

MdBio Webinar Series

Vaccine Development: Where Have We Been and Where Are We Going?

MdBio

A division of the Tech Council of Maryland and the
MdBio Foundation, Inc.

Outline

- A Brief History
- Types of Vaccines
- Vaccine Formulations and Administration
- What Makes a Good Vaccine?
- Vaccine Development
- Controversies
- Development Update

What is a “Vaccine”

- The term *vaccine* derives from Edward Jenner's 1796 use of the term *variola vaccinæ* (Latin for cow pox), which, when administered to humans, provided them protection against **smallpox**



Vaccine- Definition

- A vaccine is a biological preparation intended to produce immunity to a disease by stimulating the production of antibodies.
- Vaccines include suspensions of killed or attenuated microorganisms, or products or derivatives of microorganisms.
- The stimulates the immune system to recognize the organism as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy them if re-exposed.
- The most common method of administering vaccines is by injection, but other routes are gaining popularity.
- Recently, administration by the transcutaneous and pulmonary routes has been utilized to achieve vaccination.

Timeline of Vaccines

- Thucydides in 430 BC reported that people who had survived plague were resistant upon re-exposure.
- 7th century-Indian Buddhists drank snake venom to protect against snake bite.
- 10th century-deliberate infection (variola) to prevent smallpox in China, India and Turkey
- Early 1700s-variola introduced into England but not successful.

Timeline of Vaccines (cont)

18th Century

- 1796-Edward Jenner introduced smallpox vaccination-the first vaccine for any disease.

19th Century

- 1875 to 1910-Beginnings of immunology as a science
- 1882-First vaccine for rabies

20th Century

- 1910 to 1930-Early bacterial vaccines, toxins and toxoids
- 1930 to 1950-Early viral vaccines: yellow fever and influenza
- 1950 to 1970-Use of tissue culture in development of poliomyelitis, measles, mumps and rubella vaccines
- 1970 to 1990-Use of molecular biology in development of chicken pox, hepatitis B, *Streptococcus pneumoniae*, *Hemophilus influenzae* B vaccines
- Recently-rotavirus vaccine, human papilloma virus vaccine and herpes zoster vaccine

Variolation

- Smallpox used to occur in epidemic waves with a fatality rate of 20-30% and left the survivors scarred for life.
- Variolation was a procedure in which pustular fluids from smallpox lesions or dried scabs from healing lesions were given to susceptible subjects by the nasal route to prevent natural disease.
 - Daughters with pock marks could not be sold into marriage.
- The individual develops a limited number of lesions with a mortality of 1-2% but were subsequently immune to the disease upon re-exposure.
- This did not attract much attention in the West-risk of death was high

Edward Jenner

- Country doctors noted that milkmaids, who had contracted cowpox, had clear skin.
- Edward Jenner in 1796 took fluid from a cowpox vesicle on a milkmaid and inoculated an 8 year-old boy who resisted a smallpox challenge 6 weeks later and subsequently again 5 years later.
- Immunization with cowpox was safer than variolation but immunity was found to decrease with time.
- Soon after, vaccination against smallpox spread from Britain to Europe and the U.S. and became compulsory in many countries.

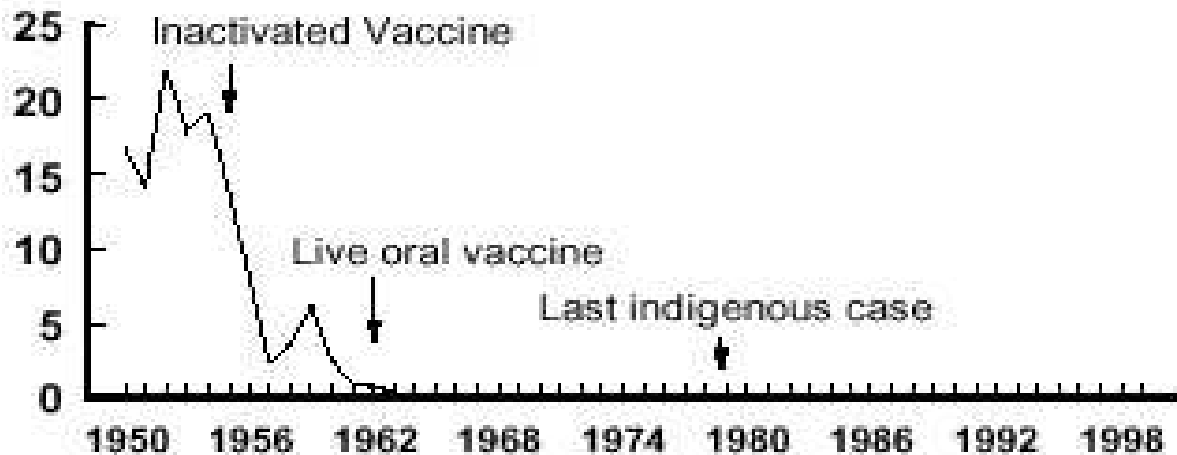
Use of Tissue Culture to Produce Vaccines

