VIRAL HEPATITIS

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CONTENTS

EDITORIAL

This issue of *Viral Hepatitis* takes a close look at the issues surrounding the development of combined vaccines, in particular, their introduction into immunization programmes, and their role in preventing HBV and HAV infection in at-risk groups. We also revisit the subject of hepatitis A, and have included an update of the report on the epidemiology, transmission routes, and means of preventing hepatitis A infection presented previously in *Viral Hepatitis* (1995: Vol 3, No 1).

Combined vaccines are the future for childhood immunization - not only for hepatitis B but for other antigens as well. They are a necessity, not a luxury, and once in widespread use will bring with them a host of benefits: fewer injections and a simplified immunization schedule; cost reductions; and better acceptance by parents and physicians. These improvements should pave the way for the introduction of new antigens and, in the case of hepatitis B, should spur countries that have not yet made HB vaccine part of their routine immunization programmes to do so. Persons at increased risk of hepatitis A and hepatitis B - such as travellers and military personnel - will also benefit from the introduction of combined vaccines. Hepatitis A and hepatitis B are the two most common vaccine-preventable diseases in travellers from low to high endemicity areas. A combined HA-HB vaccine is already available in some countries, and where risk for HAV and HBV coincide, it is the preferred choice.

When considering combined childhood vaccines that include the hepatitis B component, it is clear that these vaccines will be DTP-based. DTP is the cornerstone of the Expanded Programme on Immunization (EPI) throughout the world, and the pharmaceutical industry has already invested heavily in developing DTP-based combined vaccines. Furthermore, because 75% of the world's children live in countries with local DTP vaccine production, using DTP as the starting point would potentially make new antigens available to children in the developing world. At present, the DTP-HB vaccine is recommended as the top priority among new vaccines by the WHO International Task Force on Hepatitis B Immunization, the Children's Vaccines Initiative (CVI) Strategic Plan, the CVI Working Group on DTP-based Combined Vaccines, the CVI-PAHO Meeting in Washington, DC, USA, and the CVI Meeting in Bandung, Indonesia.

Although it would initially appear that a combined DTP-HB vaccine would be readily accepted by countries purchasing or manufacturing DTP and HB vaccines, the introduction of a combined DTP-HB vaccine will not be without obstacles, and some of the advantages of combined vaccines may also prove to be their drawbacks. That three-quarters of the world's children live in countries with local DTP production is a case in point. Countries with local production capabilities are reluctant to purchase vaccine from an outside source, and, while some manufacturers will be able to begin producing DTP-HB, many will not. Additionally, the immunization schedule will need to be revised and agreed before the DTP-HB vaccine is widely used, as will the issue of the new DTP acellular vaccines gradually replacing DTP whole-cell vaccines.

Despite these obstacles, combined vaccines are the way forward for immunization programmes - both childhood and adult. Once in widespread use, they will streamline administration of the EPI, and make more antigens available to more children worldwide, and will simplify vaccination of other at-risk groups.

Dr Elizabeth McCloy
Specialist in Occupational Medicine
London, UK

NEWS FROM THE VHPB MEETING IN ST. JULIANS, MALTA, MARCH 3 - 5, 1997

VACCINE NEWS

COMBINED PAEDIATRIC VACCINES: GOOD RESULT FROM CLINICAL TRIALS IN ITALY AND GREECE

Recent clinical trials in Italy measuring the effectiveness of two different paediatric combined vaccines, both including the HB component, showed promising possibilities for future combined vaccines, and studies in Greece provided similar findings.

The first study was a randomized, double-blind study of a trivalent, combined DT-HB vaccine. The study involved 290 participants from 14 institutions across Italy using three different lots of vaccine. Vaccine was administered to healthy infants on a 3, 5 and 11 month schedule, and serological tests were performed on 228 of the infants after completion of the vaccine course. One month after the second dose of vaccine, 100% of participants showed immunogenicity for diphtheria and tetanus, while 88.2% exhibited immunogenicity for hepatitis B (HB); one month after dose three, 99.5% showed immunogenicity for HB. In addition, the vaccine was well tolerated, with virtually no one (only 1.3% of Group B on visit two) reporting adverse reactions requiring therapy.

Immunogencity of combined DT-HB vaccine (one month after dose three)

Number of subjects	Diphtheria % responded	Tetanus % responded	Hepatitis B % responded
228	100	100	99.5

An open, randomized study to evaluate the immunogenicity and reactogenicity of a combined DT-acellular pertussis (DTPa) and hepatitis B vaccine against separate administration of DTPa and HB vaccine was also carried out. Participants included healthy infants who received vaccine on either a 3, 5 and 11 month schedule, or a 2, 4, 6 month schedule. One month after the third dose all participants in both schedule groups showed 100% sero-positivity for all antigens studied.

In Italy, pertussis vaccination is not compulsory but is offered as DTP. Recently, the acellular pertussis vaccine was also approved for use in Italy. The compulsory vaccination schedule in Italy is as follows:

Age	Schedule	Vaccine
Newborns	3 months	DT(P)-HB-OPV
	5 months	DT(P)-HB-OPV
	11 months	DT(P)-HB-OPV
	2-3 years	OPV
	5-6 years	DT(P)
Adolescents	12 years/0 months	HB
	12 years/1 month	HB
	12 years/ 6 months	HB

This edition of *Viral Hepatitis* is prepared from material presented at the Viral Hepatitis Prevention Board Meeting held 3 - 5 March, 1997 in St. Julians, Malta.

A study in Greece on the effectiveness of the combined DTP (whole-cell)-HB vaccine produced similarly positive results. Forty-two healthy two-month-olds of HBsAg-negative mothers were enrolled in the study. The study authors chose a 2, 4, 6 month schedule - the schedule currently used for administering DTP vaccine in Greece. Immunogenicity at month seven among participants was high: 97.4% for diphtheria; 97.4% for tetanus; 100% for pertussis; and 94.9% for hepatitis B.

As presented by Prof Paolo Bonanni, University of Florence, Italy and Prof Georges Papaevangelou, Athens School of Hygiene, Greece.

References:
Gabutti G, Bonanni P, Icardi GC, Bruzzone BM, Pezzano D, Rebora M, Crovari P. Results of two randomized clinical trials of combined diphtheria-tetanus-hepatitis B and diphtheria-tetanus-acellular-pertussis-hepatitis B vaccines. Abstract volume 'IX Triennial International Symposium on Viral Hepatitis and Liver Disease',Gabutti Rome, Italy, April 21-25, 1996, 273.

Papaevangelou G, Alexiou D, Roumeliotou A, Vandepapelière P, Safary A. Combined Diphtheria, Tetanus, Pertussis and Hepatitis B Vaccine in Healthy Infants. Vaccine, 1995; 13:175-178.

COMBINED HEPATITIS VACCINES EQUAL IN SAFETY AND IMMUNOGENICITY TO MONOVALENT VACCINES

In an effort to improve the convenience of vaccine administration and therefore compliance, to lower the administration costs of monovalent vaccines, and to provide dual protection to those at risk of hepatitis A and hepatitis B, vaccine manufacturers have developed combined hepatitis A and B vaccines that appear successful in meeting the above objectives.

