vaccination

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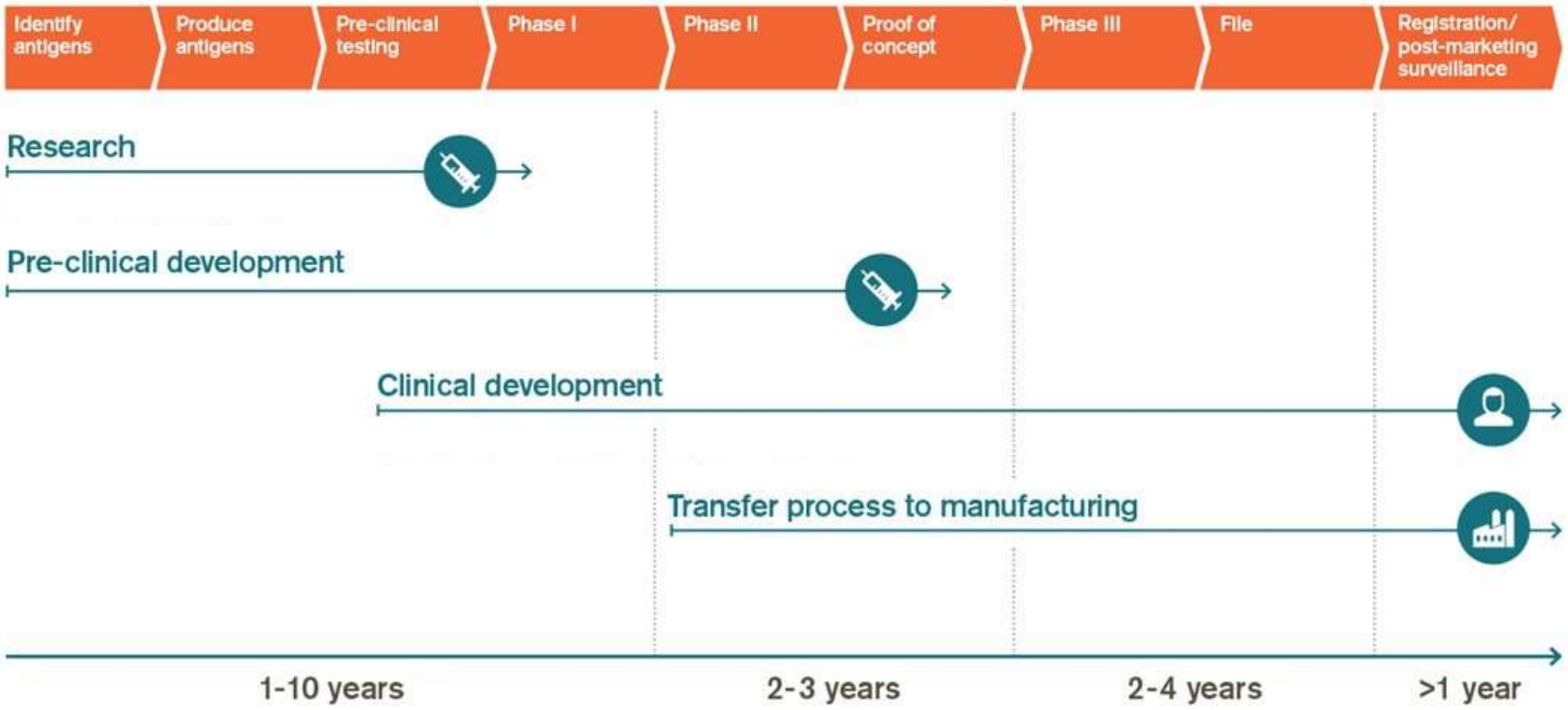
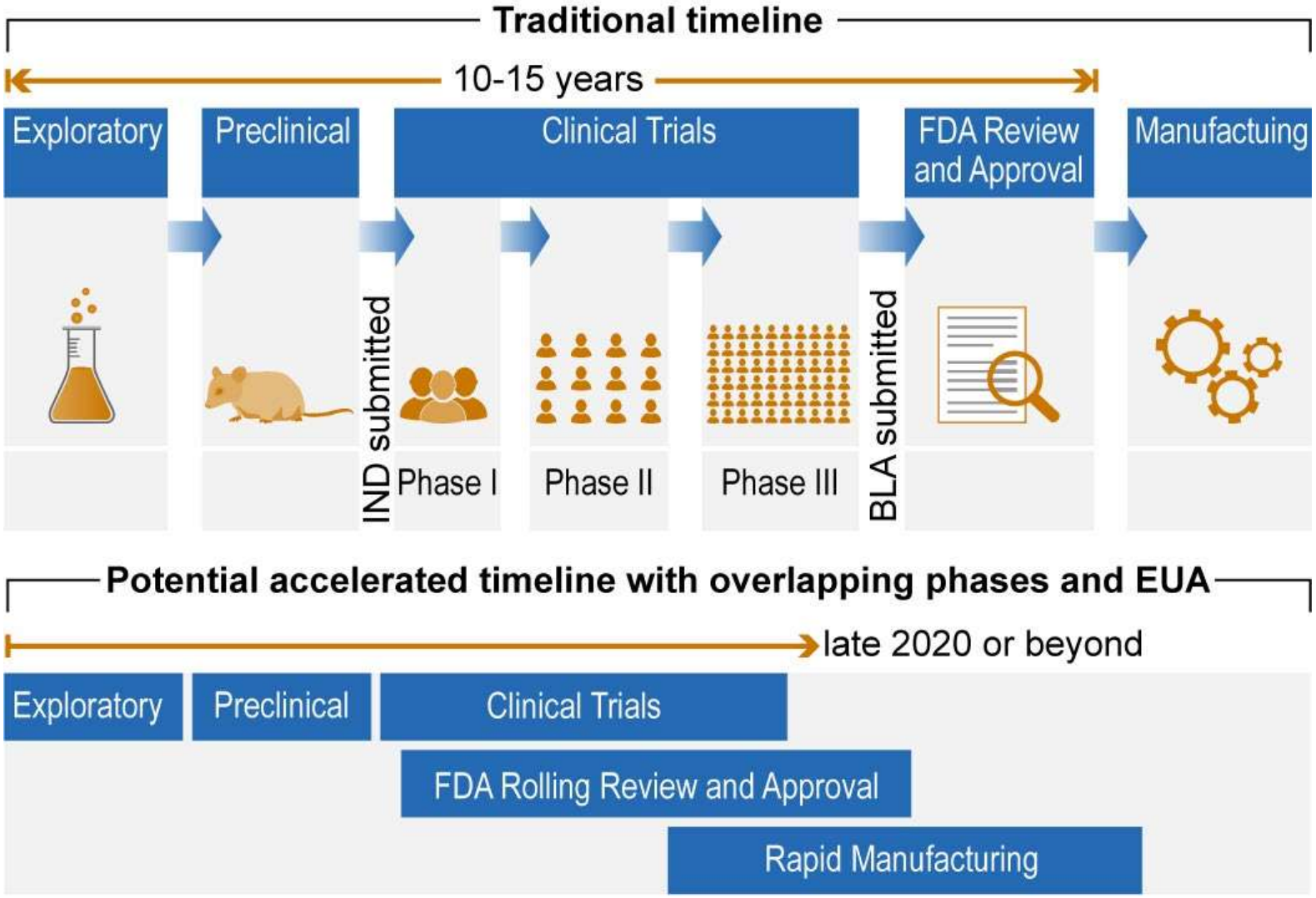
Properties of a vaccine

