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Acute Hepatitis in the U.S. — A Success Story, But the Game Isn't Over

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

This article originally appeared in Infectious Disease Alert *in June 2007. It was edited by Stan Deresinski, MD, FACP, and peer reviewed by Connie Price, MD.* Infectious Disease Alert's *Physician Editor, Stan Deresinski, MD, FACP, serves on the speaker's bureau of Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck. Peer reviewer Connie Price, MD, reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company related to this field of study.*

Source: Centers for Disease Control and Prevention. Surveillance for acute hepatitis - United States, 2005. Surveillance Summaries. *MMWR* 2007; 56(No. SS-3):1-24. www.cdc.gov/mmwr/preview/mmwrhtml/ ss5603a1.htm

Synopsis: *There have been dramatic decreases in the reported cases of acute hepatitis due to hepatitis viruses A, B and C in the U.S.*

THE INCIDENCE OF ACUTE HEPATITIS A, WHICH HAS PREVIOUSLY CYCLED at 10 to 15 year intervals, has steadily decreased since its last peak in 1995, reaching a nadir in 2005 when 4488 cases were reported. The incidence in 2005, 1.5 per 100,000 population, was the lowest ever reported and, in fact, was more than 80% lower than that observed at the previously recorded cycle nadir. The most frequently identified risk factor was international travel, accounting for 15% of cases, with most associated with travel in Mexico, Central and South America. Sexual and household contact with another individual acutely infected with hepatitis A virus accounted or 12% of cases.

The onset of the decrease in incidence of acute hepatitis A (Figure 1) infections coincides with the introduction of hepatitis A vaccines in 1995 and the issuance of public health recommendations for their use in the following year. More dramatic decreases occurred after implementation of childhood vaccination recommendations made in 1999. Not all states implemented vaccination programs and, in 2005, approximately two-thirds of cases arose in states without childhood vaccination recommendations. At the end of 2005, recommendations were made that all children aged 12 to 23 months be vaccinated.

The incidence of acute hepatitis B infection in 2005, 1.8 cases per 100,000 population, was the lowest ever reported. This represented a total of 5494

Acute Hepatitis A (Figure 1).

Incidence* of acute hepatitis A, by year — United States 1982-2005

* Per 100,000 population

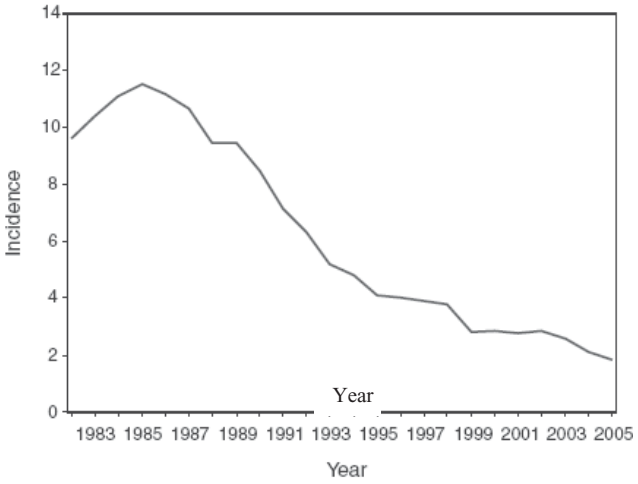
reported cases, but taking into account the asymptomatic nature of many infections and underreporting, it was estimated 51,000 cases had occurred in 2005. Approximately one-third reported a sexual risk factor; 9.3% reported undergoing surgery 6 weeks to 6 months before the onset of illness.

The decrease in incidence of acute hepatitis B infection (Figure 2) began during the middle of the 1980s and coincided with the implementation, in steps, of a comprehensive national prevention strategy. This consisted of universal infant vaccination, routine screening of pregnant women and administration of immunoprophylaxis of at-risk infants, routine vaccination of children and adolescents not previously vaccinated, and vaccination of at-risk adults. The last include healthcare workers, dialysis patients, household and sexual contacts, individuals with multiple sexual partners or a sexually transmitted disease, men who have sex with men, injection drug users, and recipients of certain blood products.

