Update Article

VACCINES - WHAT'S NEW?

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Vaccination, as a deliberate attempt to protect humans against diseases has a long history. Vaccines are excellent cost effective tools, which have led to sustained decline in mortality and morbidity of children. It is the birth right of every child to get immunized and be protected from preventable diseases. With better understanding and advancement of genetic engineering and molecular biology, plenty of efficacious vaccines have been developed and many are in the pipeline. The pioneering work of cowpox inoculation by Edward Jenner in 1796, led to successful eradication of smallpox and now we are standing close to eradicate polio by 2005 and many other diseases in years to come. Vaccines now can be safely grouped under [1]:-

- Scheduled Vaccines : BCG, DPT, Polio, Measles, MMR, Hepatitis B and Hib.
- Epidemiological need based vaccines : Typhoid, JE, Meningococcal, Varicella, Hepatitis A, Influenza and Pneumococcal.
- Traveller's Vaccines : Yellow fever, Rota Virus and Dengue etc.

BCG

The use of BCG vaccine for prevention and diagnostic testing is undisputed. It has been estimated that BCG is antigenically equal to between 5-10 TU with Tween 80 (25-50 TU without Tween 80). Several controlled trials have shown that BCG is 50% effective in preventing pulmonary tuberculosis and 50-80% effective in preventing CNS tuberculosis. A recent study on protective efficacy of BCG has shown that two doses of live BCG gave significant protection against experimental infection and disease caused by virulent *M Bovis*. Single dose vaccine protected against disease but not infection [2].

Acellular Pertussis Vaccine

2 deaths in Japan in 1970 due to whole cell pertussis vaccine causing encephalopathy led to abandonment of the vaccine and development of acellular pertussis vaccine. Two acellular pertussis vaccines have been licensed in the USA [3]. These vaccines contain two principal agents viz. inactivated pertussis toxin (PT) and filamentous haemagglutinin (FHA). These vaccines are less reactive and appear to exhibit efficacy comparable to that of whole cell vaccine in children. Advisory Committee on Immunization Practices (ACIP) advocates DTaP in all routine immunization. DTP is acceptable if DTaP is not available.

OPV

Out of two polio vaccines, OPV has wide variation in infectivity in the gut of children in different geographic regions, hence immunogenicity also varies [4]. Therefore, with four doses of OPV, around 70-75% immunization success is achieved. In order to eradicate poliomyelitis, WHO has suggested 9-10 doses of OPV because it is less expensive compared to IPV. The current IPV has enhanced its potency than the original one and protective level of antigen is produced in three doses only [5].

Measles, MMR

Nearly 26% cases of all measles in the world and 34% in Asia occur in India. Approximately 80%, cases in India occur in less than 3 years age and in developed countries measles has been seen at 4-6 years of age. Measles vaccine is given at 9 months plus under UIP program and MMR is recommended at 15-18 months age for those who can afford it. Seroconversion has been found to vary from 88% to 100%. Assuming the coverage of immunization around 95%, probably 10% population remains at risk [6]. Three types of cases are found -

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- One who has not been immunized at all.
- Primary vaccine failure, which is age dependent. Incidence is 5-10% if vaccinated at 9 months and less than 2% if vaccinated at 15 months.
- Secondary vaccine failure.

The latter has been seen at 4-6 years or 11-12 years of age due to waning immunity. Thus it is presumed that MMR at 15-18 months age will reduce the chances of primary as well as secondary vaccine failure. Proper disease surveillance is a must to identify vaccine failure, analyze data and restructure immunization schedule if required.

Hepatitis B

India with 2%-7% prevalence rate of Hepatitis B is in intermediate zone [7]. Nearly 43 million carriers are estimated to be in India alone. In the early days of HB immunization, selective approach was considered but it was soon found that it was not effective for reducing HB virus carrier pool in the community. Therefore, universal immunization of all children with HB vaccine is now routine in many countries in the world. WHO recommended India to adopt universal immunization policy in 1997, but the cost was the prohibitive factor. However, with reduction in prices, many states in India have now accepted routine immunization of all infants born to HBsAg negative mothers, screening of all pregnant women for HBsAg and immune prophylaxis of infants born to HBsAg positive mother [8]. IAP recommends giving 0.5 ml (10 mcg) IM at birth or within 48 hours of birth, at 1 month and at 6 months. Booster dose is not advocated at present. The injection should be given in anterolateral aspect of thigh of infants and deltoid of older children. Injection in buttock has not been found to have adequate sero-conversion. In one study from Taiwan, vaccination starting at 7 days after birth gave almost 24% less protection compared to early vaccination within 48 hours [9]. Increasing immunogenicity of existing hepatitis B with the aim to reduce number of doses, and the use of HBV vaccine as a therapeutic vaccine for treatment of chronic carriers of HBV is under research [10].