- Stimulate the immune system similar to natural infection and cause antibodies and memory T and B cells (Active immunity)
- Differ from the natural infection in that it is not pathogenic (causing disease)
- May not completely prevent but reduce severity and limit timing and recurrence of infection
- Last long enough and has low side effects

Vaccines research development cycle (industry average)



Source: ABPI



BLA = Biologics License Application

EUA = Emergency Use Authorization

IND = Investigational New Drug

Source: GAO analysis of GAO-20-215SP, FDA, HHS, and Pharmaceutical Research and Manufacturers of America (PhRMA) documentation. | GAO-20-583SP

Causes of fail

- The vaccine may not stimulate the immune response sufficiently because pre-existing antibodies, stress, malnutrition, steroid treatment, immune suppression, parasitism and pregnancy
- In appropriate storing, all stored at 2-8 c

eradicating infectious disease

- The success of vaccination in eradicating infectious disease is dependent on several properties of the microbes.
  - Vaccines are effective if the infectious agent does not establish latency, (HIV)
  - if it does not undergo much or any antigenic variation, (FLU and HIV)
  - Vaccines are also most effective against infections that are limited to human hosts and do not have animal

- Types
  - Killed or inactivated vaccines
  - Living attenuated
  - Toxoids
- Killed or inactivated vaccines
  - The bacteria or virus killed while retaining its immunogenicity
  - weakened or inactivated virus processed by either conventional technology by passing the virus through animal or human cells leading mutation or by chemical substances (most commonly formaldehyde and heat) that make it less virulent.
  - Less effective than live so it is given with adjuvants
  - Currently, two inactivated vaccines against SARS-CoV-2 were approved by at least one country: Covaxin (Bharat Biotech) and (Sinopharm).
  - It is short lasting
  - need booster dose
  - Examples; polio (given by injection), influenza (IM) and Hep. A and rabies viruses. Pertuses, typhoid and cholera bacteria
  - They can be used with immuno-deficient patients
  - Safety problems; contamination with endotoxins, vaccine not killed,
  - damaged by freeze

- Live attenuated
  - Alive microbe; by using a technique (reverse genetics) induce certain changes in gene that stop the virus pathogenic activity
  - The use of whole attenuated virus resembles the natural infections highly; therefore, the immunity includes all the aspects of the immune response (innate and adaptive). However, attenuated although very efficient, these vaccines require a longer time to develop, which delays the process.
  - Fear of reversal of microbe activity and causing disease mainly in immunocompromized,
  - and not for pregnant woman as it may cause fetal damage
  - May cause allergy to those allergic to egg as it is prepared in chick embryo
  - Can be freezed or refrigerated
  - Examples; oral polio vaccine, measles, mumps, rubella, Hep. A viruses. TB bacteria (BCG vaccine), flu virus by nasal spray

-Purified antigen (subunit, Toxoids)

– Subunit vaccines are composed of antigens purified from microbes or inactivated toxins and are usually administered with an adjuvant
  - Purified toxins (usually exotoxins) that loss its toxicity and retain its immunogenicity as tetanus and diphtheria toxins, given with Polysaccharides (adjuvant) for longer and stronger stimulation
  - Polysaccharides-protein vaccines (conjugate vaccines); H. influenzae, pneumococcal, and meningococcal vaccines, stay in body for long time as they are difficult to digest by microphages. Long term B cells stimulation

- **Synthetic Antigen Vaccines**
- synthesize most immunogenic epitope in the laboratory, and to use the synthetic antigens as vaccines
- It is possible to prepare large quantities of proteins by recombinant DNA technology
- hepatitis virus, herpes simplex virus, foot-and-mouth disease virus human papillomavirus, and rotavirus.
- In hep. B virus, hepatitis B surface antigen (HBsAg) is produced by yeast cells, into which the genetic code has been inserted where it is grown, harvested, and purified. A course of three vaccine injections is given, the second injection at least one month after the first dose and the third injection being administered six months after the first dose
- Manufacturing S protein. They inserted the gene into a different virus, called a baculovirus, and allowed it to infect moth cells then collect the resulting S protein (Novavax)
- Damaged by freeze

