IMMUNIZATION

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Objectives:-

K:1,3,4,5,11,16,17 .S: 1,3,4,5,13,17,18,21,23,24 ,AB: 1,3,4,5,8,9.

1- To know the importance and types of immunization
2- To know the Iraqi schedule of immunization
3- To understand the details of each vaccine(type, dose, schedule, side effect)
4- To understand proper method of vaccine storage and administration.

IMMUNIZATION

Immunization is the process by which human body can destroy or remove a specific antigen. This ability provides protection from infectious diseases, since most microbes are identified as a foreign body by immune system.

Immunization is one of the most-cost beneficial and cost-effective disease prevention measures. As a result of effective and safe vaccination, smallpox has been eradicated in 1979, and polio is close to worldwide eradication.

HISTORY

Vaccination (Latin: vacca—cow) is so named because the first vaccine was derived from a virus affecting cows: the cowpox virus, a relatively benign virus that provides a degree of immunity to smallpox (the milkmaids who exposed to cowpox were immune to smallpox).

The term was coined by Edward Jenner in 1796 and adopted by Louis Pasteur in 1885.

Immunity can be induced either passively (when antibody produced by one human or other animals is transferred to another) or actively (when a person's immune system generates the immune response).

Passive immunity:-

Is achieved by administration of performed antibodies to induce a transient protection against an infectious agent. Passive immunity can be induced naturally through transplacental transfer of antibodies during the last 1-2 months of pregnancy. Maternally derived antibodies can provide protection during the first

few months of life. Protection for some diseases may persist for as long as a year after birth. (e.g. Immune globulin, hyperimmune globulins, and monoclonal antibodies)

INDICATION FOR PASSIVE IMMUNIZATION:-

1. Immunodeficient children with B-lymphocyte defects who have difficulties in making antibodies.
2. Persons exposed to infectious disease or who are at imminent risk of exposure where there is not adequate time for them to develop an active immune response to vaccine (newborn of HBsAg +ve mother or post rabies exposure).
3. Persons with an infectious disease as a part of specific therapy for that disease (tetanus, diphtheria, and botulism).
4. Monoclonal antibodies can be used to prevent sever disease from RSV among ≤ 24 months of age with CLD, prevent transplant rejection, and treatment of some types of cancer and autoimmune diseases.

Active immunization:-

Active immunity is stimulation of the immune system by administering whole or parts of microorganism to produce antigen-specific humoral (antibody) and/or cellular immunity to prevent an infectious disease. It usually last for many years, often for lifetime. It is a prophylactic measure rather than therapeutic.

Immunological bases of vaccines:-

Vaccines can induce immunity through stimulation of antibodies formation (humeral immunity), cellular immunity or both. Protection induced by most of them is thought to be mediated primarily by B-lymphocytes which produce antibodies. Most B-lymphocytes responses require the assistance of T-lymphocytes, CD4 helper cells. T-lymphocytes are responsible for cell mediated immunity.

The antibody formation:-

1- Primary response: - after the first dose of vaccine.(usually IgM antibodies)

-Latency period:(24 hours-2 weeks) antibody appears.

-Growth period:(4 days- 4 weeks) level of antibodies increased.

-Decline period:(variable) level of antibodies will decrease.

2- Secondary response: - after a suitable period of time, the second dose of the Ag (vaccine) will trigger this response which differ from the primary response by quicker raise in the antibodies (mainlyIgG) with larger amount. The memory cells are responsible for this secondary response. The long-term protection after exposure is known as **immunologic memory**. The vaccine produces immunologic memory similar to that acquired by having the natural disease.

Types of vaccine:-

Live attenuated vaccines:-

-Modified living organisms that are weakened but can replicate, like natural infection, until immune response shut down reproduction .

-The organism can produce an immune response similar to natural infection, but does not produce the complications of the illness.

- Usually effective with one dose (except those used orally).

- May cause severe reaction.

- (measles, mumps, and rubella, OPV, varicella, rota virus, nasal live attenuated influenza vaccine, BCG, and oral typhoid).

