Havrix® Waging War Against a Common Enemy: A Case Study

Hepatitis A is one of the most common vaccine preventable diseases in the world. Although typically a relatively mild disease by medical standards, it can last weeks to months and is a serious cause of lost work time, distress and can have severe, sometimes, fatal complications. [1, 2]

In areas of high endemicity most residents contract the disease young, when the symptoms are relatively mild, and acquire a natural immunity. On the other hand, inhabitants of areas of low hepatitis A endemicity, like the United States, do not harbor a natural immunity to the virus. Therefore, they are more likely to contract the disease later in life when there is a greater chance for incidence of serious clinical hepatitis A and it complications. [1, 4] Complications such as fulminant hepatitis, which may lead to liver failure, and death are possible.[1, 2]

When people, such as military personnel and travelers, from areas of low hepatitis A endemicity, journey to regions with higher prevalence of hepatitis A infection there is a need for them to acquire immunity to this disease. Thus, active immunization against hepatitis A is an important public health strategy as more people reach childhood, adolescence and adulthood without natural immunity to the disease.[1, 2]

Epidemiological Features of Hepatitis A

Hepatitis A is an acute, usually benign disease characterized by the inflammation of the liver that is transmitted through personal contact with oral secretions or stool as well as food and water contaminated with infected fecal matter. A prominent characteristic of hepatitis A is recurrent epidemics.[2, 5] Communities with high rates of hepatitis A typically have epidemics every 5-10 years that can last for several years.[6] Thus, hepatitis A continues to be a major public health problem.[2, 5]

Morbidity associated with hepatitis A infection ranges in severity based upon the age at which the infection is contracted.[2] The clinical manifestation of hepatitis A are similar to influenza and include symptoms such as nausea, vomiting, severe abdominal pain, malaise, and muscle pain. Hospitalization and mortality due to hepatitis A infection is rare.[1, 5 7]

Epidemiological Features of Hepatitis A

Epidemiological Measure	Statistics
Incidence	
U.S.	125,000 – 200,000/yr
Worldwide	1,500,000/yr
Hospitalization (U.S.)	9,200 – 28,500/yr
Prevalence	
U.S.	33% of population
Worldwide	15 –100% of population
Mortality	0.1 – 2.1% of reported cases
Morbidity	
Asyptomatic	80 – 95% children 10 – 25% adults
Symptomatic	5 –20% children 75 – 90% adults

Demographics of Hepatitis A

Epidemiological Measure	Trend
Prevalence	Increases with age
Morbidity	Increases with age
Mortality	Increases with age
Incidence	Decreases with age males > females (1.6x) Western U.S. > other U.S. regions Hispanics, American Indians > other ethnic groups Alaskan natives

Management and Prevention of Hepatitis A

There are no specific treatments for hepatitis A. However, an outbreak of hepatitis A can be managed and controlled through educational campaigns on proper hygiene and sanitation as well as immunization with sterile antibodies (Immune Globulin) or vaccines.

Prior to 1995 the only option for prophylaxis in the United States was through the intramuscular injection of immune globulin (IG).[2] IG is routinely used to protect soldiers and travelers destine for a country with high endemicity of hepatitis A virus (HAV).[3] IG prophylaxis is safe and effective as well as useful in curbing hepatitis A epidemics.[5]

IG must be administered within 6 days before onset of the disease which requires early diagnosis and treatment.[2, 8] Additionally, due to its short duration of action IG prophylaxis requires frequent injections which is cumbersome for large deployments of soldiers and inconvenient for those regularly traveling to highly HAV-endemic regions.[3, 5] Risk of shortages is also a potential problem with this method of prophylaxis.[3] Furthermore, IG interferes with routinely administered vaccines.[5]

Using hepatitis A vaccines circumvents these problems.[5] The first of these, Havrix®, was approved by the Food and Drug Administration (FDA) in 1996. Havrix® eliminates the need for frequent immunization since it induces antibody levels indicative of 5-8 years of protection. Virtually 100% of adults develop protective antibody levels within one month of receiving a single dose.[5] And, Havrix® does not interfere with routine vaccinations.[4]

Side effects may include induration at injection site, headache, malaise, fatigue, fever, nausea and loss of appetite and muscle pain. Havrix® is contraindicated in patients hypersensitive to vaccine components or with severe febrile illness. [9]

Development of Havrix®

Hepatitis A vaccines have been used widely since they became commercially available in the 1990s. Over 6.5 million doses of Havrix® and the comparable Merck product VAQTA have been administered in the United States between 1995 and 1999. As of

1999, more than 65 million doses of these vaccines were administered worldwide.[5]

Role of Federal Laboratories

Havrix® was developed through the collaboration of SmithKlineBeecham (SKB; now GlaxoSmithKline) and branches of the U.S. federal government.[3, 6, 7] National Institute of Allergy and Infectious Disease (NIAID) researchers developed the hepatitis strain HM-175 and inactivated vaccines. The NIH, U.S. Army and the Centers for Disease Control were significantly involved in the development and clinical testing of the vaccine. These federal labs conducted investigations in part through Cooperative Research and Development Agreements (CRADA) with SKB.[10, 11]

