

Review

A Role for Combined Vaccination against Hepatitis A and B?

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ABSTRACT

This report reviews hepatitis A and B immunization recommendations and assesses the potential role of a combined hepatitis vaccine. Although hepatitis A and B are very different diseases, overlap exists in their epidemiologic patterns. Both are most prevalent in developing countries, with areas of low endemicity in industrialized nations. Potential sources of infection common to both hepatitis A and hepatitis B (i.e., international travel, close contact with residents of institutions or young children and infants, male homosexual activity, and drug use) indicate that certain groups may be at increased risk of both diseases. Well-tolerated and immunogenic vaccines are available for both hepatitis A and hepatitis B. Although hepatitis B vaccine is now being introduced into universal infant immunization programs in many countries, hepatitis A vaccination is currently recommended for high-risk groups only. This review examines the potential role of a single vaccination against both forms of hepatitis.

Key Words: *hepatitis A, hepatitis B, immunization, risk groups, vaccination*

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Hepatitis A and B pose serious public health concerns worldwide. Every year, approximately 1.4 million cases of hepatitis A are reported,¹ and worldwide, there are between 300 and 350 million chronic carriers of hepatitis B.²

Hepatitis A virus (HAV) and hepatitis B virus (HBV) are very different: HAV is a small, nonenveloped RNA virus of the *Picornaviridae* family, whereas HBV is larger, with a DNA genome and lipid envelope.^{3–5} Although modes of HAV and HBV transmission differ, considerable overlap exists between the populations that they affect.

There has been a marked decline in the incidence of hepatitis A in industrialized countries, starting shortly

before World War II and becoming more rapid during the past 25 years, largely due to improved standards of living. As a result, levels of natural immunity to HAV infection are decreasing. Some groups remain at increased risk of infection because of their work or lifestyle. Similarly, rates of HBV infection are generally low in these countries, but high within certain at-risk groups.

After hepatitis B vaccine became available, many countries adopted immunization strategies targeting high-risk groups. However, these strategies have two major limitations: (1) individuals at increased risk cannot always be identified before infection and (2) many reported cases of hepatitis cannot be related to identifiable risk factors. A routine, universal vaccination policy has been cited as a more effective means of control for hepatitis A and hepatitis B.^{6,7}

In less developed countries, both forms of viral hepatitis remain highly endemic and present a serious health issue within these countries. Because of increasing international travel and the resulting exposure of non-immune individuals from countries where these viruses are less prevalent, distance is no longer a barrier to the spread of these diseases.

TRANSMISSION

Direct, person-to-person contact is the most important mode of HAV transmission worldwide; it spreads rapidly within closed communities via the fecal-oral route.^{1,5,8} Asymptomatic, infected infants and children who have not yet been toilet trained may pose particular risks to family or caregivers; in addition, frequent hand-to-mouth contact in these age groups also facilitates transmission through nurseries, schools, and daycare centers. In a variant of the fecal-oral route, oral-anal contact between homosexuals is also a high-risk activity for hepatitis A.⁹

Food or water contaminated with the virus may cause outbreaks of infection.^{10–12} In a study addressing the survival of HAV in food and water, survival in samples of fresh, sea, and waste water, sediment, and various soils ranged from less than 0.1% to 3.2% after 84 days at 25°C.¹³ The same study demonstrated that more than 10% of HAV survived for 5 days in live oysters, and more than 1% survived on contaminated confectionery maintained at 21°C for 1 month.