Inactivated vaccine:-

- Contain whole dead organisms.
- Cannot replicate.
- Immune response mostly humoral.
- Antibody titer diminished with time.
- tend to require multiple doses to induce an adequate immune response and are more likely to need booster doses to maintain that immunity than live-attenuated vaccines.
- However, some inactivated vaccines appear to induce long-term immunity, perhaps life-long immunity, after a primary series, including HepB vaccine and inactivated polio vaccine (IPV).
- (injectable polio, hepatitis A, and intramuscular influenza (trivalent inactivated influenza vaccine TIV).

Parts of the organism: -(acellular pertusis vaccine, HPV, and hepatitis B vaccine).

***Toxoids* :-** it is modified bacterial toxin that is made non toxic but is still able to induce an active immune response against the toxin (tetanus, diphtheria).

Polysaccharide capsule:-(pneumococcal and meningococcal polysaccharide vaccines).

Polysaccharide capsule conjugated to protein carriers(Hib, pneumococcal and meningococcal conjugated vaccines).

Recombinant vaccines:- use genetically engineered organisms (recombinant ***hepatitis B vaccine).***

Most inactivated vaccines, including DTaP, HepA, HepB, Hib, TIV are administered IM, while live-attenuated vaccines MMR, and varicella given by SC route, and rotavirus vaccine administered orally. For IM injections, the anterolateral thigh muscle is the preferred site for infants and young children.Vaccines with adjuvants should be injected deep into muscle masses to avoid local irritation, granuloma formation, and necrosis associated with SC or intracutaneous administration.

Benefits of immunization:-

- Primary protection against the development of specific infectious disease.
- Post exposure protection to prevent or attenuate symptoms.
- Protection for specific patient populations, including patients who are pregnant and immunosupressed.

Storage of vaccines

The vaccines have to retain its strength in order to be effective, so most vaccines must keep at a temperature of (+2 C° to +8 C°). We have:-

1. **Set chain(cold chain)**
   We use the refrigerator for storage of vaccines. Cold accumulators should be placed in the freezer to maintain the temperature in case of breakdown of electricity and also to use them in mobile ice boxes. Empty places should be left between the packages of vaccines to allow air circulation for cooling. The temperature should checked twice daily.

2. **Mobile chain**
   We use isothermic boxes or ice boxes and inside it we put cold accumulators that should cover the packages from all sides.

- Exposure of inactivated vaccines to freezing temperature is the most storage error. (E.g. DTP, hepatits A, and hepatits B (cold sensitive).
- Live virus vaccines, including MMR, varicella and OPV vaccines are sensitive to increased temperature (heat sensitive).
- Physical appearance is not appropriate basis to determine vaccine acceptability.

Factors influencing vaccination:-

1. **presence or absence of maternal antibodies** (may disappear as early as 5 months and may persist to 9-12 months, this may occur mostly with live attenuated vaccines)

2. **The nature and dose of vaccine** (live attenuated vaccines tend to induce long-term immune response. They replicate, often similar to natural infection, until immune response shutdown reproduction. Most live attenuated vaccines used in single dose , while inactivated vaccines tend to require multiple doses to induce an adequate immune response and are more likely to need booster doses to maintain immunity)

3. **Mode of vaccine administration and appropriate administration** (parenteral administered vaccines not induce mucosal secretory IgA, whereas oral vaccines are likely to do, vomiting within 10 minutes of receiving OPV is an indication to repeat the dose).

4. **Immunological adjuvant** (adjuvant are non-specific potentializing substances that affect the immune response of the body, they will cause production of more antibodies with smaller amount of Ag and fewer doses).

5. **Nutritional status** (children may have impairment in their immune responses to vaccination, this occur because of the involution of thymus due to malnutrition, so there will be involvement of the cell-mediated immunity and the main affected vaccine is BCG).

