

Mixed Vaccines Against Diphtheria, Pertussis, and Tetanus

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Abstract

Vaccination is the most cost-effective investment in public health. It not only could prevent transmissible diseases, save considerable medical costs, but also improve health and life quality of the general public. Mixed vaccines are single vaccine containing mixtures of antigens from multiple pathogens in an attempt to prevent multiple diseases by just having one injection. It eliminates the need for multiple injections and hence increases compliance and total coverage rates. Currently, DTP vaccine is one of the most commonly used mixed vaccines, containing diphtheria toxoid, tetanus toxoid, and *Bordetella pertussis*. However, side effects including fever, and redness and swelling of the injection sites can occur in a certain percentage of infants. Hence, new generations of mixed vaccines against diphtheria, tetanus, and pertussis have emerged, including acellular DPT, 5 in 1, and 6 in 1 vaccines. These new mixed vaccines are as effective as traditional DTP vaccine, but with significantly fewer side effects. For concerns regarding schedule and mixed uses of mixed vaccines of different vendors, the Committee of Vaccination Consultation of Department of Health discussed the issues in the second meeting in 2007 and suggested that since there

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was no sufficient evidence concerning effectiveness of mixing mixed vaccines from different vendors, vaccines of the same vendors should be used consistently, unless the vendors is unknown or out of stock.

Keyword: Diphtheria-pertussis-tetanus (DPT) vaccine, Mixed vaccine, Mixing vaccines

Introduction

Vaccination is the most cost-effective investment and the top strategy in public health. Preventing diseases through vaccination could not only save significant amount of medical expenses, but also increase health and life quality of the general public. Policy for vaccination in a country should be set according to local epidemiology and cost-effectiveness of vaccination. For example, the timing of vaccination is determined by the susceptible ages of transmissible diseases, and the ages when effective immunity can be achieved [1]. Hence, countries around the world have different routine vaccination types and schedules due to epidemiology and other considerations. According to the vaccination schedule in our country, vaccines that children have to receive before 3 includes BCG, HBV, DTP, OPV, MMR, Japanese encephalitis, and infant influenza. The cost of vaccination is subsidized by the government.

What are mixed vaccines? They are mixtures of antigens of multiple pathogens that give children multiple protections by single injection. Once the trouble of multiple vaccinations is eliminated, coverage rates are higher and more convenient for parents. Currently, the most commonly used mixed vaccines are DTP and MMR. Since the traditional DTP could cause side effects including fever, redness and swelling at the injection site in certain percentages of children, vaccines including DTaP, mixed vaccine containing DTaP and Hib, 5 in 1 (DTaP,

Hib, and IPV), 6 in 1 (DTaP, Hib, IPV, HBV) have been announced. Many people have heard about them, but do not understand the differences between these vaccines. What they know is merely that "they are not free, but can prevent more diseases". Multiple choices on the market have resulted in many questions from the parents. Many doctors are also confused by the different vaccination schedules of different vaccines.

Varieties of DTP mixed vaccines and side effects

Amongst all current routine vaccines, most side effects are from the traditional DTP vaccine. About 30-50% of children will have high fever, restlessness, redness and swelling of the injection site, and anorexia 2-3 days after receiving the DTP vaccine. Seizure may happen in rare cases. These are due to the inactivated whole cell diphtheria in the traditional DTP. Many components in the diphtheria can trigger stronger immune responses, leading to aforementioned side effects [1].

Newer generation of DTP vaccine belongs to acellular DTP vaccine (DTaP). Components that could result in side effects are eliminated and effective antigens, including pertussis toxoid, pertactin, filamentous haemagglutinin, are preserved to stimulate immunity against pertussis. Side effects would be lower than 10-20% [2,3]. In addition to DTaP, in the mixed vaccine containing DTaP and Hib, 5 in 1, and 6 in 1, DTaP is the main component, and hence have fewer side effects. Addition of components such as Hib, IPV or HBV will increase protection against other diseases and eliminate the trouble and discomfort of multiple injections, and hence increase the willingness of receiving the vaccination. However, the vaccines cost will have to be shared by the general public. The following table compares mixed vaccines containing DTP:

The mixed vaccine containing DTaP and Hib is made from two separate vaccines (DTaP and Hib). Vaccines from the same provider can be mixed and injected together, and vaccines from different providers cannot be mixed. The 5 in 1 vaccine is made from DTaP, IPV, and Hib, which is as effective as single DTP and Hib vaccines [4-8]. The 6 in 1 vaccine is made from DTaP, IPV, Hib, and HBV, and is as effective as single vaccines of DTP, Hib, and HBV [9].