- Jonas Salk polio vaccine was termed a miracle but virus could be shed
 - Cutter incident involved ineffective inactivation of the virus that caused 56 cases of polio and five deaths
- Albert Sabin live attenuated polio vaccine for oral administration
- Measles, mumps, rubella and smallpox followed

The Eradication of Polio

Poliomyelitis - United States, 1950-1999

Cases
(Thousands)



The Eradication of Smallpox

- In the early 20th century epidemics occurred every 4-7 years in developing countries.
- Smallpox immunization in developed countries showed reduced disease frequency after WWI and transmission ceased after WWII, but remained a problem in developing countries.
- Development of freeze-dried vaccine overcame the problem of vaccine viability for use in developing countries.
- Little progress until 1967 when dedicated resources became available.
- At the time smallpox cases were estimated at 10-15 million in 31 countries representing 1.2 billion of the world's population,
- By 1977 smallpox eradication was achieved and on May 8, 1980 the world was certified smallpox-free by the CDC.

The Molecular Era of Vaccines 1970-1990

- Hepatitis B vaccine: Antigen produced by recombinant DNA technology. First vaccine used to protect select target populations, now throughout the developing world
- First anti-cancer vaccine for kidney cancer in Russia
- Pneumococcal and Hemophilus influenza b subunit vaccines

Today and Tomorrow

- Glycoconjugate vaccines (alter natural exposure, meningitis), rotavirus vaccine (diarrhea in kids), human papilloma virus vaccine and herpes zoster vaccine (shingles)
- HIV/AIDS vaccines, malaria vaccines, tuberculosis vaccines, anti-cancer vaccines, anti-addiction vaccines, anti-fertility vaccines, therapeutic vaccines.

Preparation of Vaccines

- **Live attenuated** organisms which have been passed repeatedly in tissue culture or chick embryos so that they have lost their capacity to cause disease, but retained an ability to induce antibody response, such as polio (Sabin), measles, rubella, mumps, yellow fever, BCG, typhoid and plague. Immunity similar to natural infection and is sometimes effective with a single dose.
- **Inactivated or killed** organisms which have been killed by heat or chemicals but retain an ability to induce antibody response. They are generally safe but less efficacious than live vaccines and require multiple doses; e.g. polio (Salk), influenza, rabies and Japanese encephalitis.

Preparation of Vaccines (cont)

- **Cellular fractions:** usually polysaccharide fraction of the cell wall of a disease causing organism, such as pneumococcal pneumonia, Salmonella typhi, meningococcal meningitis
- **Recombinant vaccines:** produced by methods in which specific DNA sequences are inserted by molecular engineering techniques, e.g. DNA sequences spliced to vaccinia virus grown in cell culture to produce an effective influenza vaccine, and Hepatitis B vaccine by similar methods.

“Vaccination” by Passive Immunity

- ***Toxoids or antisera*** are modified toxins made non-toxic to stimulate formation of an antitoxin, such as those produced to protect against toxins of tetanus, diphtheria, botulism, gas gangrene, snake and scorpion venom.
- ***Immune globulin*** is an antibody containing solution derived from human blood in the form of pooled plasma, used primarily for immunity for passive immunization such as for immunocompromised persons and protection from biological weapons.
- ***Antitoxin*** is an antibody derived from serum of animals after stimulation with specific antigens and used to provide passive immunity in humans.

Disadvantages of Live Attenuated Vaccines

- Severe reactions are possible in immunocompromized hosts.
- Reversion of vaccine strain can produce vaccine associated disease.
- Costly
- Fragile – must be stored and handled carefully

Disadvantages of Inactivated Vaccines

- Cannot replicate
- Generally not as effective as live vaccines
- Generally require 3-5 doses
- Antibody level may diminish with time requiring re-vaccination

Disadvantages of Pure Polysaccharide Vaccines

- Not consistently immunogenic in children younger than 2 years of age.
- Immunologic memory not induced

DNA Vaccines

- Plasmid DNA injected into muscle (also SC and ID) with expression of encoded protein antigen
- Single plasmid can be tailored to make variety of vaccines.
- Refrigeration not needed for handling and storage of plasmid DNA
- Can be administered by needle and syringe
- Electroporation boosts immunity

Vaccine Formulation

- Process in which different chemical substances including the desired immunogenic component are combined to produce the final product.