6. Immunological status.

7. Age and gender.

The program of vaccination in Iraq:-

Time	Vaccines
At birth(within 24 hours)	HBV_1
Within 72 hours	BCG , OPV_0
2 Months	$DTaP_1$, HiB_1, $Rota_1$ OPV_1 , HBV_2
4 Months	$DTaP_2$, HiB_2, $Rota_2$, OPV_2
6 Months	$DTaP_3$, OPV_3 , HiB_3, $Rota_3$, HBV_3
9 Months	Measles, vitamin A 100,000 U
15 Months	MMR (1^{st} dose)
18 Months	DTaP, & OPV (1^{st} booster doses), vitamin A 200,000 U
4-6 Years	DTaP& OPV (2^{nd} booster doses) MMR (2^{nd} dose)

The previous program is compulsory but there are other optional vaccines used in special circumstances, which are:-

1. ***Typhoid vaccine***: -

used for swimming pools users, food handlers, sewage and water workers, contacts and in epidemics.

- It used as 2 doses, the 2^{nd} one being 4 weeks after the 1^{st} dose.
- Dose: - age < 20 years -----0.5 ml. > 20 years ----- 1 ml.
- Site: - in deltoid (S.C.)
- Booster doses are given every 2 years.

2. ***Meningococcal vaccine: -***

It is given to pilgrims and to those in crowded places. The dose is 0.5 ml (i.m. or s.c.). the first booster dose is given after 3-5 years then a subsequent boosters is given every 5 years.

3. ***Pneumococcal vaccine: -***

It is given every year as a prophylaxis in children with nephritic syndrome, immune deficiency, splenoectomised children, and malignancy.

4. ***Influenza vaccine: -***

In U.S.A. it is given to all children aged 6-59 months (annually). Children aged ≥ 59 months with certain risk factors (chronic pulmonary diseases, heart disease, immunecompromise, sickle cell anemia, chronic renal failure, health workers are recommended to receive influenza vaccine)

5. ***Hepatitis A vaccine (HepA):-***

It is recommended for all children aged 1 year (i.e. aged 12-23 months). It is given in 2 doses at least 6 months apart.HepA is recommended for children aged older than 23 months who live in areas where vaccination programs target older children, who are at increased risk for infection, or for whom immunity against hepatitis A is desired.

6. Varicella vacc***ine.*** (minimum age : 12 months)

Some children are not vaccinated before 1 year old what can we do for them?

1. First visit: - DTP1, OPV1, HBV1.
2. 1 month later: - MMR.
3. 1-2 months later: - DTP2, OPV2, HBV2.
4. 1-2 months later: - DTP3, OPV3, HBV3.
5. 15-18 months later: - booster doses of DTP and OPV.

DT & OPV are given to 11-13 years old.

Rubella vaccine given to girls in reproductive age.

Contraindications for vaccinations

1. Serious allergic reaction (anaphylaxis) to prior dose.
2. Anaphylactic hypersensitivity to vaccine constituents (e.g. egg protein in measles, mumps, yellow fever, and influenza vaccines). However, the amount of egg protein in MMR is so small not to require a special procedure prior to administration of vaccine to someone with history of anaphylaxis following egg ingestion.
3. Vaccines usually deferred in child with moderate to severe illness, regardless the presence of fever, until child recovery.
4. Live attenuated vaccines are contraindicated in immunodeficient persons or immunosuppresed (cytotoxic, radiotherapy, prolonged steroid use, and pregnancy).
5. Pertusis vaccine is not recommended if there is high grade fever, convulsion, and shock (we can use DT).
6. BCG vaccine should be delayed if there is burn, skin infection, or eczema at the site of injection.

Corticosteroids can suppress the immune system. Children receiving corticosteroids (≥2 mg/kg/day or ≥20 mg/day of prednisone or equivalent) for 14 or more days should not receive live vaccines until therapy has been discontinued for at least 1 month. Children on the same dose levels but for <2 wk may receive live viral vaccines as soon as therapy is discontinued, although some experts would wait 2 wk post-therapy. Children receiving lower doses of steroids may be vaccinated while on therapy.

Preterm infants generally can be vaccinated at the same chronologic age as full-term infants. An exception is the birth dose of HepB vaccine.

ADVERS REACTIONS TO VACCINATION

1. **Local reactions:-**

   - Immediate pain at the site of inoculation, it disappear after few minutes.

   - Sometimes this pain is replaced by tenderness lasting for hours or day (e.g. DTP, TYPHOID vaccines).

   - A painless nodule may develop at the injection site especially with adsorbed vaccines (with adjuvant) and may turn into aseptic abscess. -Local ulceration may occur in BCG vaccinated persons, and it is self limited and not need treatment.