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Hepatitis B virus can be present in almost any body fluid or secretion and can be transmitted via parenteral, percutaneous, or permucosal routes. Sexual transmission, during heterosexual and homosexual intercourse, is the major route of infection in industrialized countries, where it may account for over 50% of new cases.¹⁴⁻¹⁶

Perinatal, vertical transmission from a carrier mother to her child usually occurs during delivery. Transmission rates of 70 to 90% have been reported in the offspring of hepatitis B e antigen (HBeAg) and serum HBV DNA positive women, with the lowest transmission rates found in the children of mothers with antibody to HBeAg (anti-HBe).^{17,18} Before the introduction of vaccination programs in Southeast Asia, this type of transmission was responsible for up to 40% of chronic HBV carriers.¹⁹ In contrast, in the Middle East and Africa where there are also high rates of childhood hepatitis B and, hence, chronic infection, horizontal transmission appears to be the principal pathway.²⁰⁻²²

EPIDEMIOLOGY

In general, hepatitis A and B are more endemic in developing countries and less prevalent in industrialized countries (Table 1). Improved socioeconomic conditions, safer water supplies, and better hygiene have markedly reduced HAV infection in an increasing number of countries. In Europe, for example, this trend was initially demonstrated in Germany,²³ and currently, hepatitis A is no longer a common childhood infection in most European countries.²⁴

As a result of the changing epidemiology of hepatitis A, immunity to HAV is decreasing. The prevalence of anti-HAV in children and young adults is falling, leaving generations susceptible to infection (Figure 1).¹ Because

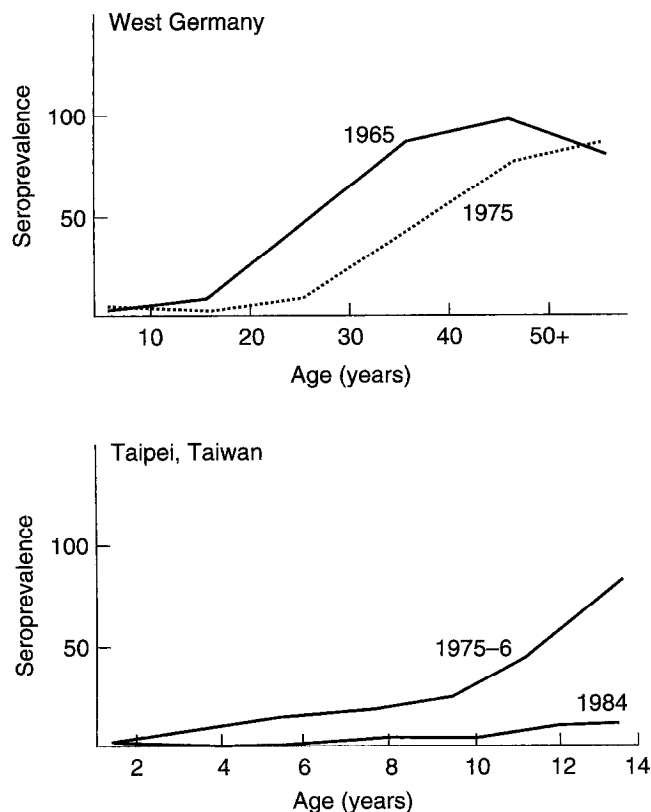


Figure 1. Changes in HAV seroprevalence over 1 decade in two countries. (Reproduced with permission.¹)

the severity of hepatitis A is age-related, decreasing levels of naturally acquired immunity are complemented by an increase in outbreaks of overt hepatitis A among older children, adolescents, and young adults. Recent outbreaks in Italy and in Tarragona, Spain, suggest that this change is in progress.²⁵⁻²⁷ A French study of school children reported that outbreaks often occurred at the start of the