A study carried out by the University of Antwerp, Belgium found the combined hepatitis A and B vaccine Twinrix® to be safe, well tolerated and highly immunogenic in adults as well as children. The immune response elicited by the vaccine compared favourably with the sero-responses and GMTs reached after the separate administration of hepatitis A vaccine and hepatitis B vaccine.

For the adult formulation of the vaccine, six vaccine trials involving 843 healthy volunteers between the ages of 17 and 60 were conducted in five countries. Volunteers were vaccinated according to a 0, 1, 6 month schedule and were asked to complete symptom checklists; vaccine immunogenicity was evaluated by measuring antibody titres at several intervals after vaccination.

Safety and reactogenicity did not differ from other widely used injectable vaccines. Of the 99.3% of volunteers who returned the symptom sheets, soreness was the most frequently reported local symptom (43.1%) and temporary fatigue (< 24 hours) the most common general symptom (10%).

By month two of the trial, over 99% of the vaccinees had titres of anti-HAV above the cut-off; one month after the third dose of vaccine was given all participants were sero-positive. With regard to anti-HBs titres, 97% of vaccinees had sero-protective titres (≥10 mIU/ml) by month six, and 99% showed protective titres one month after a third dose was administered. Follow-up data also indicated long-term antibody persistence that perfectly mimicked that elicited by monovalent vaccines. Trials in children (aged 1 - 15 years) also confirmed safety and immunogenicity in younger subjects.

Immunogenicity profile of adults vaccinated with combined hepatitis A and B vaccine

MONTHS		ANTI-HAV		ANTI-HBs	
		Sero-positivity (≥ 33mIU/ml) percent	GMT (mIU/ml)	Sero-protectivity (≥ 10mIU/ml) percent	GMT (mIU/ml)
MONTH 1	(N=768)	94	306	34	10
MONTH 2	(N=759)	99	748	84	62
MONTH 6	(N=755)	99	434	97	236
MONTH 7	(N=741)	100	5,404	99	4,814

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

Reference:
Thoelen S, Van Damme P, Beutels M, Matheï C, Meheus A. Immunogenicity of a combined hepatitis A and hepatitis B vaccine in healthy adults. Hepatology 1996; 23:180.

STATUS ON THE DEVELOPMENT OF COMBINED VACCINES

That combined vaccines are the future of immunization is clear. With more antigens being added to the EPI, and the increasing cost and complexity of administering the vaccine schedule, combined vaccines offer obvious benefits on a number of levels: added convenience, better patient compliance, increased vaccine coverage, cost savings, and improved control over the EPI.

With a view towards drastically reducing the number of injections needed to complete the EPI, vaccine manufacturers are currently developing a wide array of combined vaccines, using DTP as the basis. Once the vaccines currently under development are licensed, the number of injections needed in childhood could be reduced to as few as five, as compared with a present scheme that, in the US for instance, includes 13 injections.

Although the end goal would be to develop a DTPa-IPV-HB-Hib or DTPa-HB-Hib vaccine, attaining that goal is still a number of years off. Immunization priorities differ between countries, as do vaccination schedules, local production capabilities, and demands for specific vaccine combinations. Furthermore, producing combined vaccines is considerably more complex than producing single-antigen vaccines, necessitating a step-by-step approach.

At present, therefore manufacturers must pursue intermediate goals, developing combined vaccines that incorporate fewer antigens but which will be compatible with current country-specific immunization priorities.

Issues complicating the development and acceptance of combined vaccines:

- the potential for increased reactogenicity;
- greater interference from components of combined vaccines (antigens, preservatives, adjuvants, excipients and pH);
- the potential for decreased immunogenicity of individual antigens;
- higher development costs and longer development times; and
- greater difficulty in ensuring that all components of a combined vaccine are potent and meet the criteria for lot release.

Among the combined vaccines in development and on the market, the DTP-HB vaccine is recommended as the top priority among new vaccines by the WHO International Task Force on Hepatitis B Immunization. Although it would initially appear that a DTP-HB vaccine would be readily accepted by countries buying both DTP and HB vaccine, this is not necessarily the case. DTP-vaccine producing countries are reluctant to purchase vaccine from an outside vendor, and, while some local manufacturers are in a position to begin producing DTP-HB, many are not.

Another obstacle to be overcome before combined DTP-HB vaccines are widely accepted is the issue of vaccine schedules. The simplest way to introduce the HB component would be to administer it with DTP. Currently, the DTP schedule is most often based on a 6, 10, 14 week schedule, and DTP cannot be administered at birth. 'We need to find a solution for the issue of birth doses,' says Dr Mark Kane of the World Health Organization. 'The simplest way to introduce the HB vaccine is to administer it with DTP without changing the schedule. This will decrease the schedule complexity and increase compliance.'

Combined vaccines are already licensed in certain countries. These include:

- DTPw-HB
- DTPw-IPV
- DTPw-Hib
- DTPw-IPV-Hib
- DTPa-IPV-Hib
- DTPa-Hib
- DTPa-HB
- Hib-HB
- HEP AB

In addition, the changeover to acellular pertussis vaccines - which are clearly effective and less reactogenic than whole-cell pertussis vaccines but much more expensive - is yet another hurdle.

Long-term trends for immunization:

- the further development of combined vaccines including more antigens;
- protective immunization that will extend beyond childhood, with the goal being to develop vaccines that produce life-long immunity;
- a shift from whole-cell to acellular vaccines;
- development of a vaccine that will include most of the major antigens, and that will drastically improve delivery and coverage of immunization.

As presented by Dr Francis André, SmithKline Beecham Biologicals, Rixensart, Belgium and Dr Benoit Soubeyrand, Pasteur Mérieux MSD, Lyon, France.

Reference:
André FE, Development of combined vaccines: manufacturer's viewpoint. Biologicals 1994; 22: 317-321.

UPDATE ON HEPATITIS A

Based on the *Viral Hepatitis* Report on the Hepatitis A meeting in Marlow, UK (*Viral Hepatitis*, 1995; 3: 3-14) and on information presented by Dr Beth Bell of the Centers for Disease Control and Prevention, Atlanta, GA, USA. Prepared by Dr Pierre Van Damme, Dr Mark Kane and Margaret Van der Elst.

1. HEPATITIS A: DISEASE AND EPIDEMIOLOGY

1.1. Introduction

Hepatitis A is an inflammatory disease of the liver caused by the hepatitis A virus (HAV), and spread by faeco-oral transmission[1-3]. HAV has a worldwide distribution which relates to the level of economic development, and transmission often occurs in epidemics.

In many developed and developing countries, disease incidence and prevalence decline as hygiene, sanitation and living standards improve. As HAV endemicity decreases, the average age of exposure and subsequent infection shifts to older age groups. As severity of clinical disease is age-related, this shift increases the number of clinical infections, morbidity and mortality[3].

1.2. Transmission

The faeco-oral route is by far the most common mode of HAV transmission (> 95 %). Infection is usually acquired by ingesting viral particles from hands, food or water contaminated with faecal material[4-6].

HAV is excreted in the faeces of infected persons, primarily during the late incubation period and the first weeks of illness. Consequently, infected people may unwittingly pass the virus to others before they develop symptoms.

