New York State Department of Health
Immunization Program
Combined Hepatitis A and B Vaccine Dosing Schedule Policy

Policy Statement

The accelerated four-dose schedule for combined hepatitis A and B vaccine (Twinrix®) should only be considered for use in patients with impending travel to occur in less than 28 days from the first dose of the vaccine series. Not every traveling patient is a candidate to receive the accelerated dosing schedule. If the traveling patient seeks initiation of vaccination 28 days or more prior to their departure, there would be no benefit to the use of the accelerated dosing schedule, and the standard dosing schedule should be used.

Immunogenicity data reveals that the first three doses of the accelerated Twinrix schedule provide equivalent protection to the first two doses in the standard Twinrix schedule. The first three doses of the accelerated Twinrix schedule provide equivalent protection to the first dose in the standard monovalent hepatitis A vaccine series and the first two doses in the standard monovalent hepatitis B vaccine series.[1]

Aside from travelers, there is insufficient evidence to support the use of the accelerated Twinrix dosing schedule in other settings, such as STD clinics, jails, clinics for migrant farm workers and substance abuse treatment facilities. In these settings and all other sites participating in the New York State Department of Health Adult Immunization Program, the standard Twinrix dosing schedule or the standard monovalent hepatitis A or hepatitis B vaccine schedules should be used.

Background

In 2001, a combined hepatitis A and B vaccine was licensed by the Food and Drug Administration (FDA) for use in persons 18 years or older. The vaccine, whose brand name is Twinrix®, is manufactured by GlaxoSmithKline. Twinrix was initially approved for a three-dose schedule similar to that of monovalent hepatitis B vaccine (0, 1, and 6 months).[2] In April 2007, the FDA approved an alternative four-dose schedule (0, 7, and 21-30 days, and 12 months). The intended purpose of the alternate schedule is for those patients who start the vaccination series but are unable to complete the standard three-dose schedule due to impending travel that will put them at higher risk of exposure to hepatitis A and/or B.[1]

Statement of the Problem

Since the FDA approval of an alternative four-dose schedule for Twinrix, the manufacturer has promoted the use of the accelerated schedule for certain groups of patients other than travelers. This includes patients at high risk for exposure to hepatitis A and B, such as clients in substance abuse treatment centers, jails, clinics for migrant farm workers or STD clinics. These are indeed high-risk populations worthy of intentional focus and efforts to achieve maximal immunization rates. However, the use of the four-dose accelerated schedule in these populations does not add any additional benefit over the standard three-dose schedule.

The level of immunity achieved by the first two doses of the standard schedule (0 and 1 months) is essentially equivalent to that achieved by the first 3 doses of the accelerated schedule (0, 7 and 21-30 days).[1] Therefore, within the time frame of the first month after start of the vaccine series, the same level of immunity is achieved with the administration of two doses versus three doses of vaccine. To be maximally effective and achieve adequate immunity, both schedules ultimately require the administration of a final dose (at 6 months for the standard schedule; at 12 months for the accelerated schedule).

The current available evidence does not support the use of the accelerated vaccination schedule in high-risk patients other than travelers. Rather, this practice only serves to needlessly increase cost.

Vaccine Description

Twinrix contains the same antigenic components as the monovalent hepatitis A vaccine called Havrix and the monovalent hepatitis B vaccine called Engerix-B. Each dose of Twinrix contains 720 ELISA units of inactivated hepatitis A virus and 20 mcg of recombinant hepatitis B surface antigen (HBsAg).[2]

When given separately, the monovalent hepatitis A vaccine called Havrix contains 1440 ELISA units per dose; two doses are recommended at 0 and 6-12 months.[3] The monovalent hepatitis B vaccine called Engerix-B contains 20 mcg HBsAg per dose; three doses are recommended at 0, 1-2 months, and 4-6 months.[4]

Indications and Usage

Hepatitis A

The Advisory Committee on Immunization Practices (ACIP) recommends hepatitis A vaccination for those adults at increased risk of infection.[3] This includes:

- Persons traveling to or working in countries with high or intermediate levels of endemic infection;
- Persons living in high prevalence communities;
- Men who have sex with men;
- Persons at increased risk due to their sexual practices;
- Current or recent users of injection and non-injection drugs;
- Persons who have occupational risk for infection;
- Persons with clotting factor disorders who receive therapeutic blood products;
- Persons with HIV infection; and
- Susceptible persons with chronic liver disease.[3]

Hepatitis B

ACIP recommends hepatitis B vaccination for all unvaccinated adults at risk for hepatitis B infection. However, acknowledgment of a specific risk factor should not be a requirement for vaccination.[4] Those at increased risks for hepatitis B infection include:

- Persons seeking evaluation or treatment for a sexually transmitted disease;
- Sex partners of HBsAg-positive persons;
- Men who have sex with men;
- Persons at increased risk due to their sexual practices;
- Current or recent users of injection and non-injection drugs;
- Household contacts of HBsAg-positive persons;
- Residents and staff of facilities for developmentally disabled persons;
- Healthcare and public safety workers with reasonably anticipated risk for exposure to blood or blood contaminated body fluids;
- Persons with end-stage renal disease, including predialysis, hemodialysis, peritoneal dialysis and home dialysis patients;
- Persons traveling to or working in countries with high or intermediate levels of endemic infection;
- Persons with clotting factor disorders who receive therapeutic blood products;
- Persons with HIV infection; and
- Susceptible persons with chronic liver disease. [4]

Combination hepatitis A and hepatitis B vaccine

ACIP recommends the use of combination hepatitis A and hepatitis B vaccine for use in any susceptible adult who has an indication for both hepatitis A and hepatitis B vaccine, including:

- Persons traveling to or working in countries with high or intermediate levels of endemic infection (for hepatitis A and hepatitis B);
- Men who have sex with men;
- Persons at increased risk due to their sexual practices;
- Current or recent users of injection and non-injection drugs;
- Persons with clotting factor disorders who receive therapeutic blood products;
- Persons with HIV infection; and
- Susceptible persons with chronic liver disease. [2,3,4]

Patients with known immunity to hepatitis B virus should be offered monovalent hepatitis A vaccine. Patients under the age of 18 should be vaccinated with appropriate monovalent vaccines.

Accelerated Dosing Schedule Research

There have been no studies that directly compare the efficacy of the standard Twinrix dosing schedule with the accelerated Twinrix dosing schedule. The research that has been done to support an accelerated dosing schedule compares Twinrix to the monovalent hepatitis A and B vaccines. One such study was a randomized controlled trial by H.D. Nothdurft and colleagues which compared Twinrix administered at 0, 7, and 21 days with hepatitis A administered at day 0 plus hepatitis B vaccine administered at 0, 7, and 21 days. Both groups were given a booster dose of the appropriate vaccines at 12 months. The seroprotection rates against hepatitis A and hepatitis B were comparable to those seen with Twinrix at all time points.[5] A second randomized trial by Joines and colleagues compared Twinrix administered at 0, 1 and 6 months to the concurrent administration of the monovalent hepatitis A (0, 6 months) and hepatitis B (0, 1 and 6 months) vaccines. Again, immunogenicity against hepatitis A and hepatitis B was similar in both groups.[6] These studies provided the basis for FDA approval of an accelerated Twinrix schedule.[1]

To support a recommendation for a change in clinical practice requires data to demonstrate that the accelerated dosing schedule of Twinrix produces immunity that exceeds that seen with the standard dosing schedule of Twinrix. A complete picture of the immunity conferred by the Twinrix accelerated schedule versus the Twinrix standard schedule cannot be determined by any of the existing studies alone. To gain more information requires the comparison of markers of immunity among several different studies, with the caveat that this data is not directly comparable, as the studies were done in different populations and settings and under varying protocols.

According to the Twinrix package insert, a study was done that compared Twinrix given at 0, 7, 21-30 days, and 12 months with monovalent hepatitis A at 0 and 12 months and monovalent hepatitis B at 0, 1, 2, and 12 months.[7] The choice of this particular hepatitis B dosing schedule for comparison creates a challenge for interpretation, as this is not the three-dose standard schedule (0, 1 and 6 months) that is more commonly used for vaccination with monovalent hepatitis B. No reference was provided for this data in the package insert.

