COMBINATION VACCINE - THE IMPORTANCE AND ROLE IN PUBLIC HEALTH SET UP

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ABSTRACT

Infectious diseases are the world's leading cause of death. Vaccines have been shown to be the most cost-effective tool with demonstrable public health results in the form of decreased mortality and increased human survival. Advances in technology have enabled the development of a whole range of new and improved vaccines. The successful combination of vaccines has opens up exciting prospects for present and future vaccine development. One of the major advantages of combination vaccines is the practicality of requiring one versus multiple injections. This in turn leads to a higher compliance and enhanced coverage needed for successful implementation of immunisation programme especially in the rural health set up. Combination vaccines have the potential to lower the overall cost of immunisation as the cost of immunisation is the cost of vaccination plus the cost of vaccine procurement, storage, transportation and delivery. Combination vaccines appear to be a public health cost effective solution.

INTRODUCTION

The childhood vaccine initiative of the WHO has announced the ultimate goal of developing a vaccine that would provide protection against all the major vaccine preventable childhood disease with single oral dose given at birth (1). The development of such an ideal vaccine requires that numerous scientific, economic and political issues be addressed. Until that goal is achieved, combining several antigens into a single formulation is the most logical approach to the problem. (2)

- The role of immunisation assumes vital proportion in developing countries where treatment of infectious disease is costly.
- Childhood immunisation has been one of the most successful preventive health measures of the twentieth century.
- With the increasing emphasis on preventive approaches to health care, combination vaccines are attractive and probably highly cost effective solution.

CONCEPT/PHILOSOPHY OF COMBINATION

Advantages of a combined vaccines

Production of a combined vaccine has several advantages for parents and recipients, healthcare providers and for the wider community.

Advantage for children and parents

1. Fewer clinic visits makes participation in the vaccination programme more convenient for parents of vaccinees. This may be particularly important in areas where travel to the clinic is a major obstacle.
2. The reduced number of injections required makes the vaccination more acceptable to parents and their infants, lessening the distress that is often associated with injection of very young babies.
3. Improved acceptability to parents and infants will ensure better uptake of the vaccines.

Advantage for healthcare providers

1. Fewer clinic visits release clinic staff to cope with other healthcare needs.
2. Incorporation of the new vaccine into an existing schedule reduces the need for extra staff training in administering the vaccine.
3. Delivery logistics are simplified. Vaccine delivery, storage and administration are less costly and simpler if vaccines can be combined.
4. Patient compliance is increased, leading to simplified record keeping and surveillance activities.

Advantage for the community

1. Improved uptake (through greater acceptability of the combined vaccine) should reduce the number of cases of disease and with respect to hepatitis B, the number of carriers over time, and even the number of deaths.
2. Widespread immunity to a disease within a population will reduce the incidence of that disease and therefore reduce the associated hospital and community costs of treatment.
3. The overall cost of a vaccination programme is reduced with combined vaccines. For example, cold chain storage expenses, costs associated with delivery of the programme and the costs of providing separate needles and syringes for each vaccine is reduced.

These are major advantages since the cost of vaccines represents only 10% of the total cost to fully immunise an infant. The other 90% are allocated to other costs such as cold chain and other equipment, transportation, labour, training and surveillance activities. (3)

ESSENTIAL ISSUES

I . Physio-chemical compatibility of antigens and antigenic stability in formulation

2. Potential of competition among different antigenic components and epitopic suppression which may reduce the immunogenic response.
3. The indication of the antigens being combined at the same age and immunogenicity of each component antigen.
4. The theoretical potential for side effects increases with combination vaccines due to increased endotoxin load, toxoid load or simply as an additive effect of the individual component's side effect.
5. Difficulty in assessing severe adverse reactions due to complexity of the formulation of combination vaccines. This could provoke unjustified concern over the safety of antigens not directly involved in the reactions and may decrease he public acceptance

OTHER ISSUES

Manufacturing Issues

1. Antigenic compatibility with other antigens.
2. Immunological interference with live virus vaccine.
3. Volume of the vaccine that can be given.
4. Use of adjuvants in the combination.

Developmental issues

1. Each component antigen to be indicated at the same time in the immunisation schedule.
2. Each antigen should produce good immunogenic response.
3 Products should be stable for at least 18-24 months.

