CHAPTER

29 Combination Vaccines

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1. What was the need to develop combination vaccines?

Congestion of pediatric vaccination schedule is increasing day by day with the development of newer vaccines. Economics, covenience and manpower are other factors stimulating the efforts to provide new combination vaccines. However, developing combination vaccine involves many complex issues.

2. What do you mean by combination vaccine? How they are different from simultaneous or concurrent vaccination?

A combination vaccine is defined as a vaccine containing more than one immunogen that have been physically combined in a single preparation. On the other hand, simultaneous vaccines are those which are administered concurrently but are physically separate. Simultaneous vaccines are either injected at separate sites or are administered by separate routes. Simultaneous vaccination is as effective and as safe as administering various vaccines alone.

3. What are the types of combination vaccines?

Combination vaccines are either single pathogen or multiple pathogen vaccines. Single pathogen vaccines contain various antigens or serotypes of a pathogen while multiple pathogen vaccines contain various antigens or serotypes from multiple pathogens.

No	Type of vaccine	Examples
1	Single pathogen	Oral polio, IPV, Influenza, Pneumococcal, Rotavirus, HPV, Meningococcal
2	Multiple pathogen	DTwP, DTaP, DT,Td, Tdap, MMR, DTwP+Hib, DTwP+Hep B, DTwP+Hib+Hep B,DTaP+Hib, DTaP+Hib+IPV, Hep A+Hep B.

4. What about adverse events after combination vaccines as compaired to monocomponent vaccines?

As far as local adverse events are concerned, these occur more commonly and are more severe at the injection site. But this increase is offset by the absence of injections and hence the absence of local adverse events in other

limb. On the other hand, systemic adverse events are increased only modestly, if at all. Given the numerous advantages combination vaccines offers, a modest increase in minor adverse reactions is considered acceptable.

5. What are the advantages of combination vaccines?

There are various advantages of combination vaccines from the viewpoint of consumer as well as health planner of a country.

Advantages to consumer	Advantages to health planner
1. Reduced number of needle sticks	1. Reduced burden on shipping, handling and storage of vaccines
2. Reduced parental and patient anxiety	2. Decreased possibility of errors
3. Reduced vaccination visits	3. Reduced paper work
4. Decreased likelihood of missed vaccinations	4. Increased compliance of vaccination program
5. Increased satisfaction	5. Economic benefit from 1 (above), reduced cost for labor and supplies, reduced vaccination visits
6. Timely completion of indicated vaccinations	

6. What are the various immunological problems involved in mixing multiple antigens in the same syringe? What are the immunological issues concerning the production of combination vaccines?

There are various challenges in developing the combination vaccines.

- Antibody levels: Antibody levels to individual antigen in combination may be different as compared to antibody levels induced by those component antigens if given separately, for example:
  a. Whole cell pertussis vaccine is a potent adjuvant and combining three antigens in DTwP actually improves the immunogenicity of the toxoids as compaired to separate administration.
  b. Administering DTwP and Hib in combination result in reduced mean PRP antibody levels compaired to giving these components separately. This fact has no clinical relevance, as levels were still higher than those needed for protection from the Hib disease.
  c. The addition of HepB to DTwP results in significantly increased mean HepB antibody levels.
  d. Combining DTaP with Hib tends to reduce, often markedly, the Hib antibody response. But this is a relevant issue only in the context of an immunization schedule that fails to provide a booster dose in the second year of life.
  e. Competition amongst viruses can lead to altered immune responses in case of combination vaccines containing live attenuated viruses. This problem is tackled either by increasing the number of doses of vaccine (e.g. OPV) or increasing the concentration of the individual viral strain (e.g. increased varicella component in MMRV).

f. Live vaccines can interfere immunologically with each other by one vaccine stimulating interferon production which inhibits replication of another viral vaccine strain, e.g. in case of OPV, type 2 strain replicated faster than type 1 and 3 inducing interferon and hence interfered with growth of the latter viruses. To overcome this problem, the quantity of type 1 and 3 viruses was increased in mixure. This led to partial success but the administration of multiple doses became necessary to ensure optimal intake of all three serotypes.

