Vaccination and other Immunotherapeutics

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VACCINES

- **The introduction of vaccination has been one of the most decisive advances leading to the dramatic downward trend in the incidence of many viral diseases**
- Refer history - **Smallpox vaccination**

Vaccination

- Principle of vaccination is the priming of the adaptive immune system to Ags of a particular microbe.
- so that, following exposure to a pathogen (1st infection), a rapid **secondary immune response** is generated leading to the accelerated elimination of the organism and protection from clinical disease.
- So that 1st infection of a pathogen induces a rapid secondary response – stronger & long duration than primary response.
- Success depends on the generation of **memory T and B cells** and the presence in the serum of **neutralizing antibody**.

Aims of vaccination. - Eradication of disease (e.g. small pox)

<u>Most ambitious aim</u>.

- Protection of an individual against infection.
- Protect against symptoms & pathology where the presence of microbe is not harmful. Eg- Diphtheria, Tetanus
- Block transmission

Requirement of a good vaccine

- Adequate response & right type
- Safety
- Stability
- Cost
- Protein >CHO>Lipid>NA
- Complexity
- Size>1000K
- Foreignness

Routes of administration

Subcutaneous-CMI, Oral-Mucosal, IM-Systemic (humoral), IP

Type of Vaccine

Attenuated(live)

Killed/inactivated

Toxoid(detoxified bact.exotoxcins)

Heterologus(live)

Subunit(subcellular)

Vectors for cloned gene (Genetically Engineered)

Inactivated vaccines

Rabies	β Propiolactone
Influenza	β Propiolactone
Polio(Salk)	Formaldehyde
S.Typhi	Heat+Phenol or acetone
B.Pertussis	heat or formaldehyde

Comparison of live and killed vaccine

Live	**Killed**
1.Prepared by Attenuation	inactivation
2.May be natural route administration	injection
3.Single dose	multiple dose
4.Not safe, reversion to virulence	Safe
5.Cold chain (Not stable)	Satisfactory stability.
6.Cost low	High
7.Duration years long	May be short
8. Immune Response	
IgG ,IgA	mainly IgG
CMI	little or No CMI
Herd immunity	No

Live virus vaccines:

Measles

Measles+ Rubella (MR)

Measles+mumps+rubella(MMR)

Oral polio (OPV)

Rubella

Mumps

Yellow fever

VZV

General Guidelines For immunization

1.Inactivated vaccines –safe. Only absolute contraindication is severe reaction to previous dose

2.Live vaccine are contraindicated in –

Pregnancy

immune-susppressed people

Those on systemic corticosteroid therapy

3.Time allowed to elapse between two live vaccine should be 3wks.

4.Immunisation best avoid in acute febrile illness.

5.Eczema,hayfever,asthma,topical steroid therapy are not contraindications to immunizations

(Except BCG should not be given to eczema patients).

6.Premature infants-immunized at times recommend for full term babies.

7.HIV Ab+,asymptomatic –immunized normal way, except B.C.G. ,Yellow fever vaccine.

HIV Ab + symptomatic –inactivated vaccine

Immunization schedule for EPI vaccine : Refer 3rd June 2011 EPI schedule

1st year of life	**Vaccine/s**
0-4 weeks	BCG (before leaving hospital- within 24 hrs)
Soon after completion of	
2nd month	Penta (D, T, P, HepB & Hib) OPV 1st dose
4nd month	Penta (D, T, P, HepB & Hib) OPV 2nd dose
6nd month	Penta (D, T, P, HepB & Hib) OPV 3rd dose

9th month	a dose of live JE vaccine (on completion of 9 months)

2nd year of life

12 months	MMR (1st dose) (on completion of 1 year)
18 month	DPT & OPV (4th dose) (on completion 18 months)

Pre-school age

3 years	MMR (2nd dose) (on completion of 3 years)

School going age

- 5 years: DT & OPV (5thdose) (on completion of 5 years)
- 12 years: aTd (adult tetenus & diptheria) (on completion of 12 years)

Female in the child bearing age group

15-44years: Rubella containing vaccine (MMR)

One dose to all females who have not been immunized with rubella earlier.