Infection can easily be spread by person-to-person contact within families, day-care centres, and among those living in close quarters such as military barracks and institutions for the mentally handicapped.

In areas with substandard water supply and sewage disposal, contamination of drinking water can occur, causing outbreaks of hepatitis A[3,7,8,9]. Salads, fruits and other uncooked foods washed in contaminated water are another source of infection, as is shellfish infected by sewage-contaminated sea water[10,11]. A major epidemic in Shanghai in 1988 (over 300,000 cases reported) was traced to contaminated clams and mussels[10,12].

A second route of transmission, accounting for less than 5%, is through infected plasma[13], and some transmission in intravenous drug users may occur via this route.

Modes of HAV transmission

- Faeco-oral route (95%)

==> person-to-person contact
==> contaminated food or water
==> salads and fruits washed in contaminated water
==> contaminated shellfish

- Infected plasma (<5%)
- Sexual route (<5%)

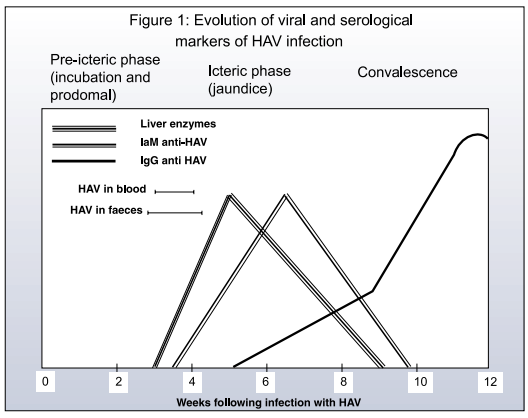
1.3. Disease

HAV is a single-stranded RNA virus which chooses the hepatocyte as the primary target cell. HAV has no cytolytic activity on liver cells. It seems more likely that liver cell damage is caused by activation of the T-cell mediated immune response as a result of the presence and replication of the virus. Infection with HAV is usually self-limiting.

The incubation of a HAV infection varies between 15 and 50 days, with a mean duration of approximately one month[14,15]. Prodromal symptoms such as malaise, fatigue and loss of appetite are not obviously related to liver disease. Patients are infectious during the period in which HAV is secreted in the bile and present in the stool, usually between two and five weeks after exposure (Figure 1). Specific symptoms, such as jaundice, vomiting, dark urine and yellow eyes occur within the first two weeks following the incubation period.

Two to three weeks after exposure elevation in serum concentration of liver enzymes (transaminase) can be observed, followed by the elevation of bilirubin levels. Liver enzymes generally peak about the time of onset of jaundice. As jaundice begins to resolve liver enzyme levels gradually return to normal.

Figure 1: Evolution of viral and serological markers of HAV infection



IgM antibodies to HAV can be detected by immunoassay three to five days before onset of clinical symptoms; this IgM response is typically short-lived, lasting approximately four to six months. The IgM-HAV test is the specific test for acute HAV infection. IgG antibodies

to HAV are produced within three months and persist for years after infection, conferring life-long immunity.

Age plays a major role in the severity of HAV disease[16-18]. Asymptomatic hepatitis A infection among adults is estimated to occur in 10% to 25% of cases[14]. By contrast, only 10% of young children (<2 years) experience symptomatic HAV infection. The percentage increases to 50% for children between two and four years of age and 80% for children older than five years[15,18]. Duration of symptoms commonly lasts for about four weeks[3]. HAV infection does not lead to chronic infection, chronic carrier state or chronic sequelae.

Protracted clinical hepatitis A with persistently elevated liver enzymes for two to three months has been reported in less than 10% of clinical hepatitis A cases in adults[6]. Relapsing hepatitis A can occur in six to 10% of patients who suffered from acute hepatitis A virus infection[3,6,19,20].

HAV infection carries a risk of fulminant hepatic failure in the course of a symptomatic infection that varies between 0.14 and 0.35%[21]. The case-fatality rate ranges from 0.02% to 2.5%, depending on the age at onset of HAV infection [22, 23] and other factors (e.g. presence of chronic liver disease).

1.4. Epidemiology

Worldwide, an estimated 1.4 million cases of hepatitis A (HA) are reported annually (Table 1). The highest disease figures are found in Asia, Africa and Eastern Europe[3]. Since reporting is often incomplete and highly variable, the true incidence data may be three to 10 times higher[3].

Table 1: Estimated reported number of HAV cases per continental region (ref. 3)

REGION 1990	POPULATION (in millions)	INCIDENCE PER 100,000 PER YEAR	CASES/YEAR
North America	275	10	28,000
Central + South America	453	20-40	162,000
Europe	791	5-60	278,000
Africa + Middle East	827	20-60	251,000
Asia	2,893	10-30	676,000
Oceania	28	15-30	5,000
Total			1,400,000

Five different epidemiological patterns emerge when incidence rates and age-specific anti-HAV prevalences are examined, giving rise to five geographical risk areas around the world[3,24,25] (Table 2). These patterns correlate with socio-economical and hygienic conditions.

In the poorest developing countries, the very high endemicity pattern is characterized by infection with HAV at very young age, with over 90% of children infected by the age of five[26]. This pattern is seen in Africa, parts of South America, the Middle East and South East Asia, where overcrowding is common, and where hygiene and sanitation are substandard.

Table 2: Epidemiological patterns of HAV infection worldwide (ref. 3)

HAV Endemicity	Regions by epidem. pattern	Average age of patients (years)	Most likely mode of transmission
Very high	Africa, and parts of South America, the Middle East and South East Asia	under 5	• person-to-person
High	the Amazon basin of Brazil, China and Latin America	5-14	• person-to-person • outbreaks/ contaminated water or food
Inter-mediate	Southern and Eastern Europe, the NIS and some countries in the Middle East	5-24	• person-to-person • outbreaks/ contaminated water or food
Low	United States, Australia and some countries in Western Europe	5-40	• person-to-person • common-source outbreaks
Very low	Northern Europe and Japan	over 20	• exposure during travel to areas of high endemicity; • outbreaks uncommon

A second pattern, high endemicity, is seen in the Amazon basin of Brazil, China and Latin America. Fewer children are infected by the age of five, but over 90% develop anti-HAV by the age of ten[27].

In the highest endemicity areas, reported disease incidence may vary from 1 to 40 per 100,000 per year. In high endemicity areas, reported disease incidence may reach 150 per 100,000 per year, because infection occurs (more symptomatically) primarily in older children (Table 2).

A third epidemiological pattern, intermediate endemicity, is characterized by relatively high levels of viral circulation, significant cohorts of susceptible older children and adolescents, and high rates of hepatitis A associated morbidity. This pattern is seen throughout Southern and Eastern Europe and the Newly Independent States (NIS), and in some Middle Eastern countries. In countries of intermediate endemicity, 90% anti-HAV prevalence is not reached until early adulthood[28].

Paradoxically, when standards of hygiene improve, morbidity increases because a higher proportion of infections occur in adulthood when they are more likely to cause overt disease. This explains why disease incidence in areas of intermediate endemicity equals that of high endemicity countries. In 1989, the USSR, Romania and Bulgaria reported even higher incidence rates, which varied between 250 and 300 cases per 100,000[29].