A summary of the data presented in the Twinrix package insert follows, presented in such a way that allows for comparison to be made of the immunogenicity of the standard versus accelerated dosing schedules.[7]

Hepatitis A Immunity

The post-vaccination immunity against hepatitis A is swift and adequate, regardless of vaccine schedule.

Seroconversion for hepatitis A in second month[7]:

2 doses of Twinrix (standard)	97.7
3 doses of Twinrix (accelerated)	98.5

Seroconversion for hepatitis A post series completion[7]:

3 doses of Twinrix (standard)	99.6 (97.9-100)
4 doses of Twinrix (accelerated)	100 (98.1-100)

Hepatitis B Immunity

The post-vaccination immunity against hepatitis B requires more time to develop. Data regarding the monovalent vaccine suggests that the third dose confers the maximum level of seroprotection but acts primarily as a booster and appears to provide optimal long-term protection.[4]

Seroprotection for hepatitis B in second month[7]:

2 doses of Twinrix (standard)	61.2
3 doses of Twinrix (accelerated)	63.2 (56.2-69.9)

Seroprotection for hepatitis B post series completion[7]:

3 doses of Twinrix (standard)	95.1 (91.7-97.4)
4 doses of Twinrix (accelerated)	96.4 (92.7-98.5)

Cost

The CDC cost per dose for Twinrix is $37.64. The private sector cost per dose is $78.16. The addition of a fourth dose without any added immunity benefit necessitates an extra $37-78 per vaccine series.[8]

Summary

By two months after series initiation, the immunity gained following vaccination with the standard Twinrix dosing schedule is similar that following the accelerated dosing schedule. To confer maximal immunity against hepatitis B, both dosing options still require the administration of a final dose to complete the series. Therefore, at the present time, there is insufficient evidence to support the use of the accelerated Twinrix dosing schedule in settings such as STD clinics, jails, clinics for migrant farm workers and substance abuse treatment centers. These populations should continue to be vaccinated with the standard Twinrix dosing schedule or the standard monovalent hepatitis A or hepatitis B vaccine schedules, as appropriate.

The accelerated Twinrix dosing schedule should only be considered for use in patients with impending travel, with the understanding that the series will still need to be completed upon the patient's return. However, all traveling patients should not automatically receive the accelerated dosing schedule. If the traveling patient seeks initiation of vaccination 28 days or more prior to their departure, there would be no benefit to the use of the accelerated dosing schedule, and the standard dosing schedule should be used.

References

1. Centers for Disease Control and Prevention. Notice to readers: FDA approval of an alternate dosing schedule for a combined Hepatitis A and B vaccine (Twinrix®). MMWR 2007;56(40):1057.
2. Centers for Disease Control and Prevention. Notice to readers: FDA approval for a combined Hepatitis A and B vaccine. MMWR 2001;50(37):806-7.
3. Centers for Disease Control and Prevention. Prevention of Hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2006;55(No. RR-7):1-23.
4. Centers for Disease Control and Prevention. A comprehensive immunization strategy to eliminate transmission of Hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. MMWR 2006;55(No. RR-16):1-25.
5. Nothdurft HD, Dietrich M, Zuckerman JN, et al. A new accelerated vaccination schedule for rapid protection against hepatitis A and B. Vaccine 2002;20:1157-62.
6. Joines RW, Blatter M, Abraham B, et al. A prospective, randomized, comparative US trial of a combination hepatitis A and B vaccine (Twinrix®) with corresponding monovalent vaccines (Havrix® and Engerix-B®) in adults. Vaccine 2001;19:4710-19.
7. GlaxoSmithKline. Revised package insert. Twinrix® (hepatitis A inactivated & hepatitis B [recombinant] vaccine). Available at http://www.fda.gov/cber/label/hahbgsk032807lb.pdf.
8. Centers for Disease Control and Prevention. CDC Vaccine Price List. Available at http://www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htm.