- **Live viral vectors**
  - DNA encoding the antigen inserted in non cytopathic virus and injected in human, antigen expressed in situ and all the immune system respond to that antigen
  - Example
    - vaccinia vector where smallpox vaccine virus is vector for HIV and malaria
    - Canary pox virus is tried to carry HIV vectors
    - (Oxford/AstraZeneca) Replicating viral vectors (Chimpanzee adenovirus:) with COVID-19 DNA that express S protein after entering the host cells with out causing disease ;and Human adenoviruses, Johnson&Jonhson, US

- DNA vaccines

  Inoculation of plasmid containing complementary DNA (cDNA) injected in human, encoding a protein inside the host antigen leads to humoral and cell-mediated immune responses to the protein.

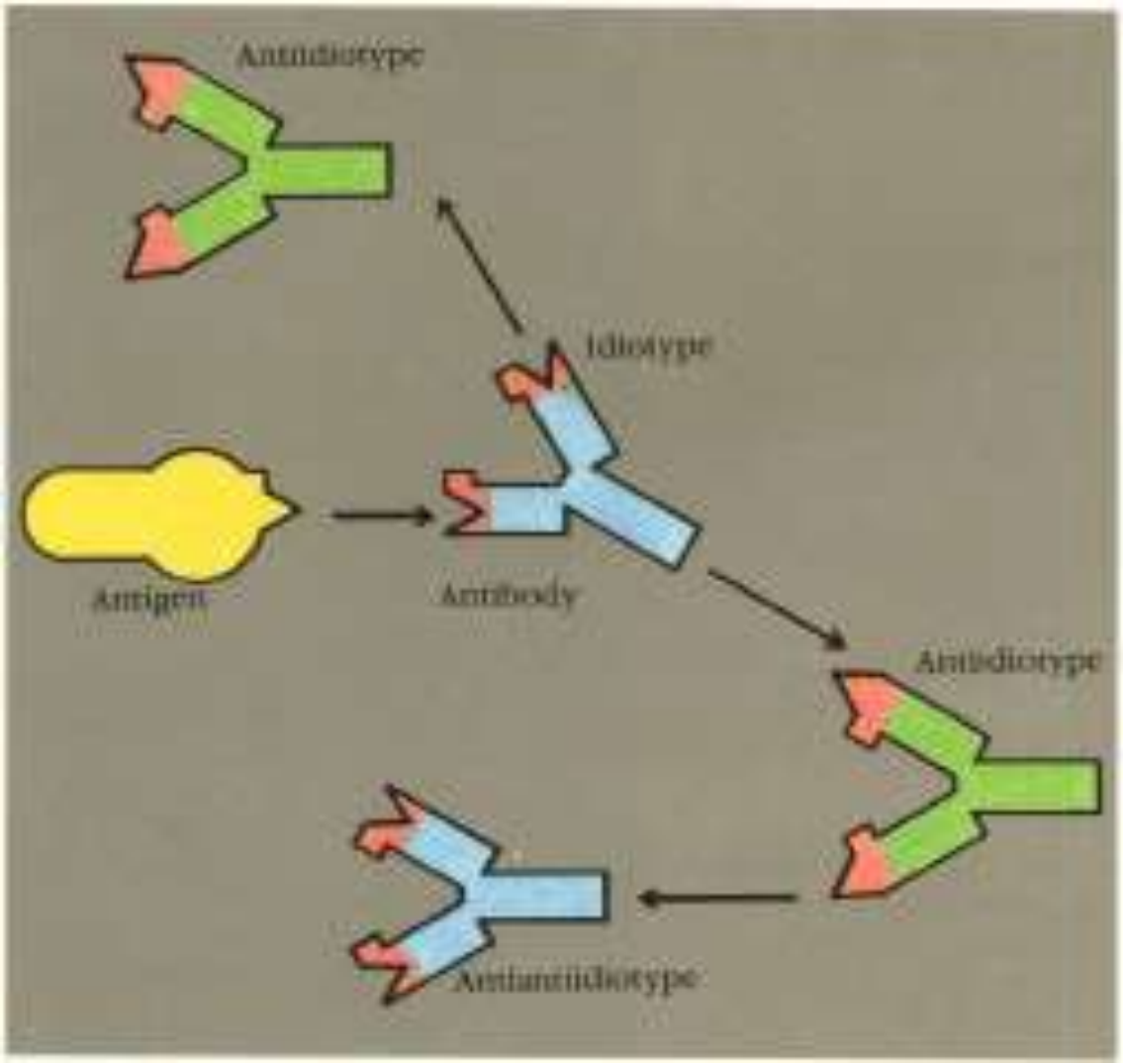
  -It is likely that APCs, such as dendritic cells, are transfected by the plasmid and the cDNA is transcribed and translated into immunogenic protein that elicits specific responses mainly in tumor vaccineare highly stable and do not require refrigeration