Table 1. Summary of Hepatitis A and Hepatitis B Endemicity

Level to which Disease is Endemic	Prevalence (%)	Chronic Carriers (%)	Distribution	Transmission
Hepatitis A				
Hyperendemic (by age 5 yr)	90	-	Africa, South America, Middle East, Southeast Asia	Person-to-person, community, school, food, water
High (by age 10 yr)	90	-	Amazon Basin, Greenland, China, Central America	
Intermediate (by age 25 yr)	90	-	Southern and eastern Europe, former Soviet Union, Middle East	
Low (by age 50 yr)	70-90	-	North America, Australia, New Zealand, Western Europe	
Hypoendemic (by age >50 yr)	<80	-	Northern Europe, Japan	
Hepatitis B				
High	>60	8-15	Africa, Southeast Asia, South America	Perinatal, person-to-person
Intermediate	20-60	2-7	Southern and eastern Europe, former Soviet Union, Middle East, Japan, South Asia, Central Asia, Central America	Perinatal or person-to-person in infancy
Low	<20	<2	North America, Australia, New Zealand, northern and western Europe	Sexual, parenteral

school year, suggesting that children became infected with HAV while on vacation in areas where the virus is highly endemic and then passed the virus on to their fellow pupils.²⁸ The shift from asymptomatic infant infection to overt infection in older children and young adults may make the initiation of routine hepatitis A vaccination programs more important in the future.

Although HBV has infected more than 2 billion people worldwide, geographic areas may be categorized as high, intermediate, or low endemicity and the disease burden is greatest in the developing nations.²⁹⁻³¹ Prevalence is lowest in regions with the highest standards of living, including North America, Australasia, and northern and western Europe (see Table 1). In the United States, 17,933 confirmed cases of hepatitis B were reported between 1990 and 1992.¹⁵

Hepatitis is not homogeneously endemic throughout a region. Within areas of low prevalence, certain ethnic groups or isolated communities may show a higher level of endemicity than the rest of the population. For example, HAV and HBV are more prevalent among Eskimo communities than in the general population of Alaska, Greenland, and Canada.³²⁻³⁵ Similar patterns of increased hepatitis A or B endemicity in isolated communities within regions where the diseases are not highly endemic have been reported for the Navajo in New Mexico,³⁶ Australian aborigines,³⁷⁻³⁹ and the Maoris of New Zealand.⁴⁰

STRATEGIES AND RECOMMENDATIONS FOR VACCINATION AGAINST HEPATITIS A AND B

Vaccines against hepatitis B have been available since the early 1980s. Initial recommendations for vaccination in countries where the diseases are not highly endemic focused on groups considered to be at high risk of hepatitis B infection. These included infants of HBsAg-positive mothers, the occupationally exposed, homosexual men, heterosexuals with multiple partners, patients exposed to blood products, intravenous drug users, travellers, inmates and staff of institutions, and certain ethnic groups.

Although this strategy offered personal protection of individuals in high-risk groups, it failed to control hepatitis B in any country.⁴¹ In many countries, only one high-risk group accounts for 80 to 90% of vaccine uptake; that is, health care workers, who generally represent less than 10% of cases. No country was able to target other important high-risk groups effectively, such as practicing male homosexuals, intravenous drug users, and prostitutes, because of problems with identification and education and awareness of the risks of hepatitis B.^{42,43} Furthermore, even in countries where hepatitis B is not highly endemic, many cases occur in individuals not readily identifiable as belonging to any high-risk group. Therefore, policy was revised to correspond with that for countries

with high and intermediate levels of endemicity where universal infant vaccination was recommended. Currently, the World Health Organization (WHO) recommends integration of hepatitis B vaccination into national childhood and adolescent immunization programs.⁷ By early 1996, 80 countries had national or regional policies of routine infant or adolescent immunization in place.⁴¹ These include Italy, France, Spain, Portugal, the United States, Canada, and New Zealand, which have low levels of hepatitis B endemicity.

Selective vaccination of high-risk groups still has a role to play, because infant or adolescent vaccination programs do not reach older subjects. In addition, a European Community directive now requires employers to offer hepatitis B vaccination, free of charge, to employees at risk from infection,⁴⁴ and in the United States, employers can be fined for failing to protect employees against blood-borne pathogens.