Hemophilus Influenza b Vaccine

Invasive disease is caused by Hemophilus type b. The risk is highest between 6 months to 2 years age. The mortality of treated *H influenzae b* (Hib) meningitis ranges from about 5% in developed countries to 50% or more in developing countries. 25-30% of survivors suffer from hearing loss, mental retardation and other sequelae. Conjugate vaccines, which were intro-

duced in late 1980s were able to confer T cell dependent immunity and it could protect infants and children less than 2 years. Use of Hib vaccines in United States has markedly reduced the incidence of the disease. The vaccine is now available in India also. Available Hib conjugate vaccines differ in their carrier protein used, length of saccharide and use of linker. PRP HbOC, PRP-T and PRP-OMP are found to be immunogenic. Recommended doses are as under [11]:-

Age at initial immunization	No. of doses 1-2 months apart	Booster dose
2-6 months	3	15-18 months
7-11 months	2	15-18 months
12-15 months	1	15-18 months
Above 15 months	1	not required

There is an ongoing debate over the need of a booster dose of Hib vaccine. It is not yet clear whether protection is dependent on immunologic priming with vaccine alone, or a minimum concentration of serum antibody is necessary. Due to these uncertainties and because some children lose antibody over time, a booster has been recommended. It has been noted that infants vaccinated with three half doses or three one third doses of Hib vaccine developed satisfactory antibody levels [12].

Typhoid Vaccine

Whole cell killed typhoid vaccine, though in use since 1896, has gone into disrepute due to systemic and local reaction. These reactions are mainly due to paratyphoid component of the vaccine. Field trials of Vi polysaccharide vaccine have shown an efficacy of 72%. The vaccine can be given to children above 2 years of age and the protection lasts for about 21 months to 36 months. Ty 21 a live attenuated vaccine is also available in capsule form. This capsule can be given orally every alternate day for three doses. Booster dose is required every 3 years. This vaccine needs a cold chain and protective efficacy is 96%. The doses for other two vaccines are as under :

- Killed typhoid vaccine : - 0.25 ml sub cutaneous/intramuscular, 2 doses in deltoid 4 weeks apart from 6-9 month age. Booster dose every 3 years.
- Typhoid Vi polysaccharide - 0.5 ml sub cutaneous/intramuscular single dose, anterolateral thigh or deltoid. Booster dose every 3 years.

All three vaccines have definite role at different ages. Removing paratyphoid component of the vac-

cine can minimize systemic and local reactions.

Meningococcal Vaccine

The four polysaccharide antigen (A,C,Y and W 135) have been combined in a tetravalent vaccine and made available in a single dose formulation. Meningococcal A & C are currently available in India. The vaccine does not induce immunity in less than 2 years old [13]. The efficacy of the vaccine is excellent in producing antibody against A, C, Y and W 135. Seroconversion with protective antibody levels develop in more than 97% subjects above 2 year age. Immunogenicity is serogroup specific. Serogroup C polysaccharide does not induce good antibody response before 18 to 24 month age. Serogroup A has an excellent efficacy of 85-95% after a single dose. The dose is as under, 0.5 ml sub cutaneous single dose for children above 4 years, 2 doses for children between 2-4 years and efficacy has not been established in less than 2 years. In asplenia it is advocated for routine use. It is also useful against *Neisseria meningitis* and septicemia.