2. **Systemic reactions:-**

   fever, digestive symptoms as vomiting and loose bowel motion, this may last for 1-2 days.

3. **Skin reaction:-**

   - urticaria rash especially with history of allergy.

   - fine macular rash may seen one to few days after measles (5%) and rubella vaccines.

4. **Renal :-**

   simple proteinuria, hematuric nephritis, and some times even heavy proteinuria (nephritic syndrome), all are transient.

5. **Neurological reaction :-**

   the vaccine which is mostly involved by this reaction is pertusis vaccine, so there may be :-

   - convulsions (1:10,000).

   - prolonged crying for 6-12 hours especially after the 1st injection. - hypotonic hyporesponsive episodes. - agitation that may disappear after few minutes.

   - Pallor.

   - cyanosis.

6. **Paralytic reactions:-**

   this occurs with OPV, and the overall risk of vaccine

associated paralytic poliomyelitis (VAPP) is 1 case/ 6.2 million doses. The risk of paralysis in the immunodeficient recipients may as much as 6,800 times that in normal subjects.

7. **Encephalitis:-**

   the risk of having panecephalitis following measles vaccine is about 12 times lower than if the child was affected by the disease itself and the prognosis is good.

8. **Joint complications:-**

   rubella vaccine may cause arthralgia and arthritis and it is more in adults.

9. **Lymphadenopathy:-**

   two vaccines could cause it, these are:-

   A- BCG vaccine:-

   6-12 % of BCG vaccinated individuals develop regional inflammatory adenitis in the left axillary lymph nodes, often fistulation and suppuration occurs that will close after few days. Sometimes there is intermittent suppuration with a 6 weeks- 6 months . some times we need INH for treatment. B- Rubella vaccine: it may cause lymphadenopathy in 20% of cases and resolves spontaneously.

10. **Teratogenic complications:-**

    the vaccines are to be avoided during pregnancy, the only safe vaccines during pregnancy are (tetanus toxoid, killed polio vaccine, cholera vaccine, HBV, and influenza vaccine).

11. **Skeletal complication:-** osteitis rarely follows BCG.

12. **Hematological complications:-**measles and rubella vaccines may cause thrombocytopenia.

BCG vaccine (Bacille Calmette-Guerin)

It is a live attenuated vaccine derived from mycobacterium bovis that has lost its virulence in humans by being specially cultured in an artificial medium for years, and given as a single intradermal injection at the left shoulder (at the insertion of the deltoid muscle), in a dose of 0.05 ml in neonates and 0.1 ml > 1 year of age. WHO recommended that a single dose of BCG vaccine administered during infancy, including asymptomatic HIV infected children in population where the risk for tuberculosis is high. It is type 4 immune response and we should wait 6-8 weeks after injection for scar appearance.

BCG is extremely safe in usual dose, local ulcer and regional suppurative adenopathy occur in 0.1-1% and usually mild not need treatment but chemotherapy is used occasionally and sometimes surgical excision of draining lymph node. Osteitis is a rare complication. Systemic complication also rare.

BCG is 50% effective in prevention of pulmonary TB and 50%-80% effective in prevention of disseminated or meningeal TB.

Measles vaccine

Is either monovalent or combined with Rubella (MR) or measles, mumps, rubella (MMR). It is a live attenuated vaccine given at 9^{th} month, 15^{th} month, and 4-6 years (i.m. or s.c). Adverse events following MMR include fever (usually 6-12 days following vaccination), rash about 5% and rarely transient thrombocytopenia.

Post exposure prophylaxis by vaccination is effective in prevention or modification of measles if given within 72 hours postexposure.

Polio vaccine:-

two polio vaccines are used throughout the world to combat polio. The first was developed by Jonas Salk, in 1955,it consist of an injected dose of killed poliovirus. Thereafter, Albert Sabin

produced an oral polio vaccine using live attenuated virus in 1962.

The two vaccines have eradicate polio from most of the countries in the world and reduced the incidence from an estimated 350,000 case in 1988 to less than 2000 case in 2006.