Hepatitis A vaccine became available in Europe in 1991 and 1992 and has, more recently, been licensed in America. At present, the WHO identifies the following groups as being potentially at increased risk of hepatitis A infection⁶:

- travellers to regions other than North America, Western Europe, Japan, or Australasia, particularly for trips of long duration and for frequent travellers
- daycare children and staff
- individuals with chronic liver disease
- individuals in residential institutions
- homosexually active men
- intravenous drug users
- food handlers.

In future these groups may be extended to include health care workers and sewage workers, after the risk of hepatitis A infection for these individuals has been further assessed.

The WHO suggests that effective control in populations with high and intermediate levels of hepatitis A endemicity will be achieved by routine, universal immunization.⁶ Because hepatitis A is an acute disease and humans are the only natural reservoir, once high levels of immunity are achieved and maintained within a population, the virus cannot re-enter. Increased awareness of the effects of shifting epidemiology may lead to incorporation of routine immunization into national programs in areas where disease is less prevalent.

INITIAL PRIORITY GROUPS FOR COMBINED VACCINATION

Adolescents and Young Adults

In areas with low endemicity, most children are not exposed to viral hepatitis at home or in school. As they

grow up and their horizons expand, however, they begin to travel, take up employment, and become sexually active, and the risk of exposure to one, or both viruses significantly increases. Therefore, routine vaccination of infants or adolescents is the most effective way to control hepatitis A and B.

The rationale for routine hepatitis B vaccination is well established, and by 1997, all countries should have programs of infant or early adolescent vaccination in place.⁷ In the short term, however, there will be adolescents and young adults who will miss out on routine vaccination, thus remaining at increased risk of HBV infection and requiring catch-up vaccination.

As most adolescents and young adults will not have been exposed to HAV during childhood, these same generations are now susceptible to HAV infection. Rather than the mild or asymptomatic infection characteristic of infant infection, hepatitis A in older generations is overt and potentially severe. Mortality is age-related, increasing from 0.3% for those 15 to 39 years of age to 2.1% for those over 40 years of age.⁴⁵

Travellers and Expatriate Workers

Viral hepatitis is one of the most common illnesses to afflict travellers. Hepatitis A is the most frequently occurring vaccine-preventable disease in travellers from industrialized countries visiting developing countries.⁴⁶ For unprotected travellers in good-quality accommodation, it is estimated that the incidence of hepatitis A is 3 to 6 per 1000 per month of stay in a developing country.⁴⁷ Among backpackers and other travellers who eat from street markets, or in unhygienic conditions, the incidence increases to 20 per 1000 per month; this includes many younger travellers.⁴⁷ Among expatriates working in developing countries, an incidence of 0.8 to 2.4 symptomatic or asymptomatic HBV infections can be expected per 1000 per month.⁴⁷ Risk factors for HBV infection in travellers to areas where disease is highly endemic include unprotected sex, surgical or dental procedures, and contaminated needles and syringes used to administer medication.

Several categories of travellers and expatriate workers at risk from hepatitis A or hepatitis B were identified by Lange in 1987.⁴⁸ Military personnel serving overseas represent a readily identifiable category at high risk of both hepatitis A and hepatitis B infection.⁴⁹⁻⁵¹ Many military personnel are young men in the age range least likely to have acquired natural immunity. They may be exposed to poor living conditions in the field, and may indulge in high-risk sexual activity, making immunization a priority for military commands that do not want to have their forces depleted by illness.⁴⁹⁻⁵¹ Missionaries and aid workers are also at high risk. For example, in a study of 360 American missionaries in sub-Saharan Africa between 1967 and 1984, 16% had anti-HAV and 3% anti-HBs before their mission; at the end of their service, seroprevalence

Table 2. Summary of Those at Dual Risk of Infection with Hepatitis A and B in Developing Countries

<ul style="list-style-type: none"> • Military personnel • Foreign service personnel • Missionaries and aid workers • Health care personnel • Travellers spending prolonged periods in Asia, Africa, the Middle East, or the Far East • Persons whose activities or life-style places them at risk

rates were 42% and 26%, respectively.⁵² Travellers and expatriate workers who may benefit from combined hepatitis A and B vaccination are summarized in Table 2.