Varicella Vaccine

Majority of cases of varicella occur by 5-10 year age and more than 90% cases have occurred by 11 year age. The disease is highly contagious and secondary attack rate is 90% in susceptible household contacts. In tropical climate more than 30% adults remain susceptible to varicella and can transmit disease to susceptible children. In less than 12 year children, single dose of varicella vaccine 0.5 ml sub cutaneous in left arm is given. Two doses at an interval of 4-6 weeks are required for children above 12 year. 95-100% seroconversion has been reported after 6 weeks of single dose and soon after the second dose in older children. Since the disease is mostly seen during December to May, all children must be immunized to prevent absence from examination. Immuno-compromised and parents of immunocompromised children should be vaccinated. Breakthrough cases of varicella following vaccinations, characterized by maculopapular lesions not exceeding 30-50, less in severity and lasting for nearly 5-6 days, sometime occur and are referred to as modified varicella like syndrome (MVLS). Protection is 70-90% against infection and 95% from severe infections. Post exposure prophylaxis revealed protective efficacy of 90% when children were vaccinated within 3 days of exposure.

Pneumococcal Vaccine

Pneumonia is the single largest killer of children and nearly 80% deaths in less than 5 years age are

caused by it [14]. The composition of capsular polysaccharide pneumonia vaccine has been determined by the relative distribution of 84 serotypes that cause invasive disease [15]. A single injection of 0.5 ml sub cutaneous gives protection to nearly 80% children but is ineffective before 3 years of age and maximum infection by the organism is caused in less than 2 years. Hence, routine use of the vaccine in children is not recommended. Vaccination is advised to those who are immunocompromised, or are suffering from nephrotic syndrome, asplenia and sickle cell disease. Recently, monovalent, bivalent and tetravalent *N meningitidis* outer membrane protein conjugate with Pneumococcal type 6B, 14, 19F or 23F were evaluated in otitis media. Fair immunological protection was observed [16].

Hepatitis A

Hepatitis A, a relatively benign disease, spreads more due to poor sanitation and unhygienic condition. A study conducted at Cochin in 1988, showed 9% subjects up to 10 year age were anti HAV seropositive and 29% in the age group of 11-20 years were seropositive. The study also revealed anti HAV seropositivity rate was 15.6% in the higher socioeconomic group, significantly lower than the rate in the lower socioeconomic group - 27.5% [17]. Hepatitis A is killed inactivated vaccine. 0.5 ml of 720 EL units is given intramuscular over deltoid after 1 year age. Booster is recommended after 6-12 months. 360 EL units and 1440 EL units is also available for three doses in children and single dose in adult respectively. The vaccine is safe and highly immunogenic and antibodies persist for more than 20 years [18]. Susceptible individuals should be immunized.

Cholera Vaccine

Whole cell killed parenteral vaccine prepared from classical V cholera is available in India. It carries an equal protection against El tor biotype also. Oral B subunit whole cell cholera vaccine consists of purified B subunit from cholera toxin. The efficacy of this vaccine has been found little more than whole cell killed vaccine. The vaccine is also associated with short term cross protection against *E coli*, that produce heat labile toxin. The current main hope for a more effective cholera vaccine is the live attenuated oral strain CVD 103 HgR, the result of deliberate deletion mutants in V cholera 01 virulence genes. Based on its high immunogenicity in children as young as 2 year age and significant protection to artificial challenge with 01 biotypes and serotypes, a large efficacy trial is being conducted in Indonesia.

Inactivated whole cell suspension vaccine is not indicated in less than 1 year old children. Two doses of the vaccine at an interval of 4 weeks is given subcutaneous / intramuscular. For 1-5 year 0.1 ml, 6-10 year 0.3 ml, and more than 10 year 0.5 ml is recommended.

Human Immunodeficiency Virus Vaccine

In case of HIV it is feared that even a small degree of infection at the portal of entry might lead to a virus carrier state. Therefore, the vaccine should be such that should cause high persisting level of antibodies to inactivate the virus particle at the site of entry. HIV vaccine therefore, should not only prevent infection, but also prevent development of disease or delay its onset. The following types of vaccines are under trial [19].

- a. Recombinant DNA
- b. Synthetic vaccine
- c. Antiidiotype base vaccine
- d. Genetic vaccine
- e. Post exposure vaccine.

The current hypothesis is that post infection vaccination with HIV specific antigen boosts the host response and perhaps elicits novel immune response of benefit to patient. Such a boost might help decrease the virus burden and slow the disease. The planning of large-scale trial of candidate vaccine in population with high incidence of HIV is already under study by the WHO. It appears HIV vaccine is still several years away.