A fourth pattern (low endemicity) is seen in the United States, Australia and some countries in Europe[3]. Reported disease incidence varies between 5 and 15 cases per 100,000. Anti-HAV prevalence reaches 10% by age 15, increasing to 70% in late adulthood (due to a cohort effect).

Finally, a fifth pattern (very low endemicity) is seen in Northern Europe and Japan, and is characterized by a low reported annual disease incidence (<5/100,000)[3]. Disease occurs almost exclusively in adults, usually when they are exposed to HAV while travelling in high endemic regions.

Western Europe encompasses three epidemiological patterns: intermediate endemicity in Greece, Spain, Italy, France and Belgium; low endemicity in Switzerland and Germany; and very low endemicity in Scandinavia. The increasing prevalence of anti-HAV from northern to southern Europe is closely associated with environmental, housing and sanitary conditions.

Significant changes in epidemiological pattern of hepatitis A have been observed in all Western European countries over the past 15-20 years. The epidemiological shift was first observed in Scandinavia in the 1930s, and later in the low endemic areas, followed more recently by the intermediate endemic countries[28].

Mediterranean countries also have witnessed a substantial decline in the age-specific prevalence rate of anti-HAV[30,31]. In Athens, anti-HAV prevalence in the 5-9 and 10-18 year age groups decreased respectively from 30.0% and 63.2% in 1977 to 2.5% and 6.0% in 1990[30].

France and Belgium too are shifting from intermediate to low endemicity status[32,33]. Studies in France show that in 1991 about 75% of those under 25 were not immune to HAV infection[34]. Anti-HAV seroprevalence studies among young French military recruits (mean age 20 years) show a 9% decrease in five years: from 50% in 1978, to 30.4% in 1985 to 21.4% in 1991[35]. More recent data (1993) among French recruits reveal a seroprevalence of 16.5%.

A study in Flanders, Belgium (1993-1994) showed that seroprevalence increased with age: from 5.4% in the youngest age group (0-14 years), to over 80% in the two oldest age groups (55-64 years and >65 years). Prevalence rates were as high as 31.7% in the 25-34 year old age group, and 60.8% among 35-44 year olds[33].

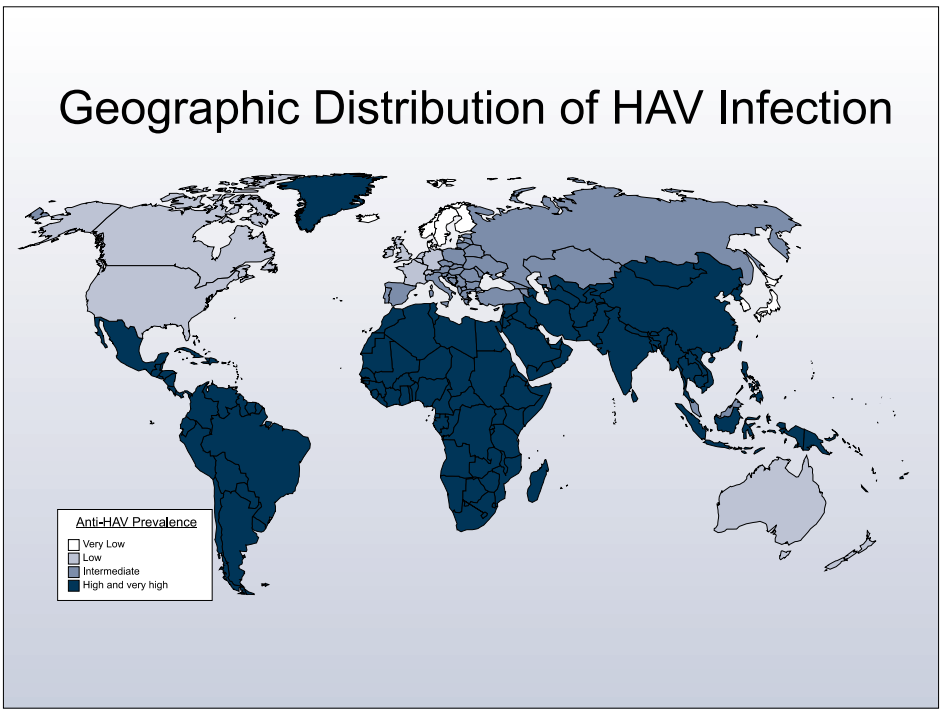
In Sweden, after a 20-year interval, researchers recently investigated the anti-HAV seroprevalence in a sample of the adult population. The authors concluded that when only the Scandinavian population was considered, the endemicity for hepatitis A had remained unchanged since the 1960s: the prevalence was 6% in those born in the 1940s. In the population born after 1950, anti-HAV prevalence was only 2%[36] .

Table 3 gives the hepatitis A incidence data for several European countries, based on reported hepatitis A cases, and estimated data corrected for under-reporting.

Table 3: Estimated and reported incidence data for hepatitis A (1993-1994)

COUNTRY	REPORTED CASES (per 100,000/year)	ESTIMATED (per 100,000/year)
Spain	ND	20-30
France	11	40-60
Italy	5-10	20-40
Belgium	4	20-30
Switzerland	13	ND
W-Germany	15	ND
USA	10-15	28

ND = No data available.



1.5. Risk groups

Population-based epidemiological studies and disease surveillance in countries of intermediate, low and very low endemicity have identified groups at increased risk of HAV infection. These include travellers, military personnel, development and relief workers, children and staff in day-care centres, residents and workers in institutions, contacts of HA patients, injecting drug users and homosexually active men[37-39].

There is consensus that frequent business travellers, healthcare staff, development and relief workers, and military personnel deployed from areas of low endemicity to areas of intermediate and high endemicity for HAV are at risk and should be vaccinated[40-42]. Where areas of high and intermediate endemicity for HAV and HBV coincide, the combined vaccine is preferred.

Sound epidemiological evidence to substantiate the claims of others such as healthcare personnel, institutional staff and sewage workers that they are at increased risk of HAV is lacking[40-42] but vaccination of sewage workers might be considered as part of an outbreak control strategy[43].

Although food handlers are not themselves at increased occupational risk[40-42], infected food handlers have the potential to transmit HAV when touching unwrapped food which is to be consumed raw or without further cooking. When taking into account the consequences of compensation claims from infected customers, the disruption of business and the adverse publicity that would arise from proven causation, employers might consider that prophylactic vaccination of all or selected staff would be economically attractive.

National disease surveillance systems in England[1], the United States[39,44], Sweden[45], Switzerland[46], Austria[47], Spain[48], and France[49] have identified the major sources of infection of HAV.

The most commonly reported risk factor associated with acquiring hepatitis A is personal contact with a hepatitis A patient (7-31%). Employment or attendance at a day-care centre accounted for 12% to 18% in the UK and the US. Day-care centre outbreaks appear to be specific to the UK and US, suggesting low hygiene standards in the centres.

A history of recent international travel accounted for a small proportion of cases in the US (4-6%), as compared to Sweden (16%), Switzerland (41%), Austria (23%), Spain (21%) and France (19%). This could be explained by the difference in epidemiological patterns between low and very low endemic countries[3].