g. Chemical interactions can sometimes leads to reduced immunogenicity, e.g. thiomersal present in some DTwP and Hib decreased the potency of IPV vaccine with more effect on type 1 poliovirus than on types 2 and 3. Unlike the situation with OPV, there is no evidence of interference between the inactivated vaccine strains themselves. To overcome this problem of chemical interaction, other preservatives were substituted and enhanced potency IPV was introduced.

- Carrier induced epitopic suppression: Simultaneous exposure to multiple conjugate antigens (i.e. polyvalent conjugate vaccine) results in either enhanced or diminished immune response. Antibody response to haptens presented on a carrier are inhibited by prior immunization with the specific carrier and this phenomenon is known as carrier induced epitopic suppression. Dose, route, choice of carrier protein and presence of adjuvant are the factors which determine whether epitopic suppression or enhancement will occur. Suppression is likely to occur if large amount of carrier protein are used for priming, high level of anticarrier antibodies are present and two conjugate vaccines employing same carrier protein are administered concurrently. Infants given vaccine containing Hib-PRP conjugated to tetanus toxoid (PRP-T) plus quadrivalent pnemococcal vaccine conjugated to tetanus toxoid demonstrated inferior antibody levels as compaired to pnemococcal vaccine conjugated to diphtheria toxoid. Thus, it is clear that effect of concomitant administration of carrier protein in conjugate vaccines is unpredictable and should be evaluated for each and every combination vaccine.
- Chemical and physical interaction among vaccine components: these interactions can result into altered immune response to vaccine components. If one vaccine that is administered with adjuvant is combined with a vaccine without adjuvant, the adjuvant might get displaced from first antigen and may get combined with second antigen. This would result into reduced immunogenicity of first antigen and altered immune response to second antigen. Other components (like buffers, stabilizers, excipients) in one vaccine may interfere with components of second vaccine, e.g. thiomersal can significantly reduce the potency of IPV.
- Multiple antigens and immune overload: some parents are concerned that normal immune system of infants is capable of becoming overloaded and multiple antigens in combination vaccines may induce such overload. It should be clearly and strongly communicated to them that,

there is no scientific evidence to support such an assertion and there is much evidence to refute it. It should be explained that newborn is naturally exposed to thousands of antigens in first few months of life and simultaneous exposure to multiple vaccine antigens will not overwhelm the infant immune system. In fact infant immune system requires fairly intense challenge to develop normally and insufficient stimulation leads to increased risk of autoimmune disorders.

- Relationship of multiple immunizations to type I diabetes and allergic diseases like asthama. There is evidence to reject the causal relationship between these diseases and multiple immunizations.

7. What are the practical issues concerning the administration of combination vaccines?

There are various issues regarding administration of combination vaccines.

- Administration of superfluous antigen: As numerous combination vaccines are available, one may have to give an extra dose of an antigen which patient may not need (as he has already received the recommended doses of that antigen). It has been demonstrated for many antigens that giving an extra dose involves no adverse consequence. Low reactogenicity of Hib, IPV and HepB makes it unlikely that giving an extra dose would cause a problem. When patients have received the recommended immunizations for some of the components in a combination vaccine, administering the extra antigen(s) in the combination vaccine is permissible if they are not contraindicated and doing so will reduce the number of injections required. One should be careful about some antigens which are known to be associated with increased adverse effects if administered too frequently, e.g. diphtheria and tetanus toxoid leading to extensive local reactions.
- Brand interchangeability: The question of whether vaccines from different manufacturers can be used interchangeably also applies to monocomponent vaccines. It is reassuring to know that interchanging one brand of vaccine for another has never been shown to result in performance that is outside the range expected for the vaccine in question. The Advisory Committee on Immunisation Practices has recognized DTwP (and it's individual components), IPV, OPV, Hib (as long as one uses complete three doses) and HepB as interchangeable. For the vaccines for which robust data on the interchangeability is not available (e.g. DTaP, newer combination vaccines), this committee has recommended that same product be used throughout the primary series. Still it is recommended that the opportunity to administer a vaccine, for which the child is eligible, should not be missed even if earlier brand is not available or it's identity is not known.
- Ad hoc combinations: Health care practitioners should not create their own ad hoc combinations by mixing separate vaccines in same syringe unless there is evidence establishing the stability, safety and immunogenicity of the resultant combination, as reflected in the package inserts.