- Nucleic acids (mRNA) injected in human, synthesize the S protein of COVID-19 in side the host , RNA-based(BionTech/Pfizer) was approved, (Moderna), and Univ Oxford, UK, Can be freeze if storage is for long time

Anti-idiotype

- Anti-idiotype ; Use mono-clonal antibody that resemble antigen as a vaccine,
- May be used tumor vaccination
- Form antibodies that bind tumor antigens in mice then these antibodies are isolated and injected into another mice forming antibodies against the injectable antibody idiotype"anti-idiotypic". that mimics the original antigens. These antibodies are humanized and combined with an adjuvant and given as a vaccine.

Anti-idiotype



Adjuvants

- Adjuvants in immunology are often used to modify or augment the effects of a vaccine by stimulating the immune system to respond to the vaccine more vigorously, and thus providing increased immunity to a particular disease.
- The initiation of T cell–dependent immune responses against protein antigens requires that the antigens be administered with adjuvants
  - lipopolysaccharide (LPS), components of bacterial cell walls acting as prolonged natural infection, example is adjuvant with diphtheria and tetanus toxoid
  - Inorganic salts like aluminum salt. Example diphtheria and tetanus toxoids activate B cells
  - microdroplets of oil called sequalene. Activate phagocytes
  - Cytokines as IL-12, IL2 or costimulatory protein B7

Antibody Titer test

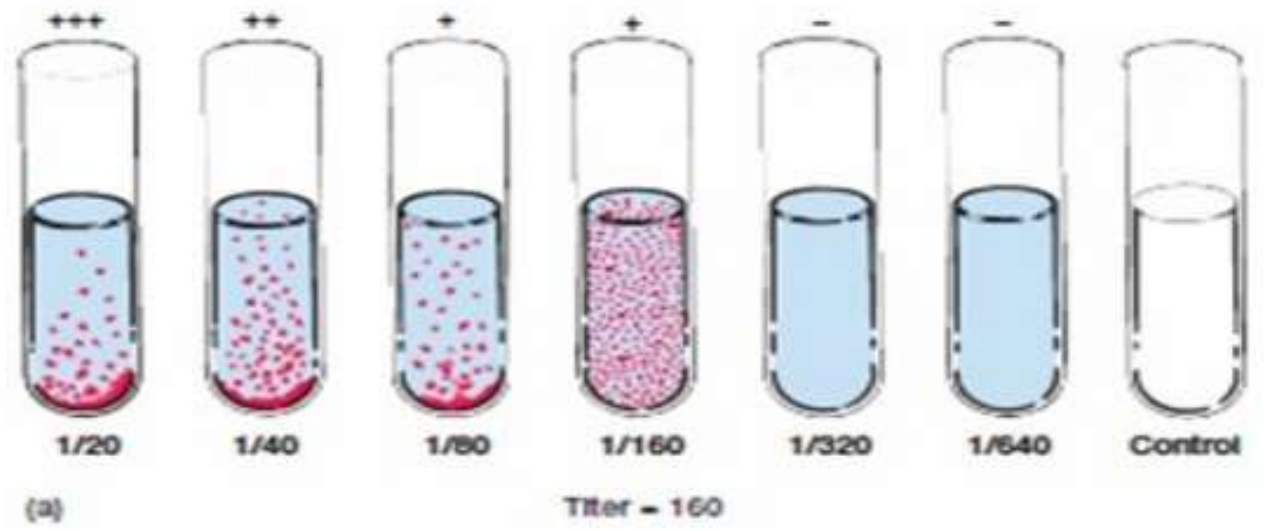
- The term titer, refers to the strength or concentration of a substance in a solution. Testing vaccine titers is done through a blood test that can identify the presence of antibodies induced by vaccinations and should be IGG. If IGM is high means acute infection.
- If the levels are satisfactory, the person is considered to have "protective antibody IGG" and is considered to be "sufficiently immune" to the disease. You can argue that no further vaccination is necessary at this time. The tests can be ordered for both children and adults and the "protective levels" are the same in all age groups.
- Vaccine titers can be used to determine the need for additional vaccines and are a reflection of the ability of the immune system to respond to an antigen