Illicit drug use is a risk factor in Sweden, Switzerland and the US. Poor hygiene is thought to account for the majority of cases, although contamination of drugs or transmission through needle sharing may also account for a small proportion of disease[45].

A common situation is illustrated by Austria, where foreigners residing there and visiting their country of origin each year represent a separate source of HAV infection. Usually, children of foreign workers contract the infection on holidays abroad and cause secondary morbidity upon their return[47]. A similar source of HAV infection has been identified in the Netherlands (J. van Steenbergen; personal communication), in France, and in the US among Hispanics.

While common source (waterborne or foodborne) outbreaks of hepatitis A can have significant impact on communities, overall they do not account for a large proportion of cases.

No known risk factor could be identified for a high proportion of reported hepatitis A cases.

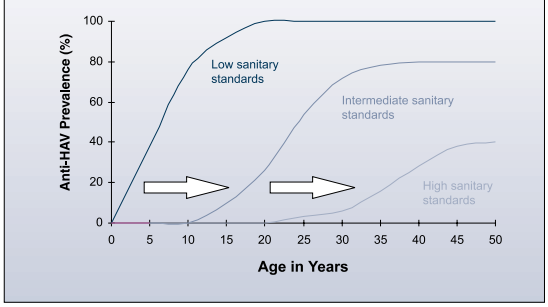
Groups that may be at increased risk of hepatitis A virus infection

- Travellers to endemic areas
- Military personnel
- Development and relief workers
- Children and staff in infant (<3 years) day-care centres
- Residents and workers in institutions
- Contacts of hepatitis A patients
- Injecting drug users
- Homosexually active men

1.6. Epidemiological shift

Improvements in hygiene and sanitation over the past 20 years have reduced the circulating levels of HAV and resulted in the emergence of a growing population of non-immune subjects[3,50,51], causing an epidemiological shift of HAV prevalence to older age groups (Figure 2). This has important implications. While improvements in hygiene and sanitation are rewarded by a drop in HAV incidence, natural immunity to infection shifts to older age groups, leaving greater numbers of children, adolescents and young adults susceptible to the residual circulating virus. Consequently, the average age of exposure and subsequent infection is later in life, where clinical illness is more frequent and the rate of morbidity higher[3].

Figure 2: **HAV Infection**
Prevalence and Sanitary Standards



2. EFFECTIVENESS OF HEPATITIS A VACCINE IN CONTROLLING OUTBREAKS

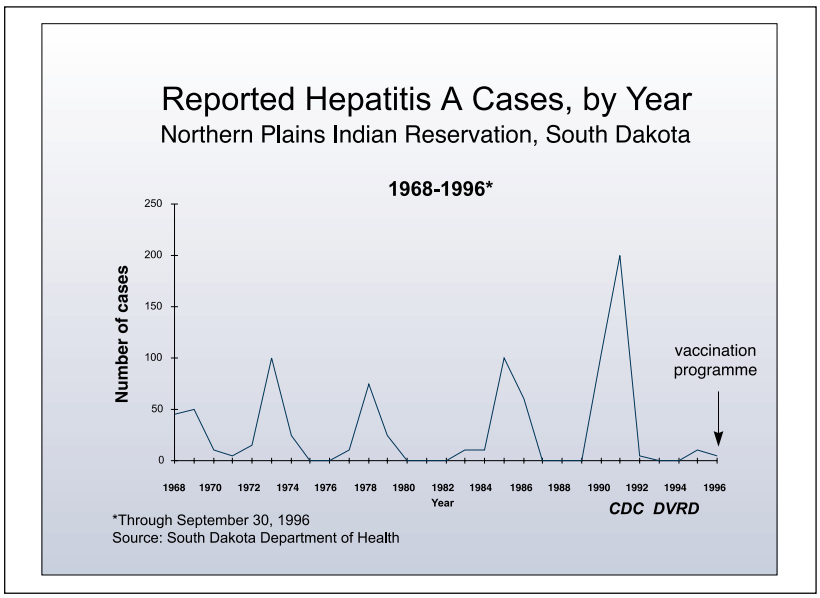
A number of communities in the United States with high rates of hepatitis A have implemented hepatitis A vaccination programmes to control community-wide outbreaks. These communities typically have epidemics of hepatitis A every 5-10 years during which peak rates reach 700-1,000/100,000 population. Few cases occur in persons >15 years of age and seroprevalence data indicate that 30%-40% of children in these communities acquire infection before five years of age and almost all persons become infected before reaching adulthood. These communities often are relatively well-defined, either geographically or ethnically; examples include many American Indian and Alaska Native communities[42]. Hepatitis A vaccination programmes conducted in these communities with high rates of hepatitis A appear to have been effective, provided the programme is begun early in the course of the outbreak and a sufficient proportion of the target population, generally children and some adolescents, is vaccinated.

Alaska experiences cyclical hepatitis A epidemics every 10-15 years, and immune globulin has not been effective in controlling them. The highest rates of hepatitis A in Alaska occur among Alaska Natives, particularly children >15 years old. In several Alaska Native villages in which hepatitis A outbreaks were occurring, vaccination of an estimated 79% of susceptible persons with one dose of hepatitis A vaccine resulted in a rapid decrease in the number of reported cases. In contrast, in an area where an estimated 49% of susceptible persons received one dose of vaccine, cases continued to be reported among unvaccinated persons for more than a year[52].

In a Northern Plains Indian Community in South Dakota with high rates of hepatitis A, outbreaks occur approximately every 5-7 years, and an outbreak was predicted for 1995-1996. During 1970-1994, a total of 95-320 cases were reported during outbreaks. In late 1995, a hepatitis A vaccination programme was begun in which approximately 70% of children aged 2-12 years received at least on dose of vaccine. The 20 hepatitis A cases reported in 1995 occurred before or early in the course of the vaccination programme; no cases have been reported since June 1996[53]. Thus, it appears that the vaccination programme, initiated shortly after cases had started to occur, may have prevented a larger outbreak.

Although hepatitis A vaccination appears to be effective in terminating hepatitis A outbreaks in communities with high rates of hepatitis A, there are still a number of unresolved issues surrounding the best use of vaccine to control outbreaks in communities with intermediate rates of hepatitis A. In these communities, which are often large metropolitan areas, most disease occurs among children, adolescents, and young adults. Overall disease rates during epidemic periods typically range from 50-200/100,000, but within some neighbourhoods disease rates may be as high as those in communities with high rates of hepatitis A[42].

A vaccination programme in Memphis, Tennessee targeted the approximately 50,000 children aged 2-9 years living in an inner city area with the highest hepatitis A rates. At least one dose of vaccine was administered to approximately 50% of eligible children. Although hepatitis A rates decreased in the target population, this decrease began before the vaccination programme was initiated, making it difficult to determine the effectiveness of the vaccination programme[54].



In Butte County, California, the incidence of hepatitis A decreased concurrently with the implementation of a primarily school-based vaccination programme in late 1994 in which approximately 38% of children aged 2-12 years received at least one dose of hepatitis A vaccine. During the outbreak in 1993-94, the highest rates of hepatitis A occurred among persons aged 5-9 and 25-29 years. With ongoing implementation of the vaccination programme, rates among children have remained low[55].

