Combination Vaccines

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Abstract

Recently multiple individual vaccines were put together into one syringe. This is ideal to simplify the administration of vaccines and reduce emotional distress from multiple injections. However, combination of many vaccines may interfere with the properties of each individual antigen and complicate the schedule. From earlier studies, most of the combinations of diphtheria-tetanus-pertussis (whole-cell) vaccine (DTPw), *Haemophilus influenzae* type b vaccine (Hib), hepatitis B vaccine (HBV), and inactivated polio vaccine (IPV) were safe and adequately immunogenic. On the other hand, there was a notable reduction in anti-PRP when Hib was combined with acellular pertussis vaccine (DTPa). Combination of hepatitis A vaccine and HBV was safe and effective. Those coming soon in the pipeline are DTPa-Hib-HBV, MMR-varicella, pneumococcal-meningococcal. With the increase in demand, health-care providers need to be acquainted to these combination vaccines. The bottom line is to make sure that the children get vaccination appropriately.

Key word : Combine Vaccines, Vaccines, Immunization, Children

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With more availability of effective vaccines to prevent important childhood diseases, it has recently been recommended that children receive many vaccines in early infancy resulting in a complicated schedule and multiple injections in each visit. Multiple injections may cause pain and motional distress for both the child and the parents. The combination of vaccines into a single injection would be ideal. The combination vaccines available and under development are shown in Table 1. The vaccines to be put together in a single injection are those recommended to be given at the same age e.g. the vaccine

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against diphtheria-tetanus-pertussis (DTP), polio (IPV), hepatitis B (HBV), and *Haemophilus influenzae* type b (Hib). The issues concerned with these combination vaccines are the followings.

Compatibility

Combination of vaccines produced by different companies may be incompatible. Therefore, the vaccines produced for individual use should not be mixed in the same syringe. The exceptions to this is that the Hib vaccines (PRP-T and HbOC) for individual use can be mixed with DTPw (DTP with whole-cell pertussis) produced by the same company e.g. Act HIB™ can be mixed with DTPw produced by Aventis, and Hiberix™ can be mixed with Tritanrix-HB™ produced by Glaxo SmithKline (GSK).

Effectiveness of the combination vaccines

Some components of one vaccine may reduce the effectiveness of another vaccine. For example, the alum adjuvant in a vaccine may bind to the antigen of another vaccine that is mixed in, resulting in reduction of immunogenicity of the first vaccine. The buffer or stabilizer of a vaccine may inactivate another vaccine. A live vaccine may induce interferon production to inhibit the replication of another live vaccine, and thereby reduce the immunogenicity. The same vaccine produced by different manufacturers may not be equally immunogenic. Therefore, any new combination vaccines produced require a new efficacy study to assure that the immunity developed against each antigen of the combination vaccine would not be significantly different from that of the separate vaccine. The significant difference was defined as difference in antibody titer of more than 10 per cent.

From the studies, the results showed that DTPw and Hib (PRP-T and HbOC) were able to mix without interference in antibody response against each antigen[1-4]. However, when Hib (PRP-T) was mixed with DTPa, the anti-PRP antibody was reduced significantly. The proportion of patients with anti-PRP $\geq$ 1 μg/ml, the level believed to confer long-term protection, was also reduced by 10-20 per cent with the use of DTPa-Hib combination vaccine. On the other hand the antibody against D, T, and P were not different from that after DTPa alone[5]. The reduction of antibody against Hib was of concern because the diseases caused by Hib are serious in young infants. The lower antibody response, although still higher than 0.15 μg/ml (the level believed to be protective), may create re-emergence of disease if it happened in a large population. Therefore, the US-FDA did not approve DTPa-Hib vaccines to be used in the primary series for children at 2, 4 and 6 months of age.

However, the anti-PRP response after vaccination with DTPa-Hib was mostly $\geq$ 0.15 μg/ml and can be boosted when the infants come across the bacteria in the environment. Therefore, the DTP-Hib vaccine has been approved in Europe. Studies conducted in Germany after a period of routine use

Table 1. Combination vaccines available.