Only 671 cases of acute hepatitis C infection were reported in 2005, for an incidence of 0.2 per 100,000 population. Taking into account missed diagnoses of asymptomatic cases and underreporting, it was estimated, however, that 20,000 new infections had occurred. Injection drug use accounted for 50% of cases; 14% reported having had surgery, 23% had had multiple sex partners, and 8% reported occupational exposure to blood.

Acute Hepatitis B (Figure 2).

Incidence* of acute hepatitis B , by year – United States, 1982-2005



* Per 100,000 population

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The incidence of reported acute hepatitis C infections peaked in the late 1980s and has declined since. While in 2005, the most commonly identified risk factor remained injection drug use, the overall decrease in incidence was due in large part to a decrease in cases among that group. The second most frequently reported risk factor was having multiple sexual partners. Transfusion was rarely identified as a risk factor.

Overall, these results illustrate the results of a remarkably successful public health program in the prevention of viral hepatitis in the U.S. — but there is still a long way to go. ■

Varicella-Zoster Virus Vaccine (Zostavax)

SPECIAL REPORT

By Jessica C. Song, MA., PharmD, and Paul Hsiao, Pharm D

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Jessica C. Song and Paul Hsiao report no financial relationships relevant to this field of study. This article originally appeared in Infectious Disease Alert *in June 2007. It was edited by Stan Deresinski, MD, FACP, and peer reviewed by Connie Price, MD.* Infectious Disease Alert's *Physician Editor, Stan Deresinski, MD, FACP, serves on the speaker's bureau of Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck. Peer reviewer Connie Price, MD, reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company related to this field of study.*

HERPES ZOSTER RESULTS FROM REACTIVATION OF latent varicella-zoster virus (VZV) residing in the sensory ganglia of the cranial and spinal dorsal root ganglia. It is estimated that up to one million adults in the United States experience this debilitating illness yearly, and the number of cases will likely increase in the future, because of the aging population. Furthermore, affected individuals may experience serious adverse consequences, including postherpetic neuralgia, paresis, myelopathy, and vasculopathy. Postherpetic neuralgia has been shown to persist for longer than one year in 36% and in 47%, respectively, in those older than 60 years and 70 years.[1]

Concerns about the burden of illness associated with herpes zoster (HZ) episodes have stimulated the development of a novel method of prophylaxis against HZ in the elderly patient population. In December 2005, the Food and Drug Administration (FDA) approved the live attenuated VZV vaccine (Zostavax) for use in the prevention of HZ in adults, 60 years and older. Moreover, the Advisory Committee on Immunization Practices (ACIP) has recommended that this vaccine should be administered to all individuals age 60 and older.[2] This article will: (1) review the pharmacology and FDA indications of VZV vaccine, (2) review the safety and efficacy of VZV vaccine, and (3) review the dosage and cost of this new vaccine.

VZV vaccine is marketed as a lyophilized preparation of the Oka/Merck strain of live, attenuated VZV derived from children with varicella. The next step in the production of this vaccine involved the introduction of virus into human embryonic lung cell cultures and propagation in human embryonic lung cell cultures. Finally, propagation occurred in human diploid cell cultures.[3]

The commercially available VZV vaccine is marketed as a single-dose vial of lyophilized vaccine, that should be stored frozen at -20C° or colder. Reconstitution of the vaccine involves the use of the manufacturer-supplied, preservative-free diluent. In order to minimize potency decay of VZV vaccine, the reconstituted vaccine must be administered immediately. If the reconstituted product is not used within 30 minutes, it should be discarded.[3]

The FDA-approved dose of VZV is a single dose of ~ 0.5 ml of the vaccine (minimum potency, 19,400 plaque-forming units) administered subcutaneously to adults age 60 and older. Individuals who have a history of anaphylactic/anaphylactoid reaction to gelatin or neomycin, who are immunocompromised (AIDS; leukemia; any type of lymphoma; receiving immunosuppressive therapy), who have active/untreated tuberculosis, or are pregnant, should not receive VZV.