Experience with implementing hepatitis A vaccination programmes in these communities with intermediate rates of hepatitis A indicates that hepatitis A vaccine may be effective in controlling ongoing community-wide outbreaks and preventing future outbreaks in some of these communities. However, more experience is needed to determine the most effective methods. Unresolved issues include determining the optimum time to intervene, identifying appropriate target groups, determining the proportion of the target population that must be vaccinated, and evaluating the feasibility and cost-effectiveness of these programmes.

3. VACCINATION POLICY

3.1. Prevention of HAV infection

Various means can be used to control the spread of HAV infection: provision of clean water, proper disposal of faeces, and passive and active immunization.

The protection rate of passive immune globulin (IG) is 85% and protection at the recommended dose of 0.02 ml/kg lasts for two to three months. Immune globulin is effective when administered before exposure or within two weeks after exposure to the virus.

In terms of active immunization with vaccine, a number of types of vaccine are currently available: inactivated, life attenuated or vaccines using reconstituted influenza virisomes as the carrier system. Inactivated vaccines have been evaluated for efficacy in controlled clinical trials.

Two live attenuated hepatitis A vaccines are now licensed in China, and several live attenuated vaccines are currently under development.

Inactivated hepatitis A vaccines can generally be prepared by purification of virus propagated in cell culture, followed by inactivation (e.g. with formalin) and possibly adjuvanting with aluminium hydroxide.

Several inactivated hepatitis A vaccines are now commercially available and are mentioned in alphabetical order*. Avaxim® (Pasteur Mérieux Connaught) is an inactivated hepatitis A vaccine (160 antigenic units administered according to a 0,6 month schedule) registered in many European countries. It is currently available in France, the Netherlands, Sweden and the United Kingdom[56].

An inactivated virosome hepatitis A vaccine has been developed (Epaxal®, Swiss Serum Vaccine) and is currently marketed in Switzerland and Argentina[57].

Havrix® (SmithKline Beecham Biologicals) is an inactivated hepatitis A vaccine commercially available in Europe since 1991/1992. It is currently licensed in three formulations; the formulation and number of doses differ according to the age of the vaccinee. For children and adolescents 1-17 years of age, the formulation is 360 EL.U. per dose according to a 0, 1, 6 to 12 month schedule; and 720 EL.U. per dose in a two-dose schedule (0, 6 to 12 months). For adults above 17 years of age, the formulation is 1,440 EL.U. per dose in a two-dose schedule (0, 6 to 12 months)[58-61].

Another inactivated hepatitis A vaccine, Vaqta® (Merck & Company, Inc.) is licensed in two formulations. The formulation and number of doses differ according to the person's age: for children and adolescents 2-17 years of age, 25 units in a 0, 6 to 18 month schedule is recommended. For adults over 17 years of age, 50 units per dose in a two-dose schedule (0, 6 months) is recommended[62,63].

These inactivated hepatitis A vaccines are highly immunogenic, inducing anti-HAV titres above those observed following administration of IG in more than 99% of adults already at one month after first vaccination; 14 days after a single dose the seroconversion reaches approximately 90%. No serious adverse events have occurred in phase II and phase III trials. Field trials (double-blind, placebo-controlled, randomized clinical trials) with two separate inactivated vaccines produced from different strains (Havrix® and Vaqta®) have demonstrated 94-100% efficacy in preventing clinical hepatitis A[64,65].

Long-term persistence studies on vaccine-induced hepatitis A antibodies show similar antibody decline rates over time for different inactivated hepatitis A vaccines. The exact duration of protection after HA vaccination is unknown. However, antibody decay studies and estimates of antibody persistence derived from kinetic models indicate that protective levels of anti-HAV could be present for 10 to 20 years[61,66]. Continued observation of immunized groups will be required to determine the need for subsequent booster doses of vaccine and to design a booster policy. Whether cellular memory also contributes to long-term protection is unknown.

Anti-HAV screening prior to vaccination depends upon the expected prevalence of anti-HAV in the population, the cost of the screening test and the cost of the vaccination. In industrialized countries it is usually cost-effective to screen persons born before 1945, as more than 50% are likely to be anti-HAV positive.

Twinrix® (SmithKline Beecham) is a combined hepatitis A and B vaccine, containing inactivated hepatitis A (Havrix®) and recombinant hepatitis B (Engerix-B®). It is available in Australia, Canada and some countries in Europe, and is licensed for children and adolescents 1 to 15 years of age (360 El.U hepatitis A + 10 mcg HBs antigen) and for persons over 16 years of age (720 El.U hepatitis A + 20 mcg HBsAg) on a 0,1,6 month schedule[67,68].

** Use of trade names is for identification only.*

Means to control hepatitis A

- provision of clean water
- proper disposal of faeces
- passive immunization
- active immunization

3.2. Vaccination strategies

The optimum hepatitis A vaccination strategy for a region is dependent on the epidemiological pattern of HAV, the risk groups involved, the duration of protection, the possibility of post-exposure protection, and the cost of the intervention.

A number of groups at high risk of HAV infection as a result of behaviour, lifestyle or occupation have been identified; these include travellers to endemic areas, military personnel, children and staff in day-care centres, intravenous drug users, homosexually active men, and contacts of hepatitis A patients. These groups have been the primary targets of hepatitis A vaccination programmes.

Pre-exposure vaccination of travellers and military personnel has been shown to be feasible and economically convenient[69,70]. As travellers, however, account for only a small proportion of reported hepatitis A cases (except in very low endemic countries), this intervention will not have a significant impact on the burden of hepatitis A disease.

Contacts of hepatitis A cases form a larger risk group, and passive immunization has been shown to confer post-exposure protection, if given up to two weeks after exposure.

Other risk groups, particularly IV drug users, are more difficult to reach. In addition, it is important to note that many cases of hepatitis A have no identified risk factor or infection source. Immunization programmes directed only to high-risk groups would miss those with unidentified risks, and subsequently would not be expected to reduce the impact of the disease or eliminate hepatitis A.

Hepatitis A vaccination has been shown to be effective in controlling outbreaks of hepatitis A in communities that have high rates of hepatitis A (VHPB Report on the IX Triennial International Symposium on Viral Hepatitis and Liver Disease. *Viral Hepatitis*, Rome, Vol 5, nr 2, April 1997). In communities with high rates of hepatitis A, routine vaccination of children two years of age combined with catch-up immunization of older, previously unvaccinated children can be implemented to control ongoing outbreaks, provided that a sufficient rate of coverage (at least 70%) is achieved[42].

Vaccination of children or adolescents in communities with intermediate rates of infection may also be used to control hepatitis A outbreaks. Targeting defined populations with the highest rates of disease for immunization may be the most feasible and cost-effective approach for an immunization programme[42].

The frequency of outbreaks in day-care centres, hospitals, institutions and schools is not high enough to warrant routine hepatitis A immunization in these settings. When outbreaks do occur, aggressive use of IG is recommended. Although further study is needed, the available data from hepatitis A vaccine post-exposure efficacy studies suggest that the vaccine may be able to replace IG in the control of day-care centre outbreaks. Further studies should be carried out to evaluate the effectiveness of hepatitis A vaccination in controlling these outbreaks[40].