Salk's polio vaccine

- Inactivated polio vaccine (IPV), killed polio vaccine. It confers IgG-mediated immunity in the blood stream which prevents polio infection from progress to viremia and protects the motor neurons, thus eliminating the risk of bulbar polio and post polio syndrome.
- Because it offers no protection to the mucosal lining of the intestine, people vaccinated with IPV can still carry the disease and spread it to unvaccinated individuals.

Sabin polio vaccine

- Oral polio vaccine (OPV) is a live attenuated vaccine.
- It replicates very efficiently in the gut, the primary site of infection and replication, but is unable to replicate efficiently within nervous system tissue.
- The OPV proved superior in administration, and also provided longer lasting immunity than IPV.

Rota vaccine

Worldwide, rotavirus is estimated to cause more than 111 million cases of diarrhea annually in children younger than 5 year, with approximately 500,000 death per year.

A live attenuated, oral, pentavalent rotavirus vaccine was approved in 2006 for use in United states. It contains 5 reassortant rotaviruses isolated from human and bovine proteins. It protects against rotavirus gastroenteritis when administered as a 3 dose

series at 2, 4, 6 months of age. The 1st dose should be administered between 6-12 week of age, with all 3 doses completed by 32 week of age. It provides a 96% reduction in hospitalization for rotavirus gastroenteritis through the 1st 2 years after the 3rd dose. Its effective 98% against severe rotavirus gastroenteritis, and 74% against rotavirus gastroenteritis of any severity.

Another monovalent vaccine appear to be safe and effective. It is an attenuated monovalent human rotavirus and is administered as 2 oral doses at 2 and 4 months of age. The vaccine has 85% efficacy against severe gastroenteritis, and reduce hospital admission for all diarrhea by 42%.

Haemophilus influenzae vaccine

An effective vaccine to prevent Hemophilus influenza type b disease introduced in many countries has result in dramatic decrease in the incidence of infection caused by this organism(meningitis, epiglottitis, otitis media). It is given in 3 dose series at 2,4,6 months of age. It is type is polysaccharide capsule conjugated to carrier protein.

Hepatitis B virus prevention

Hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) are available for prevention of HBV infection. The safety profile of HBV vaccine is excellent. The most reported side effects are pain at the injection site (up to 29% of cases) and fever (up to 6% of cases). Household, sexual, and needle-sharing contacts should be identified and vaccinated if they are susceptible to HBV infection. HBV is not spread by breast-feeding, kissing, hugging, or sharing water or utensils. Children with HBV should not be excluded from school, play, child care, or work, unless they are prone to biting.

Hepatitis B Immunoglobulin

HBIG is indicated only for specific postexposure circumstances and provides only temporary protection (3-6 mo) . It plays a pivotal role in preventing perinatal transmission when administered within 12 h of birth.

Both HBIG and vaccine should be administered within 12 hr of the infant's birth and within 24 hr of identifiable blood exposure. HBIG can be given up to 14 days after sexual exposure.

Universal Vaccination

A main focus is universal infant vaccination, beginning at birth, to provide a safety net for preventing perinatal infection, prevent early childhood infection, facilitate implementation of universal vaccine recommendations, and prevent infection in adolescents and adults. Seropositivity is >95% with all vaccines, achieved after the 2nd dose in most patients. The 3rd dose serves as a booster and may have an effect on maintaining long-term immunity. In immunosuppressed patients and infants <2,000 g birthweight, a 4th dose is recommended, as is checking for seroconversion. Despite declines in the anti-HBs titer in time, most healthy vaccinated persons remain protected against HBV infection.

Current HBV vaccination recommendations are as follows :-

- For all medically stable infants weighing >2,000 g at birth and born to HBsAg-negative mothers, the first dose of HBV vaccine should be administered before hospital discharge. Single-dose antigen HBV vaccine should be used for the birth dose. Subsequent doses to complete the series are given

at 1-4 mo and at 6-18 mo of age.

- Preterm infants weighing <2,000 g at birth and born to HBsAg-negative mothers should have their initial dose delayed until 1 mo of age or before hospital discharge.

Administration of 4 doses of vaccine is permissible when combination vaccines are used after the birth dose; this does not increase vaccine response.