Dengue Vaccine

Attenuated dengue type 1,2,3 and 4 vaccines are under development in Thailand and clinical trials have been carried out in adult volunteers. Moreover, it is not known whether attenuated vaccine virus would remain virulent when given to a person with preexisting heterologous antibody. Therefore, research is underway for a synthetic and recombinant vaccine for dengue. Until such time an effective vaccine becomes available, vector control seems to be the only viable preventive method available [20]. In a country like India, effective vector control does not seem to be in near future.

Malaria Vaccine

Globally there are around 500 million cases of clinical malaria with 2-3 million deaths. The *P. falciparum* is the killer. Control strategy will get a boost if a vaccine gives even partial protection. However, development of such vaccine seems difficult due to complex life cycle of the parasite. Clinical trials of

phase I and II have been directed against ineffective sporozoites and liver forms. The antigen-circumsporozoite proteins have been expressed in different ways including use of multiple antigen peptides and live viral vectors [21]. A vaccine consisting of CS protein antigen coexpressed in yeast with HBsAg induced potent cytotoxic T lymphocytes, γ interferon, and interleukin 2 responses in animals as well as human volunteers, but detailed trials are still pending. However, it is the asexual blood stage vaccine SPf66 developed by Colombian scientists which holds promise for the future [22]. This is a unique composite antigen consisting of three synthetic peptides representing antigen epitopes from merozoite proteins. These peptides are linked by the NANP repeat sequence of the CS protein of *P. falciparum*. This vaccine has shown protective effect against any malaria episode to the tune of 66.8% and against single episode of 60.2%. In Colombia study, the protection was 33.6% against first episode and 50.5% against second episode. The protection was 77.2% in 1 to 4 year old children. Antigamete antibodies ingested by the mosquito during the blood meal can block gamete fertilization in the gut. Yet, another ingested antibody blocks differentiation of the zygote into an ookinete. Such antitransmission vaccination has no effect on the human. Thus, parasite resistance to vaccine antibody may be prevented.

Controlled Release Vaccines

Many new vaccines in use today depend on two or three dose schedules to ensure an effective response and if social and logistic factors do not allow patients to receive the necessary number of injections, vaccinations may be ineffective. Therefore, a vaccine is needed which with a single dose, will give prolonged and protective immunity. This can be achieved by use of controlled release system to allow the vaccine antigen into the body at a known rate [23]. Controlled release vaccine systems are polymers of lactic and glycolic acids. Trials are going on for tetanus toxoid, rabies virus, hepatitis surface antigen etc.

Combined Vaccines

Many new vaccines are being developed. Administration of number of vaccines to a child will cause problem for pediatricians and for patients alike. Combined vaccines will help patients by reducing number of pricks, number of visits and will increase compliance. It will also help administrator by reducing storage problem, reducing burden on cold chain, improving logistics, distribution and better inventory control. DPT and MMR are examples of combined

vaccines. Other combined vaccines are :

- a. DPT + IPV
- b. DPT + Hib
- c. DPT + IPV + Hib
- d. Hep A + Hep B

Following combination vaccines are under trial [23].

- a. MMR + Varicella
- b. DaPT + Hib + Hep B

Virosomes Based Vaccines

Immunopotentiating reconstituted influenza virosomes (IRIV) have been developed as an alternative to alum adjuvant. These are liposomes, which carry the glycoproteins, haemagglutinins and neuraminidases on their surface. By utilising these glycoproteins, the antigen is effectively brought to antigen presenting cells. Due to the size and structure of IRIV, it is possible to attach additional number of different immunogenic proteins and to develop multigenic vaccines. Influenza A and B, Hepatitis A, tetanus and diphtheria vaccines can be incorporated as single multivalent vaccine with IRIV [24].

DNA Vaccines

Various vaccine antigens are inserted in the bacterial plasmids. They are then amplified in *E. coli* and are purified. This recombinant DNA plasmid is used as intramuscular or intradermal injection for immunization purposes. DNA, after entering muscle cells initiates protein production. Specialised cells of immune system take up the vaccine antigens and immune response is initiated [25].

Of the major scourges of mankind, malaria and helminthic diseases remain without useful vaccines, although they have now been joined by HIV infection. Communicable diseases are still number one killer ailment with 16.5 million deaths every year. Most of the diseases are vaccine preventable. Technology and immunology are accelerating at an ever-faster rate, and the future, like the present will be exciting. As William Harvey said in dedication of De Moto Cordis "all we know is still infinitely less than all that still remains unknown".

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