	Trade name	Manufacturer	Note
Currently available			
DTP-Hib (PRP-T)	Tetract-HIB	AVENTIS	
DTPw-IPV-Hib (PRP-T)	Pentact-HIB	AVENTIS	
DTPw-HBV *(+Hib)*	Tritanrix-HB (+*Hiberix*)	GSK	May mix with Hiberix to make a single injection
DTPw-IPV	Tetracog	AVENTIS	
DTPa-Hib (PRP-T)	Actacel	AVENTIS	
DPTa-IPV *(+Hib)*	Infanrix-IPV (+*Hiberix*)	GSK	May mix with Hiberix to make a single injection
DTPa-HBV	-	GSK	Not available in Thailand
HBV-Hib (PRP-OMP)	Comvax	MSD	Not available in Thailand
HBV-HAV	Twinrix	GSK	Not available in Thailand
Under development			
DTPa-Hib-HBV	-	AVENTIS, GSK	
MMR-Var	-	GSK, MSD	
Pnc-MnC	-	Wyeth	
Pnc-Mnc-Hib	-	Wyeth	

of DTPa-Hib vaccine (Infanrix/Hib™, Infanrix-IPV/Hib™, Or Pentavac™) found a 95 per cent efficacy after 2 doses and 99 per cent efficacy after 3 doses[6,7]. Finally, a product of DTPa-Hib (Acta-cel™) produced by Aventis was found to be equally immunogenic against Hib compared to the separate Hib vaccine[8]. This vaccine is more acceptable for those concern about Hib protection.

The meningococcal protein conjugated Hib vaccine, PRP-OMP, was combined with HBV without interference in immunogenicity. The PRP-OMP can not be mixed with DTP. The inactivated polio vaccine (IPV) can be combined with DTP and Hib (PRP-T) without any reduction in immune response of each antigen. The antibody against hepatitis B may be reduced with DTPa-IPV-HBV, however, the antibody level yielded was still over a hundred fold higher than the protective level[9].

The vaccine against hepatitis A virus (HAV) combined with HBV has been found to be effective without immuno-interference[10,11]. This combination is useful for older children and adults who are susceptible both hepatitis viruses.

Other combination vaccines under development are DTPa-IPV-HBV-Hib (all-in-one), MMR-varicella, and pneumococcal-meningococcal vaccines. Early studies found a reduction in immunogenicity of varicella when mixed with MMR[12]. More work has to be done to make these combination vaccines possible in routine use. Most of the time clinical trials are needed to assure efficacy because protection may not always correlate with antibody response. In many instances, postmarketing data is the virtual answer to the efficacy of a vaccine.

Safety of the combination vaccines

It has been shown that children can receive many antigens at the same time without harm[13]. In previous studies[1-8], there have been no excess side effect from combining the vaccines so for. However, many rare adverse events are not demonstrated in the trials with a limited number of vaccinees. These adverse events will only show up after massive use. A good example is the case of rotavirus vaccine. The intussusception was not appreciated as an associated adverse event in trials that included more than 10,000 children until 10 months after licensure with 1.5 million doses being administered[14]. Therefore, post marketing surveillance is needed to secure the safety of combination vaccines.

Vaccine interchangeability

Vaccines produced by different manufacturers may not be completely similar. Although head to head comparisons have not been done on each vaccine, it is generally agreed that the vaccines approved for use in EPI are equally effective and interchangeable. Using a combined vaccine may inadvertently change the manufacture from previous doses. Most changes are acceptable except for 2 cases. First, PRP-T and PRP-OMP can not completely substitute. When a change between PRP-T and PRP-OMP occurs, the total doses should follow that recommended for PRP-T regardless of the order of PRPT or PRP-OMP used. Second, acellular pertussis from each manufacturer contains different components. The efficacy of each cellular vaccine may be different and there is no study on interchangeability. Pertussis is serious in young infants. Therefore, it is recommended that the same acellular pertussis vaccine should be used in the primary series (at 2, 4 and 6 months old). For booster doses (at 18 months and 4-6 years), however, any acellular pertussis vaccines can be use and are interchangeable.

Excessive doses of vaccine

The use of some combination vaccines may result in more doses of some vaccine than the total doses recommended. For example, the use of DTPw-HBV at 2, 4, and 6 months old resulted in an extra dose of HBV, or the use of DTPw-IPV-Hib at 2, 4, 6 and 18 months resulted in an extra dose of IPV. It was found that some vaccines such as diphtheria and tetanus toxoid cause more reaction with excessive doses while most others had no problem with one extra dose[15]. In particular, Hib, IPV, HBV are very low reactogenic vaccines, an excessive dose has a very low risk of adverse outcome.