Suggestions concerning mixed vaccines containing the DTP component from Department of Health Committee for Vaccination Consultation

Mixed vaccines contain multiple components, and injection ages for different components might be different. To combine multiple components together, the vaccination schedule has therefore needed to be adjusted. This is a common problem for using mixed vaccine. Hence, the Department of Health Committee for Vaccination Consultation suggests the following schedule:

The Committee suggests that DTaP and Hib mixed vaccine and DTaP-IPV-Hib 5 in 1 vaccine should be given as the same schedule for DTP, that is, 2, 4, 6, and 18 months. As the DTP vaccine, OPV vaccine has to be given together with DTaP+Hib vaccine [1]. Since DTaP, DTaP+Hib, and DTaP-IPV-Hib are given separately from the HBV vaccine, these vaccines are given according to their original schedules with further changes.

Recommended schedule for the 6 in 1 vaccine

The Committee suggests that infants should be given a single HBV vaccine 2-5 days after birth. If the 6 in 1 vaccine will be followed, it should be given at 1.5, 3, and 6 months. Two injections should be separated by more than 1 month. This is the most significant differences when comparing with other mixed vaccines containing DTP components.

Why does the Committee suggest that infants should receive 1 HBV vaccine 2-5 days after birth? Although the 6 in 1 vaccine has HBV components and the recommended youngest age for 6 in 1 vaccine is 1.5 months, in Taiwan, the recommended schedule for the first HBV vaccine is still 2-5 days after birth. As a result, the 6 in 1 vaccine cannot substitute the first HBV vaccine; hence the first HBV vaccine should still be given in those receiving 6 in 1 vaccine. However, the second HBV vaccine is not required at 1 month since the 6 in 1 vaccine will follow at 1.5, 3, and 6 months to replace HBV and DTP mixed vaccine. It is worth mentioning that the routine single HBV vaccine contains 20 mcg recombinant HBsAg, and the 6 in 1 vaccine contains 10 mcg. Clinical immunology studies have shown that 2-5 days after birth, 3 shots of HBV vaccine (20 mcg) or 6 in 1 vaccine (10 mcg) could generate antibodies against HBV for effective immunity [9].

Issues concerning mixed administration of traditional DTP and mixed vaccines from other providers

Parents usually have concerns about the effectiveness of new vaccines after receiving the traditional DTP vaccine. The Department of Health Advisory Committee on Immunization Practices (ACIP) has suggested in 2007 after the second meeting that although vaccines made from different providers against the same pathogens would have similar effects, the fact that different providers may use different components, professional suggestions from doctors are still needed regarding to vaccine providers, vaccine schedule, and frequencies of injections.

Alternative administration of traditional DTP and DTaP vaccines

Since the traditional DTP and DTaP both generate effective immunity, infants could therefore receive DTaP vaccine after receiving DTP vaccine. DTaP may result in fewer side effects especially in those infants previously experienced

side effects from traditional DTP, .

Alternative administration of mixed vaccine containing DTP components from different providers

Concerning the issue that there are in fact many providers for DTaP, DTaP+Hib, and 5 in 1 vaccines, the ACIP suggested in the second meeting in 2007 that vaccines from the same providers should be continued since there is still no sufficient evidence supporting the effectiveness of alternative administration of mixed vaccines containing DTP components from different providers. In special situations where the original provider is not known or the vaccines are in back order, vaccines from other providers might then be considered to protect the health of infants. Switching providers is not a problem for 6 in 1 vaccine, given that there is only one provider so far for the 6 in 1 vaccine.

