Update on infectious disease prevention: Human papillomavirus, hepatitis A

**ABSTRACT**
Key studies on the prevention of human papillomavirus and hepatitis A published during the past year found that:

- A quadrivalent vaccine against human papillomavirus prevents cervical intraepithelial neoplasia, vulvar and vaginal intraepithelial neoplasia, and anogenital disease in young women. The vaccine is likely cost-effective when given to girls, but perhaps not when given to boys.

- Although hepatitis A immune globulin is modestly better than hepatitis A vaccine for postexposure prophylaxis against hepatitis A, both are highly effective. Hepatitis A vaccine is now recommended by the Advisory Committee on Immunization Practices as the preferred agent in healthy individuals between the ages of 2 and 40.

How we prevent human papillomavirus (HPV) infection, and how we prevent hepatitis A following exposure to an index case have changed, based on the results of several key clinical trials published during the past year. The results of these studies should influence the measures we take in our daily practice to prevent these diseases. Here is a brief overview of these “impact” studies.

**QUADRIVALENT HPV VACCINE PREVENTS CERVICAL LESIONS**

Cervical cancer is the second most common type of cancer in women and is the leading cause of cancer-related deaths in developing countries. More than 500,000 new cases of cervical cancer are reported worldwide each year, and about 250,000 women die of it.¹

Nearly all cases of cervical cancer are caused by HPVs, and the oncogenic types HPV-16 and HPV-18 together account for about 70%. These two types also cause vulvovaginal cancer, which accounts for about 6% of all gynecologic malignancies.² Two other HPV types, HPV-6 and HPV-11, cause genital warts and, less often, cervical intraepithelial neoplasia and cervical invasive cancers.

Two HPV vaccines have been developed. One, sold as Cervarix, is directed against HPV-16 and HPV-18; it is not yet available in the United States. The other, sold as Gardasil, is directed against four HPV types: 6, 11, 16, and 18, and it is currently available (reviewed by Widdice and Kahn³).

The study. The Females United to Unilaterally Reduce Endo/Ectocervical Cancer (FUTURE) II study⁴ assessed the...
ability of the quadrivalent vaccine to prevent high-grade cervical lesions. Between June 2002 and September 2003, more than 12,000 women ages 15 to 26 were enrolled at 90 sites in 13 countries. Eligible women were not pregnant, had no abnormal Papanicolaou (Pap) smear, had had four or fewer lifetime sexual partners, and agreed to use effective contraception throughout the course of the study.

In a randomized, double-blind fashion, patients received vaccine or a placebo injection at day 1 and again 2 and 6 months later. They returned for follow-up 1, 6, 24, 36, and 48 months after the third injection, with Pap smears and colposcopy of cervical lesions.

The primary composite end point was the development of grade 2 or 3 cervical intraepithelial neoplasia, adenocarcinoma in situ, or invasive cervical carcinoma, with detection of HPV-16 or HPV-18 or both in one or more of the adjacent sections of the same lesion.

In all, 6,087 patients received vaccine and 6,080 received placebo; the two groups were well matched. About 23% had serologic evidence of exposure to either HPV-16 or HPV-18 at enrollment.

Findings. In the analysis of the data, the patients were divided into three overlapping subgroups. The first comprised women who had no serologic evidence of HPV-16 or HPV-18 infection at enrollment, who received all three injections, who remained DNA-negative at month 7, and who had no protocol violations. In this “per-protocol susceptible population,” at an average of 3 years of follow-up, lesions associated with HPV-16 or HPV-18 had developed in 42 of 5,260 women who received placebo, compared with only 1 of 5,305 who received the vaccine. The vaccine efficacy was calculated at 98% (95% confidence interval [CI] 86–100).

The second subgroup were women who had no evidence of HPV-16 or HPV-18 infection at baseline, but whose compliance with the protocol was considered imperfect. In this “unrestricted susceptible population,” the vaccine efficacy was 95% (95% CI 85–99).

The third group included all comers, regardless of whether they were already infected at baseline. In this “intention-to-treat population,” the vaccine efficacy was 44% (95% CI 26–58).

The authors concluded that in young women not previously infected with HPV-16 or HPV-18, vaccine recipients had a significantly lower occurrence of high-grade cervical intraepithelial neoplasia related to these two oncogenic HPV types.

**QUADRIVALENT HPV VACCINE PREVENTS ANOGENITAL DISEASE**


The study. This double-blind, placebo-controlled study tested the usefulness of the quadrivalent HPV vaccine to prevent anogenital disease. It included 5,400 women ages 16 to 24 and was conducted over 14 months in 2002 and 2003 at 62 sites in 16 countries. Women received vaccine or placebo at day 1 and again 2 and 6 months later, and then underwent anogenital and gynecologic examinations at intervals for up to 4 years.

The co-primary composite end points were the incidence of genital warts, vulvar or vaginal intraepithelial neoplasia or cancer, cervical intraepithelial neoplasia, cervical adenocarcinoma in situ, or cervical cancer associated with HPV types 6, 11, 16, or 18.

Findings. In all, 2,700 women were assigned to receive vaccine and 2,700 to receive placebo, and they were followed for an average of 3 years. Twenty percent had preexisting serologic evidence of infection with one of these four HPV types. In the per-protocol population who were seronegative at day 1 and were compliant, the vaccine efficacy was 100%. In the intention-to-treat group, vaccine reduced the rate of vulvar or vaginal perianal lesions regardless of HPV type by 34%, and reduced the rate of cervical lesions regardless of type by 20%.