The cost of combination vaccine

In general, the price of combination vaccines are much higher than individual vaccines. However, the cost of traveling if an extra visit is made for separate vaccines, as well as the reduction of emotional distress from getting multiple injections are the counter balance. It is inconclusive whether combination vaccines are more cost-beneficial in particular with a remarkable difference in various social and economical situations. The use of combination vaccines in Thailand should be discussed

Table 2. Choices of combination vaccines at each visit in infants

Visit	Vaccines to be given	Choices of combination vaccines by trade name (in italics)
2 months old	DTP, polio, Hib (HBV for those who have not received HBV2 at 1 month-old)	1. *Tetract-HIB*, OPV (HBV) 2. *Pentact-HIB*, (HBV) 3. *Actacel*, OPV, (HBV) 4. *Infanrix-IPV*+ Hiberix**, (+HBV) 5. *Tritanrix-HB* + Hiberix**, OPV 6. *Comvax**, DTP, OPV
4 months old	DTP, polio, Hib	1. *Tetract-HIB*, OPV 2. Pentact-HIB 3. *Actacel**, OPV 4. *Infanrix-IPV* + Hiberix** 5. *Comvax**, DTP, OPV
6 months old	DTP, polio, Hib, HBV	1. *Tetract-HIB*, HBV, OPV 2. *Pentact-HIB*, HBV 3. *Tritanrix-HB* + Hiberix**, OPV 4. *Actacel**, HBV, OPV 5. *Infanrix-IPV*+ Hiberix**, HBV

*Note 1. Use the same DTPa (Actacel or Infanrix) for primary series
2. Tritanrix-HB and Comvax should not be used in infants born to HBsAg positive mothers. These children should receive HBV2 at 1 months old, not 2 months old
3. Hiberix can be mixed with Infanrix and Tritanrix-HB in the same syringe
4. If Comvax is chosen, it is recommended at 2 and 4 months old. It is not needed at 6 months old

between pediatricians and parents. The bottom line is to make sure that children receive all the appropriate vaccines for their age.

The choices of combination vaccines

Table 2 demonstrates the choices of combination vaccines used at 2, 4 and 6 months old, the ages that most combination vaccines are for. As mentioned earlier, changing the vaccine in subsequent doses is mostly acceptable except for Hib (PRP-T or PRP-OMP) and DTPa. Therefore, the choices of vaccine at the 2 month-visit can be different from the 4 and 6 month-visits depending on what type of Hib is chosen, whether to give IPV or OPV, whether to give whole cell or acellular pertussis, and how many injections the parents will accept. Finally, the cost may be one of the main reasons for the choice of vaccine.

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วัคซีนรวม

*กุลกัญญา โชคไพบูลย์กิจ, พ.บ.**

ในปัจจุบันได้มีการรวมวัคซีนหลาย ๆ ชนิดที่จะต้องฉีดให้ในเด็กในเวลาเดียวกัน เข้าเป็นเข็มเดียวกัน ซึ่งทำให้เด็กไม่ต้องถูกฉีดหลาย ๆ เข็มในแต่ละครั้ง แต่การรวมวัคซีนเข้าด้วยกัน อาจมีผลกระทบต่อวัคซีนแต่ละตัวที่นำมารวม จากการศึกษาที่ผ่านมาพบว่า การรวมเข้าด้วยกันของวัคซีนในกลุ่มวัคซีนคอตีบ-ไอกรน-บาดทะยัก, วัคซีนป้องกันเชื้อฮิบ, วัคซีนตับอักเสบบีและวัคซีนโปลิโอชนิดฉีด ไม่ค่อยมีปัญหาทั้งในด้านความปลอดภัยและประสิทธิภาพ แต่การรวมกันของวัคซีนคอตีบ-ไอกรนชนิด acellular-บาดทะยัก กับวัคซีนป้องกันเชื้อฮิบ มีปัญหาทำให้ภูมิคุ้มกันต่อเชื้อฮิบ ลดลงอย่างมาก ส่วนวัคซีนตับอักเสบเอ และตับอักเสบบี สามารถผสมกันได้อย่างไม่มีปัญหา วัคซีนรวมอื่นๆที่กำลังพัฒนา ได้แก่วัคซีนหัด-หัดเยอรมัน-คางทูม ผสมกับอีสุกอีใส วัคซีนป้องกันเชื้อนิวโมคอคคัส ผสมกับวัคซีนป้องกันเชื้อมินิงโกคอคคัส เป็นต้น แพทย์จำเป็นต้องทำความคุ้นเคยกับวัคซีนรวมเพื่อที่จะสามารถใช้ได้อย่างเหมาะสม เพื่อให้เด็กได้รับวัคซีนทุกตัวอย่างครบถ้วนเหมาะสม

คำสำคัญ : วัคซีนรวม, วัคซีน, การให้วัคซีน, วัยเด็ก

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