If the infant have initially received the 6 in 1 vaccine, but for some reason cannot continue receiving subsequent doses, the suggested schedule for mixed and HBV vaccines is as the following:

| HBV or the 6 in 1 vaccine received | Following vaccines |
|--|---|
| HBV vaccines at 2-5 days after birth and 1 month | Mixed vaccine containing DTP components at 2 and 4 months, single HBV or the 6 in 1 vaccine at 6 months. However, mixed vaccines from the same vendors are recommended ¹ . |
| One HBV vaccine 2-5 days after birth, and the 6 in 1 vaccine at 1 month | Choice 1: the 6 in 1 vaccine at 3 and 6 months Choice 2: the 6 in 1 or 5 in 1 vaccine at 3 months, HBV and DTaP-IPV-Hib vaccine at 6 months ¹ |
| HBV vaccine 2-5 days after birth, the 6 in 1 vaccine at 1.5 and 3 months | Choice 1: the 6 in 1 vaccine at 6 months Choice 2: HBV and DTaP-IPV-Hib vaccine at 6 months ¹ |

¹Since there is not enough evidence concerning alternative administration of mixed vaccines containing DTP components from different providers, we recommend that mixed vaccines from the same provider should be used.

Summary

Vaccination is the most cost-efficient investment in public health to prevent diseases in infants. While we are trying to increase immunity by vaccinations against diseases in infants, at the same time, how to reduce the side effects of vaccines and inconvenience for parents becomes the main goal of enacting vaccination policies. Mixed vaccines are now the trend for vaccine development since it reduces the number of injections and increases willingness of injection and coverage rates. The plan for CDC in the next 5 years is to increase immunity of the general public, with advocating 5 in 1 and 6 in 1 vaccines as the second priority. The CDC is also asking for financial support from the government, donations, and other resources for the National Vaccination Foundation in order to put the new vaccines into routine vaccination schedule to increase the immunity of the general public.

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Table 1. Mixed vaccines containing DTP

| Vaccines | Components |
|------------------|---|
| DTP | ≥ 30 IU diphtheria toxoid, ≥ 60 IU tetanus toxoid, 4 IU <i>Bordetella pertussis</i> |
| DTaP | |
| Infanrix DTaP | ≥ 30 IU diphtheria toxoid, ≥ 40 IU tetanus toxoid, 25μg pertussis toxoid (PT), 25μg FHA, 8μg pertactin |
| Tripacel | diphtheria toxoid 15 Lf, tetanus toxoid 5 Lf, 20μg PT, 20 mcg FHA, 3μg pertactin, 5μg fimbrial agglutinogens (FIM) |
| DTaP+Hib | Tripacel plus Act-Hib: 10μg purified Hib PRP conjugated to 24μg tetanus toxoid Infanrix DTaP plus Hiberix: 10μg Hib PRP conjugated to 30ug tetanus toxoid |
| DTaP-IPV-Hib | |
| Infanrix-IPV | ≥ 30 IU diphtheria toxoid, ≥ 40 IU tetanus toxoid, 25μg PT, 25ug FHA, 8μg pertactin, 40D antigen units of type 1 (Mahoney) poliovirus, 8 D antigen units of type 2 (MEF-1) poliovirus, and 32 D antigen units of type 3(Saukett) poliovirus, 10μg Hib PRP conjugated to 30ug tetanus toxoid |
| Pediacel | ≥ 30 IU absorptive diphtheria toxoid, ≥ 40 IU tetanus toxoid, 25μg PT, 25μg FHA, 8ug pertactin, 40D antigen units of type 1 (Mahoney) poliovirus, 8 D antigen units of type 2 (MEF-1) poliovirus, and 32 D antigen units of type 3(Saukett) poliovirus, 10μg Hib PRP conjugated to 24μg tetanus toxoid |
| DTaP-IPV-Hib-HBV | |
| Infanrix-Hexa | ≥ 30 IU absorptive diphtheria toxoid, ≥ 40 IU tetanus toxoid, 25μg PT, 25ug FHA, 8μg pertactin, 10μg recombinant HBsAg, 40 D antigen units of type 1 (Mahoney) poliovirus, 8 D antigen units of type 2 (MEF-1) poliovirus, and 32 D antigen units of type 3(Saukett) poliovirus, 10μg Hib PRP conjugated to 24μg tetanus toxoid |

Table 2. Recommended schedule for mixed vaccines

| Vaccines | Recommended schedule |
|------------------|--|
| DTP | 2, 4, 6, and 18 months Given together with OPV |
| DTaP+Hib | 2, 4, 6, and 18 months Given together with OPV |
| DTaP-IPV-Hib | 2, 4, 6, and 18 months |
| DTaP-IPV-Hib-HBV | 1.5, 3, and 6 months A single HBV vaccine should be given 2-5 days after birth |

Recommended schedule for DTaP