- **Pregnant women**
  - **1st pregnancy**

    After 12wks of POA: TT 1st dose

    6-8 wks after 1st dose: TT 2nd dose
  - **Subsequent 3 (3rd, 4th & 5th) pregnancies** :

    TT 3rd dose, TT 4th dose & TT 5th dose respectively after 12 weeks of POA

Tuberculosis

BCG Attenuated tubercle bacillus of Calmatte Guerin

(70yrs in use). Immune sufficiency>70%

At birth → in high risk countries.

At school entry → UK,USA and only in patients with –ve mantaux test.

Should not be given to

Children with active eczema

Local sepsis on the limb to be used for inoculation.

+ve tuberculin test .

HIV Ab +ve patients

Pertussis

Give with diphtheria ,tetanus toxoid as a part of Triple vaccine (D.P.T.)- See EPI

Later boosters not given ,because this affect only young children.

Possible contraindications:

Personal history of convulsions

General irritation in neonates

Special consideration taken to balance the risk of disease & side effect:

In children with

Neurological disease

development delay

Parents or sibling with history of epilepsy.

Absolute contraindication

Indicate to vaccine is severe local & systemic' reaction

to the vaccine.

Not recommended after age 6yrs.

UK 1/300,000 infections severe neurological disease.

Diphtheria vaccine (toxoid)

Formaldehyde inactivation +mineral oil carrier.

Aim for disease not for the organism. Protection>70%

Given with tetanus

Success of vaccination measured by - serum Ab level &

skin testing

2^{nd} month starts, 3 doses at 2 month intervals

Booster 18 month,5years.

Skin test (Schick test)

Both toxin+toxoid infected

Absence of reaction good Ab)

Erythematous reaction at 5-7days →Inadequate Ab level.

Early response(1-2 days) →hypersensitivity

Tetanus toxoid

Formalin inactivated +mineral oil carrier.

See EPI

If expose toxoid + anti toxin given.

Poliomyelitis

- Live attenuated virus (sabin1957)

  (oral polio vaccine:opv)
- Attenuated live vaccine strain type 1,2,&3
- Should not be given to those with history of severe allergy to Polymixin, Neomycin, Penicillin
- 1/ 5million doses paralysis,
- Risk double with >50years age.
- Killed vaccine =Salk (1954)

  Recommended for

  Pregnant mothers

  Immune suppressed

  old age(>50yrs)

Measles

Live attenuated vaccine.

In developing countries measles is wide spread

Need at 6month age & another at 1year.

Candidate for eventual eradication.

Uncommon countries-wait until 1 year.

In Sri Lanka 9month, protection at least 21 years.

Contraindication:

Children with

Severe allergic reaction to neomycin or polymyxin

Anaphylactic reaction to egg protein

Risk: Neurological reaction to vaccine 1:100,000.

Mumps

Same situation as measles

Given at 6month in developing countries,

booster at 1year.

Mumps given as MMR

Mumps virus cause Mumps meningitis, deafness and death.

Rubella

Mild disease. See EPI schedule

Indication

Prepubertal girls 10-13 years

Sero –ve women of child bearing age

Pregnancy avoid 4 wks after vaccine

Contraindication Pregnancy.

Hepatitis A [Avaxim, Havirix]

- Formaldehyde inactivated HM-175 or GBM strain of hepatitis A grown on human diploid cells.
- **Single dose** of vaccine Abs persists for 1 year. Booster in 6- 12 months give immunity up to 10 years.
- Recommended for travellers (frequent or those stay >3 months) to HAV endemic areas (if poor sanitation & food hygiene), HAV lab workers

Rabies

- No safe attenuated strain of rabies virus has yet been developed for humans.
- Vaccines in current use include:
    - The neurotissue vaccine - here the virus is grown in the spinal cords of rabbits, and then inactivated with *beta*-propiolactone.
    - There is a high incidence of neurological complications following administration of this vaccine due to a hypersensitivity reaction to the myelin in the preparation.
- A human diploid cell culture-derived vaccine (also **inactivated**) which is much safer.
- Also new generation cell culture (Vero cell) vaccines are available

Rabies vaccination

There are two situations where rabies vaccine is given:

- ***a) Post-exposure prophylaxis,*** following the bite of a rabid animal:

  A course of intramuscular or intradermal injections of antirabies vaccine, starting on the day of exposure.

  For severe exposures Hyperimmune rabies globulin (RIG) may also administered on the day of exposure.

- ***b) Pre-exposure prophylaxis*** is used for protection of those whose occupation puts them at risk of infection with rabies; for example, vets, abbatoir and laboratory workers.