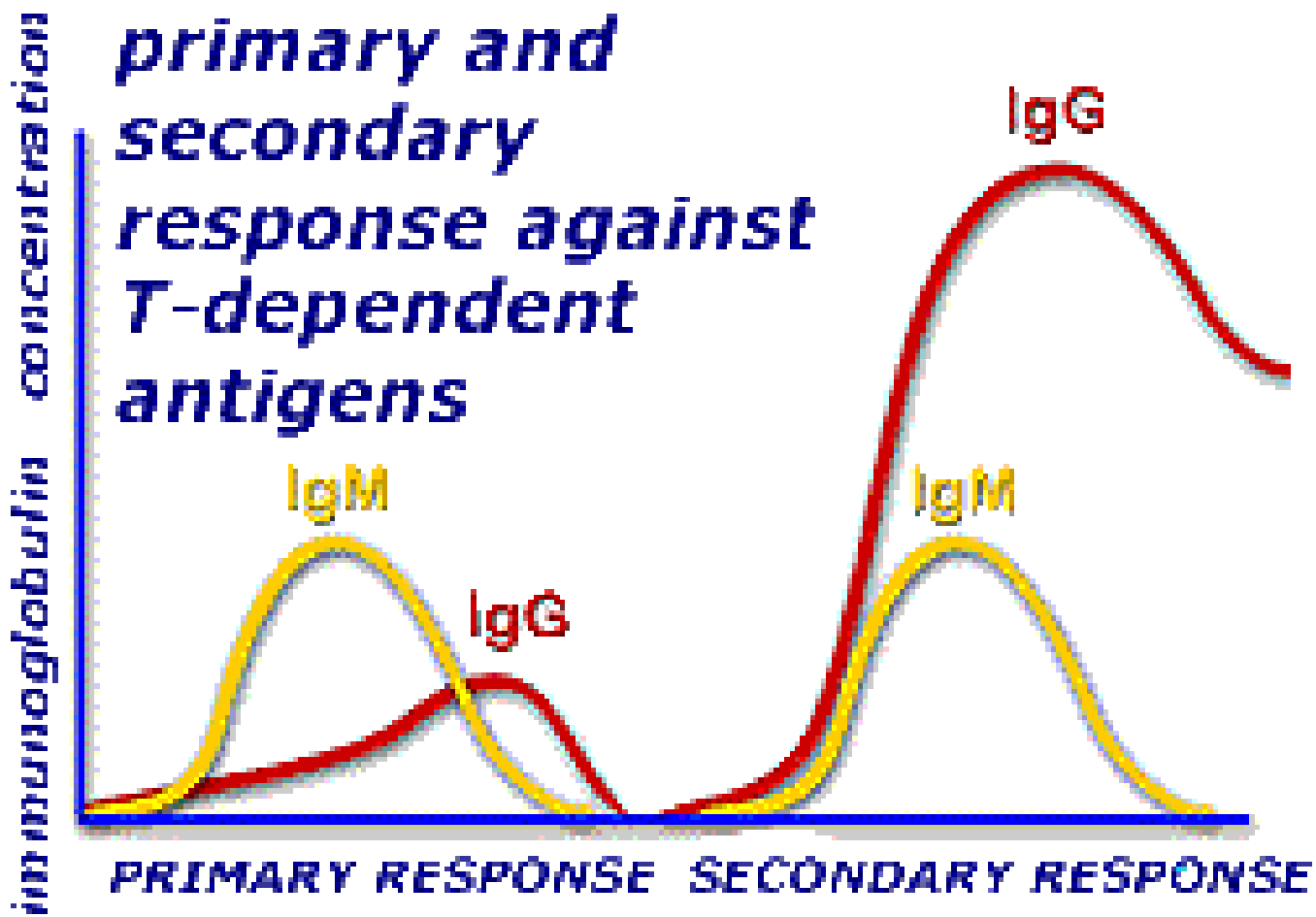
Titer

- Or level of antibody in serum is expressed as the highest dilution of antibodies that gives a positive reaction with antigen. It can be diagnostic or prognostic

2) Tube agglutination test :

- Standard quantitative method for determination of antibodies.
- Serum diluted serially by doubling dilution in test tubes.
- Equal vol of particulate antigen is added to all tubes.
- Highest dilution of serum at which agglutination occurs is antibody titre




primary and secondary response against T-dependent antigens
immunoglobulin concentration
IgM
IgG
IgG
IgM
PRIMARY RESPONSE
SECONDARY RESPONSE

National program

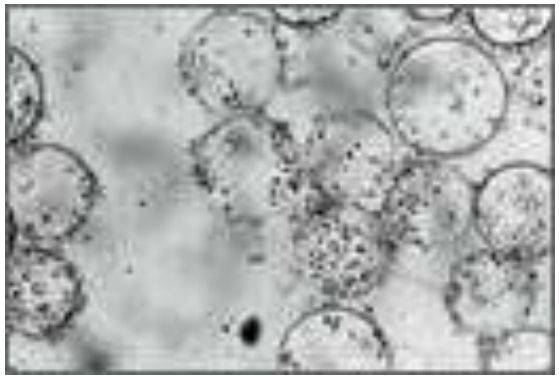
- Age Vaccine
- Newborn -BCG
- 2 months- DaPT1 IPV1+Hib1+HepB1
- 3 months- DaPT2 IPV2+Hib2+HepB2+OPV
- 4 months- DaPT3 IPV3+Hib3+HepB3+OPV
- 9 months- Measles + OPV
- 12 months-MMR1
- 18 months- DPTbooster1 +OPVbooster1 +MMR2

– School children who were completely vaccinated

- • 1st Class- OPV +Td + checked for MMR (2 doses)
- • 10th class- Td + checked for MMR (2 doses)

The Jordanian National Immunization Program			
Age	**Recommended Vaccines**		
newborne	BCG		
61 Days	DTaP-HBV-Hib	IPV	
91 Days	DTaP-HBV-Hib	IPV	OPV
121 Days	DTaP-HBV-Hib	IPV	OPV
9 Months	Measles	OPV	
12 months	MMR1		
18 Months	DaPT	OPV	MMR
6 Years (First Grade)	Td	OPV	
15 Years (10th Grade)	Td		

How are vaccines made?



