks have been observed, although periodic bouts of higher incidences of infection have been noted in communities of IV drug users.

In 1997, there were 278 notified cases of acute hepatitis A in Switzerland; in 1998, 362 cases were notified. The 0-14 year age group was most affected, accounting for 22% of cases in 1997 and 29% of cases in 1998. The most common risk factors include travel to endemic regions and IV drug use, although in a substantial proportion of cases the risk factor was unknown (34% in 1997 and 37% in 1998).

Active immunization against hepatitis A is recommended for travellers to high-endemic countries, IV drug users, infants and children who visit their families in high-endemic countries, personnel working in institutions for disabled children, and personnel working in institutions for refugees. These recommendations were first published in 1992 and later renewed in 1998. Approximately 1 million of the 6.8 million Swiss citizens travel abroad annually; an estimated 30-50% of those travelling to high-endemic regions are vaccinated.

Of the estimated 30,000 IV drug users in the country, less than 10% are thought to have been vaccinated. The prevalence of an HAV marker among drug users is between 50 and 60%.

The cost of vaccination is borne by the individual.

As presented by Dr Peter Grob, University Hospital, Zurich, Switzerland.

Overview of previous issues of *Viral Hepatitis*

Previous issues of *Viral Hepatitis* are available from the Viral Hepatitis Prevention Board. If you are interested in obtaining a copy of any of the issues listed below, please contact the VHPB Secretariat. From January 1, 2000, it will be possible to download all issues of *Viral Hepatitis* from the VHPB website at <http://esoc-www.uia.ac.be/esoc/vhpb>.

July 1995, Volume 4 - Number 1 Contents:

- Editorial: epidemiology, disease burden and prevention of hepatitis C
- Hepatitis C represents major challenge to public health
- Intravenous drug abuse poses greatest HCV risk
- Pan-European view of HCV
- Consensus statement covering hepatitis C epidemiology, infection, control measures, therapy and research priorities.

January 1996, Fact sheet 1 Contents:

- The clock is running: 1997 deadline for integrating hepatitis B vaccinations into all national immunization programmes
- Worldwide epidemiology of hepatitis B
- Epidemiology of hepatitis B in Europe

March 1996, Volume 4 - Number 2 Contents:

- Editorial: Control of viral hepatitis in Europe
- News
 - Vaccination cuts costs
 - HBV in Eastern Europe
 - Government action dependent of accurate data
 - VHPB promotes WHO target
 - Germany and Switzerland move towards universal vaccination
- Report on HB as community health risk
 - HB a community-wide risk
 - WHO guidelines
 - Epidemiology and vaccination survey in Europe
 - Strategy for eliminating HBV transmission in US
 - Progress towards universal vaccination by country
- VHPB consensus statement on the control of viral hepatitis in Europe
- Status of HBV prevention in selected countries in Europe

August 1996, Volume 5 - Number 1 Contents:

- Editorial: public health issues surrounding hepatitis C
- Viral hepatitis overview
- HAV and occupational risk
- HAV occurs in cyclical outbreaks
- Future of HAV vaccination
- Defining occupational risk for HBV
- HBV prevention and management
- Facts on HCV
- HCV a serious threat to public health
- Defining the magnitude of HCV problem
- Understanding HCV transmission
- Issues surrounding HCV screening
- Breast feeding and HCV
- HCV as an occupational hazard
- Counselling guidelines for HCV
- Treating HCV infection
- Education key to prevention

April 1997, Volume 5 - Number 2 Contents:

- Editorial: Immunization key to controlling viral hepatitis
- Hepatitis A
 - Epidemiology and public health
 - Interrupting outbreaks by immunization
- Hepatitis B vaccine news
 - The challenges ahead
 - DNA-based vaccine in pipeline
 - HB vaccine provides long-term protection
 - Combination vaccines
- Overview of hepatitis vaccines
- Evaluation of vaccination policies
 - Raising public awareness of HB immunization
 - Long-term benefits of immunization seen in endemic areas
 - Successful control programme in Italy
- Transmission and prevention of hepatitis C
- Overview of hepatitis E
- Current epidemiological trends of viral hepatitis• worldwide (by region)

Overview of previous issues of *Viral Hepatitis*

July 1997, Volume 5 - Number 3

Contents:

- Editorial: Surveillance and monitoring of viral hepatitis
- Overview of surveillance systems in Europe
- Surveillance: the France model
- Surveillance: the UK model
- Comparison of systems in Europe
- Evaluating immunization programmes
- Update on hepatitis G virus
- VHPB consensus statement on surveillance of viral hepatitis

October 1997, Volume 6 - Number 1

Contents:

- Editorial: introduction of combined vaccines into immunization programmes
- Vaccine news
 - Paediatric combined vaccines: clinical trials in Italy and Greece
 - Combined vaccines equal monovalent vaccines in safety and immunogenicity
 - Status on development of combined vaccines
 - Combined vaccines well received in France
 - No evidence that HB vaccine causes multiple sclerosis
- News on hepatitis A
 - Epidemiology of HA in the US
 - HAV outbreak in Puglia, Italy
- Update on hepatitis A: disease, epidemiology and prevention

January 1998, Fact sheet 2

Contents:

- Universal HB immunization by 1997: where are we now?
- Regional status report on HB immunization and control programmes

April 1998, Fact sheet 3

Contents:

- Injection safety and a safe blood supply
- Ensuring the safety of injections
- Safeguarding the blood supply
- VHPB recommendations on injection safety and a safe blood supply

October 1998, Volume 7 - Number 1

Contents:

- Editorial: Control of perinatal transmission
- Screening of pregnant women for hepatitis B
- Country reports
- HB vaccine effective in preventing vertical transmission
- Evaluating immunization programmes
- Duration of protection after immunization and implications for booster policy
- VHPB recommendations on prevention of perinatal transmission

January 1999, Fact sheet 4

Contents:

- Issues surrounding virus mutants should not deter push for universal HB immunization worldwide
- VHPB consensus statement of HBV mutants and variants

December 1999, Volume 8 - Number 1

Contents:

- Editorial: hepatitis A and universal immunization
- Israel implements universal hepatitis A immunization
- Catalonia, Spain introduces mass hepatitis A vaccination programme
- HA immunization recommended for children in 11 states in the US
- Mass hepatitis A vaccination considered for Puglia, Italy
- Cost of an outbreak in Puglia, Italy high to individuals and society
- Selective childhood immunization considered in the Netherlands
- Impact of media coverage on the uptake of hepatitis B vaccine
- Risk-benefit analysis of HB vaccine
- Current recommendations on HAV control
- VHPB Consensus Statement on the control of hepatitis A

VHPB consensus statement on the control of hepatitis A

The availability of highly effective and safe hepatitis A vaccines raises the possibility of achieving and sustaining a substantial decrease in hepatitis A incidence among children as well as adults. Currently hepatitis A vaccination cannot be recommended for children < 1 year of age, because there is no hepatitis A vaccine licensed for use in children < 1 year of age. Published data have shown that high coverage rates (70-80%) for hepatitis A childhood vaccination can control and prevent periodic hepatitis A outbreaks in relatively small, self-contained communities compared to the situation prior to vaccination.

Recommendations

- General hygiene and sanitary measures are the most important tools in preventing the spread of hepatitis A.
- The decision whether to adopt routine hepatitis A vaccination of children should be based on:
 - prevalence and incidence of hepatitis A cases;
 - frequency of outbreaks;
 - health impact of hepatitis A compared to other health priorities;
 - feasibility of an HA vaccination programme;
 - economic evaluation of the different hepatitis A prevention strategies.
- Universal hepatitis A childhood vaccination should be considered in communities which witness repeated outbreaks or where the hepatitis A incidence rate is substantially higher than in the overall country.
- Universal hepatitis A childhood vaccination programmes currently implemented in some regions of Europe should be followed up and evaluated.
- Universal hepatitis A childhood vaccination includes vaccinating 1 or more single age cohorts of children.
- The VHPB endorses HA vaccination of travellers from low endemic to high endemic countries, including people who travel frequently for their occupation.
- If effective hygiene measures cannot be achieved, HA vaccination should be considered in controlling outbreaks in small, self-contained communities if:
 - vaccination can be started early in the outbreak; high coverage in the target population can be achieved; multiple age cohorts are vaccinated. Vaccination efforts should preferably focus on children, with the upper age limit determined by local epidemiology.
- Vaccination is recommended for children of immigrant parents, born in Western Europe (low endemicity) visiting their parents' country of origin (high endemicity).
- Hepatitis A vaccination is recommended for persons at increased risk for hepatitis A or an adverse disease outcome, such as men who have sex with men, intravenous drug users, staff and residents in institutions for the mentally retarded, persons with chronic liver disease (regardless of its aetiology), and haemophiliacs.
- Further studies are needed to document the occupational risk of hepatitis A for health care workers.
- Post-exposure prophylaxis for hepatitis A:
 - IgG are very effective for post-exposure prophylaxis.
 - The effectiveness of hepatitis A vaccine compared to IgG has not yet been evaluated.
- In countries where IgG are not routinely used after exposure or where IgG is unavailable, administration of hepatitis A vaccine can be considered and is likely to provide protection.



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