**HPV VACCINE LIKELY COST-EFFECTIVE IN GIRLS, BUT NOT BOYS**


The study. In a review, Newall et al looked at four studies that examined the cost-
effectiveness of the HPV vaccine. These studies were not perfect and had methodologic limitations because of uncertainty about vaccine efficacy, duration of protection, and the contribution of herd immunity. The studies nevertheless suggested that immunization of young girls but not young boys may be cost-effective, though they suggested the need for further research.

**Findings.** Three of the studies showed an incremental cost-effectiveness ratio of $14,000 to $24,000 per quality-adjusted year of life gained, which is well within the range for many preventive strategies that we employ in this country.

One of the studies examined the cost-effectiveness of immunizing males, and in that study it was found not to be cost-effective.

**TAKE-HOME POINTS ON HPV VACCINATION**

Quadrivalent vaccine does indeed reduce the incidence of HPV-associated cervical intraepithelial neoplasia, vulvar and vaginal intraepithelial neoplasia, and anogenital diseases in young women, and it is likely cost-effective.

The vaccine works only against HPV types 6, 11, 16, and 18, and 30% of cervical cancers are due to types other than HPV-16 and HPV-18. Also, vaccination is much more effective in patients not yet exposed to HPV, so it would be best to vaccinate them before they become sexually active.

The Advisory Committee on Immunization Practices voted to recommend that girls ages 11 to 12 in this country should receive vaccine.

Regrettably, many third-party payers do not yet pay for the vaccine, and the cost (around $375) must be paid out of pocket. Also, this issue remains politically charged and controversial. Some states have mandated vaccination and another 15 are presently considering legislation mandating vaccination. Such legislation has been defeated in four states.

My own practice is to offer the vaccine to 11- and 12-year old girls, and to older girls and young women (not to boys), especially if the health insurance plan covers it or if the patient or the patient’s family can afford it.

**HEPATITIS A VACCINE IS AS GOOD AS IMMUNE GLOBULIN AFTER EXPOSURE**

Before 1995, when the first hepatitis A vaccine was introduced, about 30,000 cases of hepatitis A were reported each year in the United States. This was thought to be the tip of the iceberg: since this infection is often subclinical, estimates of up to 300,000 cases per year were given.

At first, immunization against hepatitis A in this country was confined to children over age 2 in states in which hepatitis A occurred more often than the norm. In 2005, after it had become clear that the vaccine was highly effective, the Advisory Committee on Immunization Practices revised its recommendations to include immunization of children between the ages of 12 and 23 months, so that they would complete this two-stage vaccination procedure by the time they reached the age of 2 years. With that strategy, the annual occurrence of hepatitis A in the United States fell dramatically, to about 4,000 cases per year in 2005, the lowest number of cases reported in the last 40 years. At present, most hepatitis A infections in this country are not from casual idiosyncratic transmission but rather are food-borne.

Still, hepatitis A remains a major problem in many parts of the world. Moreover, the availability of immune globulin, the traditional recommended agent for postexposure prophylaxis, has been limited because only one company manufactures it and the price has steadily escalated.

The study. Investigators at the University of Michigan and in Kazakhstan compared conventional doses of immune globulin vs hepatitis A vaccine as postexposure prophylaxis, given within 14 days of exposure to index cases of hepatitis A. Excluded were persons under the age of 2 years or over the age of 40, those with a history of hepatitis A or vaccination, those with liver disease, and those with other contraindications. The primary end point was the development of symptomatic, laboratory-confirmed hepatitis A, defined as a positive test for immunoglobulin M antibodies to hepatitis A; transaminase lev-
els greater than two times the upper limit of normal; and symptoms consistent with hepatitis A in the absence of another identifiable disease that occurred within 15 to 56 days of exposure to the index case.

Findings. Of 4,524 contacts randomized, only 1,414 (31%) were susceptible to hepatitis A, suggesting that the prevalence of hepatitis A in Kazakhstan was high at that time. Of these, 1,090 completed the immunization and follow-up protocol and were eligible for the final analysis. Of these, 568 received vaccine and 522 received globulin. The average age was 12 years, the average time to vaccination after exposure was 10 days; 16% of the exposures occurred in the day-care setting, and 84% of the exposures occurred from household contacts.

Symptomatic hepatitis A occurred in 4.4% of vaccine recipients vs 3.3% of immunoglobulin recipients. The authors concluded that hepatitis A vaccine met the test of noninferiority, that both strategies were highly protective, but that immunoglobulin was modestly better. Thus, in June 2007, the Advisory Committee on Immunization Practices recommended hepatitis A vaccine as the preferred regimen for postexposure prophylaxis.9

This approach has several advantages:
- Hepatitis A vaccine confers immunity and long-term protection, which globulin does not
- The supply of vaccine is abundant
- Vaccine is relatively cheap
- Vaccine is easy to give.

This study, however, does not apply to people younger than 2 years or older than 40, those who are immunocompromised, or those who have chronic liver disease. In these groups, the recommendation is still to use immunoglobulin in postexposure prophylaxis.

### REFERENCES


### Hepatitis A remains a major problem in many areas of the world

Hepatitis A remains a major problem in many areas of the world. It is a highly contagious virus that occurs worldwide, with the highest incidence rates in developing countries. In the United States, hepatitis A outbreaks have been associated with poor sanitation and unsanitary conditions. The virus can be transmitted through contaminated food and water, as well as through contact with an infected person's stool or vomitus.

Hepatitis A can cause a range of symptoms, from mild to severe. The incubation period for hepatitis A is usually 2 to 6 weeks, but it can range from 1 to 4 months. The most common symptoms of hepatitis A include jaundice, fatigue, loss of appetite, fever, and dark urine. In severe cases, hepatitis A can cause severe liver damage, leading to liver failure and death.

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