Because of the important role of children in the transmission of hepatitis A, the strategy for use of hepatitis A vaccine may be universal childhood vaccination. A routine childhood immunization programme could counterbalance the problems already discussed for high-risk group immunization, and have a tremendous impact on overall disease incidence within five to 10 years[39]. This strategy has other potential benefits: an established vaccine delivery system is in place, and vaccination would occur before the greatest risk for clinical disease. With universal vaccination, HAV could be eradicated as humans appear to be the only host of the virus.

For routine childhood immunization programmes to be effective, however, hepatitis A vaccines would have to confer long-term protection, preferably without requiring a booster.

Other issues that would need to be resolved include:
- the appropriate dose and timing of vaccination in the first or second year of life;
- the importance of the effect of maternal antibody on immunogenicity;
- the optimum vaccine dose and vaccination schedule to overcome the effect of maternal antibody;
- developing combined vaccines that incorporate hepatitis A vaccine; and
- the duration of protection following vaccination of children.

If hepatitis A vaccine were to have a limited duration of protection, infection could occur at an older age and the intervention could convert an otherwise asymptomatic childhood infection into a symptomatic disease later in life. Intervention could then do more harm than good[71,72].

In most developing countries hepatitis A is not a real public health priority. In those countries with the lowest living standards, the highest population density and poor hygiene and sanitation, hepatitis A is acquired in early childhood when infections are usually asymptomatic. Other public health priorities predominate in the choice of preventive strategies, and these countries do not at present need to consider universal hepatitis A immunization programmes.

4. CONCLUSION

Hepatitis A virus infection represents a significant cause of morbidity in many parts of the world. Passive immunization provides temporary protection and is very efficient in post-exposure prophylaxis, but it is not effective in controlling HAV on a community level.

By affording long-term protection, HA vaccines may offer great advantages to specific groups as well as on a population level, in terms of HA prevention, control of infection, and reduction of the burden of disease.

Recommendations for HA vaccination depend upon specific epidemiological circumstances and economic evaluation of preventive intervention programmes. The VHPB strongly supports the use of general hygienic measures in households and the workplace to prevent transmission of hepatitis A.

The VHPB endorses the use of HAV prophylaxis for travellers from low endemicity countries travelling to intermediate or high endemicity countries (i.e. outside the US, Canada, Western Europe, Japan, Australia, New Zealand, Hong Kong and Singapore). Vaccination is the preferred method of prevention, especially for those travelling frequently, or for long periods of time.

As there is no convincing epidemiological evidence that healthcare workers and sewage workers are at increased risk for hepatitis A, additional studies are required to formulate appropriate use of hepatitis A vaccines in these groups. Use of hepatitis A vaccine should be considered in homosexually active men and injecting drug users. Consideration also should be given to vaccination of persons with chronic liver disease.

If it is determined that vaccine provides post-exposure protection, use of vaccine should be considered in outbreak situations at day-care centres and residential institutions (e.g. institutions for the mentally retarded and prisons), as well as in food establishments. Based on a number of recent studies it was found that hepatitis A vaccine is effective in controlling outbreaks in communities with high rates of hepatitis A[42,52-55,65,73]. However, there are still a number of unresolved issues:

■ Cost-effectiveness analysis of pre-exposure vaccination of staff and children in day-care centres, food handlers, healthcare workers and sewage workers are needed to formulate appropriate recommendations.

■ It is still important to carry out detailed research into different aspects of the vaccine's effectiveness before it is administered on a wide scale. Studies should consider:

- Long-term protection of vaccine-induced antibodies.
- Post-exposure efficacy of the vaccine.
- The extent of immunological memory provided by the vaccine.
- Prevention by vaccination of shedding of virus while immunized.
- Additional HAV risk in some occupational groups.

■ The VHPB encourages countries to carry out studies addressing the cost-effectiveness of HA prevention strategies to help determine the feasibility of vaccination programmes.

■ Accurate epidemiological information is required to recommend appropriate use of HA vaccine, and the VHPB encourages surveillance of acute hepatitis (with differentiation of type of virus), including tracing of risk factors. The implementation of hepatitis surveillance programmes should be a goal of countries which do not currently carry out surveillance (see Report on the Viral Hepatitis Prevention Board meeting, Athens, Greece, *Viral Hepatitis*, Vol 5, nr 3, 1997).

Summary

- Hepatitis A virus infection represents a significant cause of morbidity in many parts of the world.
- Passive immunization does not control HA on a community level.
- HA vaccines offer long-term protection.

VHPB recommendations

- The use of general hygiene and sanitary measures are essential to prevent the spread of hepatitis A.
- The VHPB endorses HAV prophylaxis for travellers visiting high endemicity countries.
- HA vaccines should also be considered in groups such as homosexually active men and intravenous drug users.
- Further studies are needed to establish the occupational risk of hepatitis A for healthcare workers.

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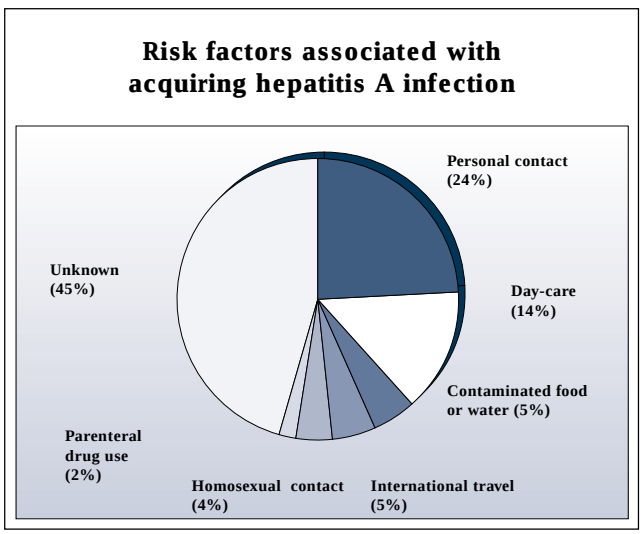
NEWS ON HEPATITIS A

EPIDEMIOLOGY OF HEPATITIS A IN THE UNITED STATES

In the United States, hepatitis A infection is very heterogeneous and dynamic, varying from region to region and even within individual states. Seroprevalence is inversely related to socio-economic status and increases with age, poor sanitation and housing, and increasing household sibling size.

Hepatitis A has been a reportable disease in the United States since 1952, and as of 1993 was the sixth most commonly reported disease in the country, although infection rates have been declining steadily since 1960.



As of 1996, risk factors associated with acquiring hepatitis A infection included: personal contact (24%); day-care (14%); contaminated food or water (5%); international travel (5%); homosexual contact (4%); and parenteral drug use (2%). In the majority of cases (45%), however, the risk factor is unknown. A pattern of hepatitis A outbreaks associated with illicit drug use has also been identified. The exact reason for these outbreaks is not fully understood, although it is assumed to be associated with lifestyle.

Most hepatitis A in the United States occurs through person-to-person transmission in the setting of community-wide outbreaks, although some communities maintain high rates of disease. Incidence rates for hepatitis A vary widely according to ethnicity, with very high incidence rates of hepatitis A found among Native Americans (100/100,000) and high rates seen in Hispanic populations (20/100,000).