CLINICAL EFFICACY OF VZV VACCINE

VZV vaccine has been studied for its efficacy in preventing HZ and postherpetic neuralgia in a total of 7 trials.[5] Data from the "Shingles Prevention Study" provided sufficient evidence in support of the vaccine's efficacy against development of HZ and postherpetic neuralgia in adults older than 60 years.[1,5]

In brief, this study included 38,546 subjects from multiple Veterans Affairs Medical Centers throughout the United States (not including Hawaii), of whom 95% were Caucasians residing in the U.S. for a minimum of 30 years.[1,5] The primary efficacy measures used in this pivotal study were incidence of postherpetic neuralgia and the HZ burden of illness score (BOI), a composite of

Table 1. Pharmacologic Properties of Zostavax ® (Live Zoster Vaccine)

Brand/Generic[3]	Zostavax® (Live Zoster Vaccine)
Classification	Vaccine
Mechanism of Action	This vaccine is a lyophilized preparation of the Oka/Merck strain of live, attenuated varicella-zoster virus (VZV), initially obtained from a child with varicella. The virus was then introduced into human embryonic lung cell cultures and underwent propagation in embryonic guinea pig cell cultures, followed by propagation in human diploid cell cultures. This vaccine is thought to protect humans against developing herpes zoster (HZ) via development of VZV antibodies.
FDA-Labeled Indications	Zostavax® (Live Zoster Vaccine) is indicated for: Prevention of herpes zoster in people ≥ 60 years
Immunogenicity	A subset of patients (N = 1395) from the Shingles Prevention Study was the focus of an immune response analysis, which revealed that 6 weeks post-vaccination, VZV antibody levels (measured by glycoprotein enzyme-linked immunosorbent assay) were increased 1.7-fold (95% CI, 1.6 to 1.8) compared with placebo.

the incidence, severity, and duration of pain/discomfort caused by HZ. Secondary efficacy measures included the incidence of HZ, duration of clinically significant HZ pain, and severity of HZ.

Because the focus of this study involved the use of a live vaccine, numerous exclusion criteria were set in place by the investigators. Immunodeficiency, inability to adhere to the study protocol, history of anaphylactic reaction to gelatin, allergic sensitivity to neomycin, prior HZ, prior receipt of varicella vaccine, premenopausal status, receipt of inactivated vaccine within the past 2 weeks, and receipt of antiviral therapy at the time of study enrollment precluded subjects from participating in the Shingles Prevention Study.[5]

Administration of a single dose of VZV (0.5 mL) resulted in a lower incidence (cases per 1000 patient years) of postherpetic neuralgia compared with placebo (0.46 vs. 1.38; relative risk, 0.665; 95% CI, 0.475 to 0.792, $P < 0.001$). In addition to superiority in prevention of postherpetic neuralgia, receipt of VZV resulted in significantly lower BOI scores compared with those observed in placebo-treated patients (2.21 vs. 5.68; relative risk, 0.611; 95% CI, 0.511 to 0.691, $P < 0.001$). The secondary endpoint of HZ incidence (cases per 1000 patient years) was noted to be significantly lower in VZV-treated subjects compared with placebo-treated patients (5.42 vs. 11.12; relative risk, 0.513; 95% CI, 0.442 to 0.576, $P < 0.001$). Of note, a post-hoc analysis revealed a much lower efficacy of VZV in preventing HZ in older patients (≥ 75 years), as vaccine efficacies were only 37% in participants 75 to 79 years of age, and 18% in participants over age 80 years. However, the proportion of subjects over age 80 years (~ 7%) and the number of HZ events were low in this study.[1,5]

CONCLUSION

To date, VZV represents the only commercially available agent shown to prevent HZ and postherpetic neuralgia in older (especially 60-69 years), adult patients. Questions that remain to be answered include the efficacy of VZV in the oldest adult population (≥70 years), the duration of immune response (data available up to 4 years post-administration), and the safety/efficacy of VZV in non-Caucasian individuals. ■

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