Dead (inactivated) pathogens

IPV – Inactivated polio vaccine (شلل الاطفال

Pertuses (Whole cell)

Live attenuated pathogens (heat sensitive)

MMR – measles, mumps, rubella viruses و الحصبه وابودغيم

OPV -- oral polio vaccine – 'Sabin' vaccine

TB bacteria (BCG vaccine) السل-

لقاحات مصنعة بطريقة الهندسة الوراثية

)Recombinant DNA Technique)

HBV -- Hepititis B surface antigen التهاب الكبد -

Conjugates (polysaccharides coupled to protein carrier)

HiB – *Haemophilus influenzae* type B الانفلونزا

PCV – pneumococcal conjugate vaccine

Toxoids

DT---diphtheria, tetanus toxoids الكزاز والخانوق

Remember Adjuvants?

-- increase immune response

e.g., aluminum hydroxide

School Immunization Schedule –

- School children who were completely vaccinated
- • 1 st Class OPV +Td + checked for MMR (2 doses)
  • 10th class Td + checked for MMR (2 doses)
- Lower-case “d and p” denote reduced doses of diphtheria and pertussis used in the a dolescent/adult
- “aP” means acellular pertuses start in jordan in 2010, vaccine contain partial cellular material
  - Tdap for teens and adults after 11 years
  - TDaP for infants and children less than 6 years

Wait before giving vaccine to

- Children with fever, infection
- Anaphylaxis in previous vaccine (flue vaccine contain eggs)
- Immune compromise

- Vaccine Handling & Storage (Cold Chain)
  - Do not store other pharmaceutical
  - Do not store the vaccine on the door
  - Discard reconstituted vaccines if not used within 6 hours or at the end of immunization session
  - Do not open more than one vial

- Vaccines to certain groups
  - BCG for TB risk,
  - Hep.B; health workers
  - Rabies for animal worker
  - Meningitis, typhoid, cholera and hep.A for traveler
  - Influenza who at risk and elderly
  - Varicella zoster for leukemia children
  - Pneumococcal pneumonia for elderly, immuncompromized and spleen dysfunction and chronic heart or lung diseases

Passive immunity

- Ready made antibodies are transferred to individual to make short lived immunity till his Abs are formed
  - Natural passive immunity; transfer of antibodies from mother to fetus (IGG) and IGA through breast milk. Give protection for 6 months after birth

- **passive immunity in emergency**
  - **Tetanus antitoxin**

  Tetanus anti-toxin after dirt wound , and has never or not for a long time (10 years) been actively immunized with tetanus toxoid,

Antivenoms

These antidote (raised in horses or sheep) provide immediate protection to people bitten by a venomous animal (e.g., a rattlesnake)

❖ **Other uses of antibodies**

- Some **immune globulin** (IG) is prepared from the gamma globulin fraction of pooled plasma of several thousand blood donors on the assumption that this large pool will contain good levels of antibodies against many common diseases such as
  - **X-linked agammaglobulinemia**, who are unable to manufacture antibodies because of a mutation in their single gene for Bruton's tyrosine kinase.
  - serum from human is less antigenic but may carry HIV or hep. infection

- **Other uses of human immune globulin**

  Intravenous injections of IG have helped patients with such autoimmune disorders as

  -immune hemolytic anemia

  -immune thrombocytopenic purpura

  – The therapeutic effect seems that the C-region portion of the antibody molecules bind to a class of receptors on macrophages, which inhibits them from phagocytosing antibody-coated cells,

Prevention of hemolytic disease of newborn

- **Rh immune globulin** (**RhIg**) or **Rhogam** is used to prevent Rh-negative mothers from becoming sensitized to the Rh antigen of their newborn child This phenomenon has led to an extremely effective preventive measure to avoid Rh sensitization. Shortly after each birth (72 hrs) of an Rh+ baby, the mother is given an injection of anti-Rh antibodies. The preparation is called **Rh immune globulin** (**RhIG**) or **Rhogam**. These passively acquired antibodies destroy any fetal cells that got into her circulation before they can elicit an active immune response in her.
- may also be used in the treatment of immune thrombocytopenic purpura (ITP).