Communities with high rates of hepatitis A include American Indian populations, Pacific Islanders, Alaskan Natives and certain religious communities. These highly defined populations experience periodic epidemics of infection which are characterized by child-based transmission. Anti-HAV prevalence in these populations reaches 30-40% by the five-year-old age group; prevalence is between 70 and 100% for those over 15 years of age.

In communities with intermediate rates of hepatitis A, children also play an important role in transmission, although epidemics among adult populations are also found. Adult-driven epidemics usually occur within specific sub-populations, such as drug abusers and homosexual men. In communities with intermediate endemicity, a 50% prevalence rate is reached in the over-15 age group.

Both immune globulin and a risk-group approach to immunization have been used in efforts to control transmission of hepatitis A in the US; neither approach has proved successful.

Currently, the Centers for Disease Control and Prevention (CDC) recommends routine vaccination of children in communities that have high rates of hepatitis A and periodic outbreaks, travellers to areas of high or intermediate endemicity of infection, homosexually active men, illegal drug users, persons who have chronic liver disease, and persons who have clotting-factor disorders. The CDC also recommends the use of vaccine to control outbreaks of hepatitis A in communities with high rates of hepatitis A; vaccination of children or adolescents may also have the potential to control hepatitis A outbreaks in communities of intermediate endemicity, although the effectiveness of using HA vaccine in these settings has not been determined and further studies are required to define the optimal immunization strategies.

Characteristics of community-wide hepatitis A outbreaks

- Prolonged, usually 1-3 years
- Slow onset, slow decline
- Incidence rate ranging from 25-2,500/100,000 per year
- Often involving large segments of the community, geographically and demographically
- Transmission is person-to-person, based in young children or adults
- Immune globulin is not effective in control

As presented by Dr Frederic Shaw, Consultant, McLean, Virginia, USA.

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PERSISTENT OUTBREAK OF HEPATITIS A SEEN IN PUGLIA, ITALY

During the first 11 months of 1996 (with peak incidence in August), an outbreak of hepatitis A occurred in Puglia, Italy, a region in the southeast of the country. This was the largest and most persistent epidemic of hepatitis A reported from Puglia since the infection became notifiable in 1989. The outbreak began in the city of Bari and subsequently spread throughout the region.

By the end of 1996, 5,620 cases had been notified, for a cumulative incidence rate of 137.3/100,000. This compares with previous rates per 100,000 of: 22 in 1990; 18 in 1991; 68 in 1992; 22 in 1993; 33 in 1994; and four in 1995. The outbreak was highest in Bari City (381.3/100,000), and overall, people aged five to 34 accounted for 96% of all cases of notified hepatitis A.

Outbreak investigation showed a strong association between illness and the consumption of raw seafood and the storage of seafood in sea water at the place of sale. Recommendations on the handling and consumption of seafood had little impact on the epidemic which did not subside until week[42].

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

Reference: Lopalco PL, Malfait P, Salmaso S, Germinario C, Quarto M, Barbuti S, A Persisting Outbreak of Hepatitis A in Puglia, Italy, 1996: Epidemiological Follow-up. Eurosurveillance, 1997; 2: 31-32.

VACCINE NEWS

COMBINED PAEDIATRIC VACCINE WELL RECEIVED IN FRANCE

In France, a combined paediatric vaccine has been available and in wide use since 1993, and is well received by physicians and the public. The combined vaccine used in France includes five components: diphtheria, tetanus, pertussis whole-cell vaccine, inactivated polio, and T conjugate Hib vaccine. The vaccine contributed to the successful integration of the Hib vaccine into the immunization schedule, and most physicians in the private sector now prescribe the combined vaccine. The official recommendation includes three doses administered one month apart starting at two months of age, with a fourth dose administered at 16 months. Vaccine uptake has been high, with 86% of children completing the four-course schedule by the age of two.

It has been estimated that only 20% of the under-two population in France is immunized against hepatitis B, despite the 1994 national recommendation for universal infant hepatitis B immunization. Experts in France are optimistic that the introduction of a combined vaccine including the hepatitis B component would help to improve dramatically the uptake of hepatitis B vaccine in infants in the country.

As presented by Dr Nicole Guérin, International Children's Centre, Paris, France.

NO EVIDENCE THAT HEPATITIS B VACCINE CAUSES MULTIPLE SCLEROSIS

Articles in the French media have raised concerns among the French public that hepatitis B (HB) immunization may be linked to new cases or flare-ups of multiple sclerosis (MS) or other demyelinating diseases. These concerns have led to significant reductions in the uptake of HB vaccine in France.

Scientific data do not support the idea that HB vaccine causes or exacerbates MS. Universal childhood and/or adolescent immunization with HB vaccine is now a policy in 85 countries, and misinformation has the potential to cause significant damage to important public health programmes.

Recently, one neurologist publicized the fact that he had seen several cases of MS or demyelinating disease in women who had received HB vaccine. This was picked up by anti-vaccination groups, and a number of patients with MS now claim that their disease was caused or exacerbated by HB vaccine.

Epidemiological evidence for a causal association requires showing that MS or exacerbations of MS occur more frequently in HB vaccine recipients than in a comparable (age, sex and ethnicity matched) population of unvaccinated individuals. This has never been demonstrated. In fact, in all studies which have examined this issue, no increase in the incidence of MS or MS exacerbations have been found in recipients of HB vaccine.

MS is a disease of the central nervous system (CNS) characterized by the destruction of the myelin sheath surrounding neurons. MS is a progressive, often fluctuating disease with exacerbations and remissions over many decades usually resulting in permanent disability and sometimes death.

The cause of MS is unknown. The most widely accepted hypothesis is that MS occurs in patients with a genetic susceptibility, and that some environmental factor or factors 'trigger' clinical exacerbations. The genetic predisposition is well supported by many studies showing an increased risk of MS in family members of cases, identical twins, certain ethnic populations, and certain HLA subtypes.

- There is no evidence of an association between hepatitis B virus (HBV) infection and MS or other demyelinating diseases. The geographical incidence and prevalence of HB are the opposite of those for MS, Scandinavia and Northern Europe having the highest rates of MS and the lowest rates for HBV infection.
- Published and unpublished studies looking for an increased rate of MS, exacerbations of MS, or other demyelinating disease in recipients of HB vaccines have found no such increase.
- While any risk of MS following HB immunization is hypothetical, the risk of HB infection and disease in non-immunized individuals is real. HB causes an estimated 4 million acute infections worldwide each year, and currently there are more than 350 million chronic carriers of HBV, approximately 25% of whom will die from cirrhosis of the liver or primary liver cancer. HB vaccines are safe, more than 90% effective in preventing disease, and very cost-effective. It is unfortunate that unsubstantiated claims that HB vaccines might cause MS are reducing the uptake of this important vaccine.

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For further information please contact the VHPB Executive Secretariat at:
The VHPB Executive Secretariat
Centre for the Evaluation of Vaccination
WHO Collaborating Centre for Prevention and Control of Viral Hepatitis
Epidemiology and Community Medicine
University of Antwerp • Universiteitsplein 1 • B-2610 Antwerp, Belgium
Tel 32 (0) 3 820 25 23 Fax 32 (0) 3 820 26 40
http://vhpb-www.uia.ac.be/vhpb/