Men Who Have Sex with Men

In the United States, between 1980 and 1985, 20% of hepatitis B cases resulted from homosexual activity.¹⁶ The risk from anal intercourse is considered particularly high and is further increased by intercourse with multiple partners. However, since the emergence of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), changes in sexual practices ("safer sex") have led to a dramatic decline in the number of cases of hepatitis B among male homosexuals; by 1992 homosexual activity accounted for only 8.4% of cases in the United States.¹⁵

Extensive outbreaks of hepatitis A have been reported among homosexual men in urban areas in the United States, Canada, and Australia.⁵³⁻⁵⁶ Transmission within the homosexual and bisexual communities is most likely to be via oral-anal contact.

Men who have sex with men are candidates for vaccination against hepatitis A,⁶ and despite the reduction in the incidence of hepatitis B since the mid-1980s, they should still be recommended for hepatitis B vaccination. Increased health awareness has made male homosexuals one of the groups most likely to seek health advice; therefore, homosexual and bisexual men should be educated about the risks of hepatitis A and B and, thus, prompted to seek vaccination.

Drug Users

Intravenous drug users in industrialized countries are routinely exposed to blood that has not been screened for viral pathogens, through sharing unsterilized needles. Furthermore, they are unlikely to be receptive to health advice or to seek vaccination. Over the past 10 years, hepatitis A outbreaks among intravenous drug users have been reported in Europe and the United States^{57,58}; hepatitis B has long been recognized as a risk to this group.^{16,59} In the United States, between 1990 and 1992, 13 to 17% of the reported cases of hepatitis B were attributed to intravenous drug use,¹⁵ and in Sweden, between 1986 and 1990, 42.6% of cases of hepatitis B occurred in drug users.⁶⁰ Hepatitis A acquired by intravenous drug use

accounted for 2.8 to 5.9% of cases in the United States between 1990 and 1992.¹⁵

The prevalence of serologic markers for viral hepatitis among intravenous drug users is far higher than among the population at large. A Danish study found that markers of hepatitis A infection were four times higher in intravenous drug users than in the general population, and the prevalence of markers for hepatitis B infection were 30 times higher.⁶¹ In addition to needle sharing, other typical aspects of the drug user's life-style, such as poor living conditions, may contribute to the risk of viral hepatitis.

Health Care Workers

Hepatitis B is among the most common occupational hazards for health care workers.⁶² Although the most frequent method of transmission is through needlestick injury with contaminated (HBsAg-positive) blood, most other body fluids are potentially infectious, including semen, vaginal secretions, cerebrospinal fluid, saliva, and even tears.^{63,64} It is estimated that 502 health care workers in northern Europe and 6423 in southern Europe contract hepatitis B each year.⁶⁵ Cleaning and support staff are to be counted among the highest risk groups, followed by nursing staff, technical support staff, physicians, and surgeons.⁶²

Since the introduction of hepatitis B vaccine, recommendations for its use by health care personnel have brought about the highest uptake rate of vaccination by any of the identifiable risk groups. In Europe, hepatitis B vaccination coverage is 40 to 60% for medical and dental workers.⁶⁶

A German study has suggested that the risk of contracting hepatitis A is two to three times greater for nursing staff than for the general population, including doctors or dentists.⁶⁷ Furthermore, pediatricians have been found to have a greater prevalence of markers for hepatitis A than other specialists.⁶² Exposure to the feces of infants with asymptomatic infections appears to be the important risk factor for pediatricians. Also, outbreaks of hepatitis A have been reported among nursing staff dealing with fecally incontinent adult patients.⁶⁸

Despite the relatively low incidence of hepatitis A outbreaks among health care workers, vaccination of those personnel at highest risk (e.g., laboratory technicians and those dealing with pediatric patients) may be appropriate. However, it should be borne in mind that staff often move from low-risk to high-risk wards, particularly young employees who may still be training. It may, therefore, be appropriate to vaccinate student nurses, medical students, and those training in the allied professions while they are still at this stage of their career. Young employees are more inclined to accept vaccination, and vaccination programs are easier to implement within training environments. Health care workers from

countries with low endemicity who undertake voluntary work in the developing world are at increased risk from both hepatitis A and hepatitis B infection and routine vaccination for both forms of hepatitis is advisable.