Hepatitis B

- Two types of vaccines: a serum derived vaccine and a recombinant vaccine. Both contain purified preparations of the hepatitis B surface protein.
- The serum derived vaccine is prepared from hepatitis B surface protein, purified from the serum of hepatitis B carriers. This protein is synthesised in vast excess by infected hepatocytes and secreted into the blood of infected individuals.
- A second vaccine, produced by recombinant DNA technology, has since become available.
- Previously, vaccine administration was restricted to individuals who were at high risk of exposure to hepatitis B, namely: infants of hepatitis B carrier mothers, health care workers, homosexual men and intravenous drug abusers.
- Now, the vaccine has been included in the universal childhood immunization schedule. See EPI

Japanese Encephalitis

- Formalin inactivated whole cell vaccine derived from mouse brains.
- Vaccines doses are given at 0, 7-14 & 28 days for full immunity
- Indicated to children in endemic areas. Travellers visiting endemic areas.

Influenza: Repeated infections with influenza virus are common due to rapid antigenic variation of the viral envelope glycoproteins.

- Current Vaccins are trivalent: 2 type A & 1 type B subtypes.
- Viruses is grown in embrynoted hen eggs, chemically inactivated, purified & used
- Antibodies to the viral neuraminidase and haemagglutinin proteins protect the host from infection.
- However, because of the rapid antigenic variation, **new vaccines**, containing antigens derived from influenza strains currently circulating in the community, are produced **every year**.

Surveillance of influenza strains now allows the inclusion of appropriate antigens for each season.The vaccines consist of partially purified envelope proteins of inactivated current influenza A and B strains. Individuals who are at risk of developing severe, life threatening disease if infected with influenza should receive vaccine.

People at risk include the elderly, immunocompromised individuals, and patients with cardiac disease. In these patients, protection from disease is only partial, but the severity of infection is reduced

Varicella Zoster

- A live attenuated strain of varicella zoster virus has been developed.
- Adults & > 13 years age, 2 doses are given 8 weeks apart (minimum 6weeks)
- Children <12 years only one dose

Yellow fever

- The 17D strain is a live attenuated vaccine developed in 1937.
- It is a highly effective vaccine which is administered to residents in the tropics and travellers to endemic areas.
- A single dose induces protective immunity to travellers and
- Booster doses, every 10 years, are recommended for residents in endemic areas.

Read notes

meningococcal vaccine

Typhoid vaccine

Pneumococcal vaccine

HIB vaccine

Cholera vaccine

Other immuno-theraputics

- Immunomodulators → interferons
- Normal immunologlobulin in passive immune therapy
- Hyper-immune globulin in passive immune therapy

Immunomodulators

(i). Interferons:

- **Recombinant alpha and beta interferons** are now available and have been used for the treatment of Chronic hepatitis B and C virus infections.
- However, **side effects** such as fever, malaise and weight loss have limited the use.
- ***gamma Interferon*** (immune interferon)
  is a **cytokine secreted by TH1 CD4 cells**.
  Its function is to enhance specific **T cell mediated** immune responses.
- **Mechanism of action of the interferons :**
- Enhancement of the specific immune response.

  By increasing the expression of MHC class I molecules on the surface of infected cells,

  the interferons increase the opportunity for specific cytotoxic T cells to recognise and kill infected cells.
- Direct antiviral effect
  a) degradation of viral mRNA
  b) inhibition of protein synthesis
- Prevents the infection of new cells

<u>Passive immunotherapy</u>

When should be given?

1.Patient already been infected. Need rapid built up of Abs than occurs naturally.

2.Patients immune system is not adequate, Unable to respond to infection or vaccine.

3.Before introduction of antibiotics. This therapy was used for most infections. Now only for selected group of disease.

Hyper-immune globulin

Immunoglobulin may be prepared from the serum of Selected individuals who have high titres of antibody to particular viruses.

Examples include:

- **Zoster immune globulin**
  Prevention of Varicella in immunocompromised children and neonates.

- **Human Rabies immunoglobulin**
  Post-exposure prophylaxis in an individual who has been bitten by a rabid animal.
- **Hepatitis B Immune globulin**
  Non-immune individual who has been exposed to HBV.
- **RSV Immune** globulin
  Treatment of respiratory syncitial virus infections in the very young.

Passive immunotherapy with antibodies.: Refer

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