The strain of HM-175 and inactivated viruses were originally developed by NIAID researchers in the laboratory of Dr. Robert Purcell. Subsequently, Walter Reed Army Hospital entered into a CRADA with SKB in 1991 in order to conduct clinical trials.[11]

In the early 1980s, NIAID scientist Dr. Richard Daemer isolated HM-175 strain in cell culture, and postdoctoral fellow Dr. John Ticehurst cloned HAV then began studying the genetics of the virus. By 1987, Dr. Jeff Cohen, also of NIAID, derived a cDNA clone capable of causing infections such that the components rendering it virulent or attenuated could be established.[12] In 1992, NIAID's Dr. Suzanne Emerson used the full length virulent HAV cDNA to characterized the single mutations making the virus inactivated vs. infectious. She later mapped the differences between the cDNA clone and the infectious wild type strain in order to map the regions important to make the virus attenuated. NIAID conducted animal studies to test the protective effect of the virus.[12]

SKB licensed key inventions from the NIAID including a vaccine against Hepatitis, a hepatitis viral antigen and a process for producing a vaccine against Hepatitis A virus, a Hepatitis A viral antigen or Hepatitis A virus strain (issued patents 4,532,215; 4,620,978, and 4,894,228).[10, 11] The founding discoveries were nonexclusively licensed to SKB while the improvements invented by Drs. D'Hondt, Purcell, Emerson and Ann Funkhouser under a CRADA were exclusively licensed to the company.[10]

Role of SmithKlineBeecham

SKB contribution to the development of Havrix® exceeds supporting the research that lead to the isolation of a virus strain that could be used to develop a vaccine. For instance in 1988, SKB scientist Dr. Erik D'Hondt initiated a project to make a commercial hepatitis A vaccine. Once SKB scientists determined that the safest kind of vaccine was inactivated, the company developed a procedure for growing commercial grade hepatitis vaccines. [12, 13]

The company conducted large intricate preclinical and clinical trials to determine the safety and efficacy of using the HM175 strain. Over 43 clinical trials were carried out during the developmental phase. Furthermore, they tested for clinical and prophylactic efficacy of Havrix® including its ability to contain and reduce the course of hepatitis A epidemics. Additional resources were dedicated to derive a reliable process for large-scale manufacture of Havrix®. [10, 11]

Havrix Related Epidemiology

The World Health Organization promotes immunization as a cost-effective public health tool to control the disease in areas where clinical hepatitis A is an important health problem.[1, 6] Hepatitis A vaccines are effective at curbing outbreaks and reducing the rates of the disease. Routine vaccination of children also prevents community outbreaks. In some instances it no additional cases of hepatitis A were reported in such communities.[5] Several studies demonstrated that when the initial vaccination schedule is followed Havrix® induces antibody levels calculated to provide 20 years of protection against HAV.

Public Health Benefits

The vaccine Havrix® is preventing hepatitis A infection in soldiers and travelers from areas with low HAV endemicity destined for areas where hepatitis A is highly endemic. Within the United States, Havrix® is being used successfully to contain, slow and/or prevent hepatitis A outbreaks. The global adoption of Havrix® as a preventative measure against Hepatitis A epidemics is a prime example of how federal technology transfer programs in partnership with commercial entities benefit the public health.

References

1. Glaxo SmithKline website http://www.worldwidevaccines.com/public/diseas/hepaTOC.asp
2. Fields Virology Vol.1 4th Edition, Editors-in chief David M. Knipe and Peter M. Howley Lippincott Williams & Wilkins pg. 799-840, 2001
3. Hoke C.H. et al. *Vaccine* 10: S75-79, 1992.
4. Gust, I. *Vaccine* vol 10 Suppl. 1 S56-58, 1992.
5. Advisory Committee on Immunization Practices *MMWR Weekly*, 1998 Oct. 01; 58 (RR12) 1-37.
6. *Weekly Epidemiological Record*; 2000 February 4; 5 (75): 37-44 (World Health Organization website http://www.who.int/wer)
7. Koff, R.S. *Vaccine* 10: S15-17, 1992.
8. Stapleton, J.Y. *Vaccine* 10: S45-47, 1992.
9. Havrix package insert
10. Office of Technology Transfer File History
11. BIOPHARMA website
12. Interview with NIAID inventors Dr. Robert Purcell and Dr. Suzanne Emerson
13. D'hondt E. *Vaccine* 10: S48-52, 1992.
14. Proceedings of the international symposium on active immunization against hepatitis A *Vaccine* 10: Suppl. 1, 1992.

Acknowledge contribution of NIH's Health Outcomes Working Group, Dr. Robert Purcell, Co-Chief, Lab. Inf. Diseases; Chief, Hepatitis Viruses Section, NIAID and Dr. Suzanne Emerson, Molecular Hepatitis Section Head, NIAID.

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