- Cost issues: At the time of commercial introduction of new combination vaccine, it's component vaccines are already available and would continue to be used instead of combination, should the combination's price exceed the amount which buyers are willing to pay for the convenience the combination represents. Hence the price of the combination is effectively capped and it's costs of research and development must be recoverable within that cap, otherwise the combination will not be developed. The premium pricing of the combination vaccines or reduced practitioner reimbursement (as result of reduced number of injections/visits) might inhibit use of combination vaccines. But given the various advantages of combination vaccines (discussed above in Que. 3), combination vaccines should be preferred over monocomponent vaccines.

8. What is meant by second shot combination vaccines?

Combination vaccines that incorporate conjugate pneumococcal and conjugate meningococcal antigens are known as second shot combination vaccines.

9. What are various multiple pathogen combination vaccines available today?

- **Combination vaccines currently licenced in India are:**
  a. DTwP+Hib, DTwP+Hep B, DTwP+Hib+HepB: These are either available as ready to use or lyophilized form. Though antibody response to Hib is reduced, there is no reduced efficacy as most subjects achieve the seroprotective level of 1 ug/ml. They have good immunogenicity and safety profile for both primary and booster immunization.
  b. DTaP+Hib, DTaP+Hib+IPV: The primary concern in these combination is reduced Hib immunogenicity noted specially for primary immunization and when vaccines were administered earlier in life and in premature babies. This lower immunogenicity to Hib was conclusively attributed mainly to nonadministration of booster dose at 18 months. The US FDA and ACIP has approved this pentavalent vaccine for primary immunization.
  c. Hep A+ Hep B: available in both pediatric and adult (for those aged 18 and above) formulations. Dosing schedule is 0, 1 and 6 months (3 doses).

- **Combination vaccines available internationally are:**
  a. DTwP+IPV, DTwP+IPV+Hib: These vaccines would have immense importance in the Indian EPI to facilitate a shift from OPV to IPV as polio eradication nears.
  b. DTaP+IPV, DTaP+Hep B, DTaP+IPV+Hep B, DTaP+Hib+Hep B, DTaP+IPV+Hep B+Hib: Hep B antibody titres following primary

immunization are lower than when Hep B is administered alone. This is due to close spacing of doses at 1 month interval rather than immune interference.

c. MMRV: The antigen content of varicella is more in MMRV vaccine as compaired to monocomponent varicella vaccine. Though MMRV has equivalent immunogenicity and efficacy, it has greater side effects in the form of fever, rash and increased risk of febrile seizures.
d. Hep A+Typhoid
e. Hep B+Hib

10. What are IAPCOI recommendations for use of combination vaccines?

IAPCOI concludes that all currently licensed combination vaccines in India have an immunogenicity, efficacy and safety profile comparable to separately administered vaccines as of currently available data. However, it recommends strict observance of manufacturer's instructions regarding mixing of vaccines in same syringe.

Suggested Reading

1. Feigin & Cherry's Textbook of Ped Inf Dis, 6th edition, 2009;p 3383-4.
2. IAP guidebook on Immunisation, Editors: Tanu Singhal, YK Amdekar, RK Agrawal.
3. Red book,AAP, 2009: p34.
4. Vaccines, 5TH edition, Editors: S plotkin, W Orenstein, P Offit, Chapter 38: Combination vaccines.