Hepatitis A Vaccine Information Paper

A licensed vaccine developed by DoD and its partners

UNITED STATES ARMY MEDICAL RESEARCH AND MATERIEL COMMAND

Product name: Hepatitis A Vaccine
Commercial name: HAVRIX
Date of U.S. licensure: February 1995
Type of product: Inactivated viral vaccine
Company of manufacture: SmithKline Beecham

Target microorganism/associated disease: Hepatitis A virus (HAV) a non-enveloped, single-stranded RNA virus is endemic in most tropical and subtropical regions of the world. The virus is transmitted when food or water becomes contaminated with feces of infected persons. In developing nations, the virus is generally acquired early in life and rarely causes severe symptoms. In developed nations with better sanitation, infection with hepatitis A may be delayed until an individual travels to an underdeveloped area, or there is an unusual breakdown in sanitation. Infections in adults may be associated with serious symptoms and rare fatalities.

Reasons for development: Epidemics of hepatitis A have repeatedly afflicted the US military during deployments to regions with suboptimal sanitation, water, and waste systems. During the Civil War, epidemic hepatitis, (most likely due to hepatitis A virus) was common, but few deaths were recorded. During the second year of the war, about 50 of every 1,000 men became jaundiced; only about half this number were diagnosed in subsequent years. While improved sanitation may have contributed slightly to the decrease, it is more likely that veteran soldiers were eventually exposed to the disease and acquired immunity. In World War I, hepatitis was a serious problem for British, French and German troops, but less of a problem for U.S. troops. U.S. forces experienced greater than 180,000 cases of infectious hepatitis in World War II, with 106,695 admissions, and a case-fatality ratio of 0.3%. The annual admission rate per 1000 was 4.37 overall, with the highest rates of disease in the Southwest Pacific and the Mediterranean. In the Korean War, an outbreak of hepatitis occurred when both American and Korean soldiers were crowded into the Pusan perimeter. In the autumn and winter of 1950, 4,000 patients with hepatitis were hospitalized.

Outbreaks of hepatitis A disease have afflicted the military during peacetime. In 1959, uncooked fish was implicated in an outbreak in Naples involving 156 persons on 14 ships. In 1974, a food handler in San Diego was suspected of causing a large number of cases (47/1000 attack rate) in San Diego. In 1980, child care centers were recognized as a focus for hepatitis A transmission on military posts.

LTC Bruce Innis led the Phase 3 HAV vaccine trial with Thai collaborators.

Immune serum globulin (ISG), previously used to protect soldiers and travelers from infection with hepatitis A, requires repeated injections, and is not readily available. Also, with large and lengthy deployments, distribution of ISG has proved impractical and unpopular.

Role of Department of Defense in product development: Much of the HAV product development is attributable to the U.S. military in partnership with the National Institutes of Health (NIH) and SmithKline Beecham (SKB, now GlaxoSmithKline Biologicals). Techniques to quantify hepatitis A virus and associated antibodies were developed at the Walter Reed Army Institute of Research (WRAIR). At the WRAIR and NIH (laboratory of Dr. Robert Purcell) numerous cell types were evaluated for their ability to support growth of hepatitis A virus, and optimal growth parameters were defined. Both guinea pigs and monkeys developed excellent titers of neutralizing antibody following immunization with a prototype formalin-inactivated vaccine created by Binn, Dubois and Eckels. Analysis of strains from international sources showed antigenic similarity, and indicated that a vaccine need contain only a single serotype to provide global protection against HAV. Human trials began at WRAIR in 1986 with formalin-inactivated vaccine; all eight volunteers developed neutralizing antibody after four small doses of vaccine antigen. The DoD established cooperative agreements with SKB for hepatitis A vaccine development in 1989. Initial small-scale collaborative investigations evaluated antibody responses in humans following immunization with two candidate vaccine strains. A 1991 study of co-administration of hepatitis A vaccine with hepatitis B vaccine to soldiers did not alter results for either vaccine. Another 1991 study showed that accelerated hepatitis A immunization schedules were effective for soldiers. A large-scale field efficacy trial of hepatitis A vaccine (showing 94% efficacy) was begun in 1991 as a collaborative project of the U.S. Army and the Ministry of Health of Thailand. (Because of improving sanitation, rates of transmission were lower than had been anticipated and a large study was required.) In this trial, approximately 20,000 volunteers received hepatitis A vaccine and 20,000 received placebo (hepatitis B vaccine).

Hepatitis A vaccine references:

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