Staff and residents of large institutions are potentially at risk from both forms of hepatitis. In homes for the mentally handicapped, for example, there is close, regular contact between individuals. Hepatitis B infection may spread from a chronically infected resident, via apparent and inapparent percutaneous transmission, to other residents and staff. Studies in Belgium have found a significantly higher prevalence of serologic markers for hepatitis B among the residents of homes for the mentally handicapped than among the general population and, in addition, evidence of horizontal transmission to relatives of hepatitis B carriers.^{69,70}

Outbreaks of hepatitis A in centers for the mentally handicapped have occurred in the past. Currently, however, outbreaks occur less frequently; controlled studies are required to assess the current risk from hepatitis A among residents and staff. Whereas hepatitis A vaccine may have a role in protecting long-term residents and staff against outbreaks, close proximity and routine contact in residential institutions make hepatitis B vaccination of residents and staff advisable as well. Inmates and staff in prisons and other closely confined groups, such as army bases or naval vessels are, likewise, at risk from both forms of viral hepatitis, and vaccination should be recommended. As in other risk groups, combined vaccination against both hepatitis A and hepatitis B could produce considerable benefits, in terms of convenience, compliance, and acceptability to recipients.

UNIVERSAL IMMUNIZATION AGAINST HEPATITIS A AND HEPATITIS B

Universal infant and adolescent immunization strategies for hepatitis B should, in the future, produce widespread immunity to this disease. Few countries, however, have catch-up or adult vaccination programs other than for health care workers, leaving, in the midterm, groups of individuals at risk from infection. Although routine immunization against hepatitis A will not be initiated in the immediate future, improved environmental and socio-economic conditions have already produced a dramatic decrease in the incidence of this disease, leaving significant numbers of people without naturally acquired immunity. Although this changing epidemiology may appear encouraging, the effect is to render generations susceptible to hepatitis A infection, with a subsequent increase in community-wide outbreaks and more serious illness.

Targeted immunization of at-risk individuals may control hepatitis A in the short term. However, the nature of the disease offers potentially exciting opportunities for a preventive approach in regions of low endemicity, which

could be achieved by routine vaccination. By reducing the number of injections required to produce protection and cutting the cost of vaccine, a combined hepatitis A and B vaccine would be more acceptable to recipients, parents, and physicians, and compliance would probably improve. Indirect savings could be achieved by saving physicians' and nurses' time, cutting administration costs and by reducing time off work for recipients.

CONCLUSION

Hepatitis A and hepatitis B remain serious public health concerns worldwide. Well tolerated and immunogenic vaccines exist for both infections, with the hepatitis B vaccine currently being introduced into large-scale immunization programs in 80 countries.⁴¹ However, because hepatitis A is often not considered a clinically severe condition, the inclusion of hepatitis A vaccine into routine immunization programs is not currently a priority.

Some groups identified as being at increased risk of hepatitis B are also at increased risk of contracting hepatitis A. A combined vaccine against hepatitis A and hepatitis B could offer advantages in terms of reducing the number of injections required, improving acceptability to the recipient, and increasing compliance. Ultimately, the use of hepatitis A and hepatitis B vaccines, either separately or as a combined vaccine, will depend upon a combination of the local epidemiology, disease burden, economic considerations with respect to vaccine cost, the health care priorities of local medical authorities, and vaccination policies.

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