Researcher's issues

1. Potential to reduce antigenic response
   - Antigenic competition
   - Epitopic suppression
2. lncrease antigenic / adjuvant ratio

Medical Practitioner's issues

1. Apprehension of cumulative side effects
2. Difficulty in assessing the severe reactions
3. Some components can be given too often.

Table 1: Combination vaccine development

VACCINE	DEVELOPED	UNDER DEVELOPMENT
DTP (WC) + IPV	(+)	
DTP (WC) + Hib	(+)	
DTP (WC) + Hep B	(+)	
DTP (WC) + IPV + Hib	(+)	
DPT (Acc) + Hib		(+)
DPT (Acc) + Polio		(+)
DPT (Acc) + Hib + IPV		(+)
DPT (Acc) + Hib + IPV + Hep B		(+)
MMR-V		(+)
DPT (Acc) + Hib + IPV + Hep B + Hep A		(+)

PRESENTLY AVAILABLE COMBINED VACCINES

DPT+IPV

This was the first quadruple vaccine in use since early 1 990's.

DPT (whole cell) + Hib

This vaccine represents a new generation of vaccines that simultaneously prevent Hib disease and 3 major childhood diseases (diphtheria, tetanus and pertussis). It has an excellent immunogenicity and response to Hib (PRP-T) is not affected by combination process when given in the primary series as DPT alone.(4) This vaccine is in use since early 1990's in the developed and some developing countries.

DPT (whole cell) + IPV + Hib

It is a pentavalent reconstituted vaccine. It has also been found that the combination does not increase the frequency and severity of side effects. It has been given as a primary schedule and a booster dose at 18 months of age. This vaccine is currently in use over 21 countries. (5)

Hep A + Hep B

A combined vaccine against Hep B and Hep A has produced good immunogenicity and tolerance results in the study trials (according to a 0, 1, 6 months schedule) with 100% seroconversion results for both the components. (6)

COMBINATION VACCINES UNDER DEVELOPMENT

DPT (Acellular) + Hib

One of the consequences of a remarkable technical advance, that in the future will greatly influence the art of immunisation. A combination vaccine of Hib and DPT (Acellular) 5 component has shown adequate antibody response to Hib at 2, 3, 4 months and will eventually replace the whole cell pertussis based vaccine. (7)

However, there were concerns in the combination of DTaP with Hib conjugate that may induce lower immune response to Hib component (8) and the combination product was not recommended for use in primary vaccination in infants aged 2, 4 or 6 months. (9)

DPT (Acellular) + IPV and Hib/Hep B

Preliminary data has indicated that immune response to the combination vaccines comparable with those seen when vaccines are administered separately. Some studies of combination vaccines that includes Hib antigen show a diminished antibody response whereas some studies have indicated the same immunogenic response as whole cell pertussis based combinations. (10)

DPT (Acellular) + Hib + Hep B

This vaccine is still at an early stage of evaluation and has so far been found to produce adequate seroresponse rates for all the components except Hib during the primary series (2, 4, 6 months) but this also increases after a booster dose. (11)

MMR + Varicella

A combination of MMR and varicella has been shown to be safe and immunogenic in children, but antibody titers to varicella are significantly lower then, if varicella is given alone. Thus, the combined MMR-V vaccine could contain attenuated varicella virus in higher quantity than when given alone. (12)

DISCUSSION

There is no doubt that the coming era in vaccinology belongs to the new and wonderful concepts of combination vaccines. However, various issues other than pharmaceutical and developmental aspects are to be considered and examined

1. Different countries follow different immunisation schedules base on social, administrative or epidemiological reasons. Combination vaccines can only incorporate those antigens which can be given at the same time. Different countries may prefer a different vaccine combination in their vaccination schedules.

2. Since epidemiological situation and immunization vary from country to country, the cost benefit of a combined vaccine will also vary. The cost benefit estimates should therefore precede the development effort and will be important in ensuring acceptance of these vaccines in the immunisation schedules of the countries.
3. Vaccine development in the future should be based on epidemiological and geographical realities rather than only on market demand. Technology is all set to outpace infrastructure in these regions and modern research will have to focus on these realities. Bridging these gaps in the developing countries will be a vaccine researcher's challenge as well as his achievement.

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