Additives in Vaccines

- Suspending fluids
 - sterile water, saline or fluids containing protein, egg protein
- Preservatives and stabilizers
 - albumin, phenols, antibiotics and glycine, MSG, 2-phenoxy-ethanol, thimerosal
- Adjuvants or enhancers
 - aluminum gels or salts

Adjuvants

- Substances that enhance the immunogenicity of vaccines

Vaccine Delivery using Needle and Syringe

- ~750 million injection given annually
- People don't like needles
- Accidental needle sticks
 - 300,000 annually in US
- Reuse of needles and syringes in third world countries

Immunization without Needles

- Oral vaccines-polio, typhoid, cholera, rotovirus, nasal influenza
- Cutaneous vaccination: liquid-jet injection deliver antigen ID, SC, or IM
- Particle bombardment of the skin-epidermal powder administration
- Topical application to skin using adjuvants and or permeabilizing agents
- Pulmonary delivery

Routes of Needle-free Immunization

Cutaneous immunization

Epidermal powder immunization
(DNA-coated gold particles or vaccine powders)

Liquid-jet injection
(Off-the-shelf vaccine formulations)

Topical application
(Adjuvant patches, colloidal carriers, ultrasound or microneedles)

Mucosal immunization

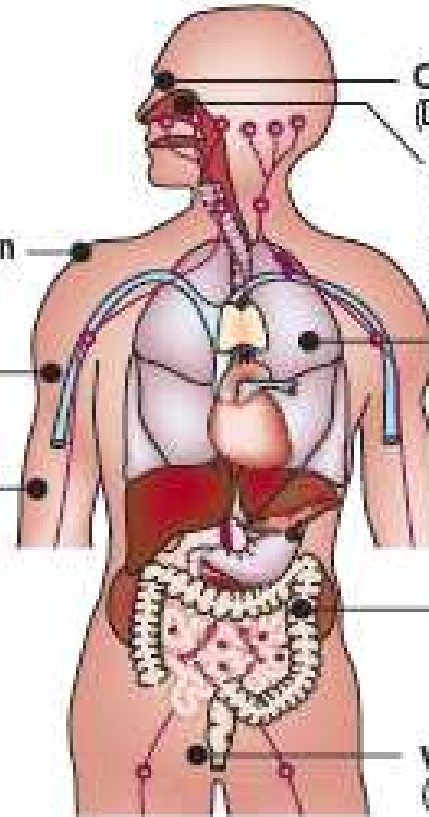
Ocular immunization
(Drops)

Nasal immunization
(Sprays and drops containing adjuvants plus liquid formulations, liposomes or microspheres)

Pulmonary immunization
(Aerosols or powders)

Oral immunization
(Liquid formulations and pills containing adjuvants plus liposomes, microspheres or bacterial ghosts)

Vaginal or rectal immunization
(Creams containing adjuvants)



Advantages of Mucosal Immunization

- Good serum antibody responses
- Good antibody responses on mucosal surfaces where the pathogen encounters the host

Properties of an Ideal Vaccine According to WHO

- Safe
- Cheap
- Heat stable
- Good immune response after a single dose
- Immunity is long-lived
- Low potential for reversion to virulence
- Safe in immunocompromised individuals
- Applicable to a number of diseases
- Administered by a mucosal route
- Suitable for administration early in life

Vaccine Safety

- Lubeck disaster-BCG vaccination of infants (30% fatal)
- Cutter laboratory incident
- MMR vaccine and autism/thimerosal
- Rotavirus vaccine and intussusception-late 90s

Affordability

- Vaccines are expensive to make
- Big pharma needs incentives
- Liability
- International, National and Foundation support (Public and private sector support)

Heat Stability

- Your primary care physician's office vs an African village

Effective in a Single Dose

- Should not be a problem in industrialized countries with adequate health care infrastructure.
- Necessary in developing countries where people may never be seen again.

Administration by Mucosal Routes

- Especially important in immunization programs involving large numbers of people.

Immunization Early in Life

- Most vulnerable at this age
- Good compliance because of dependency for care.
- Stop transmission to older susceptible members of population

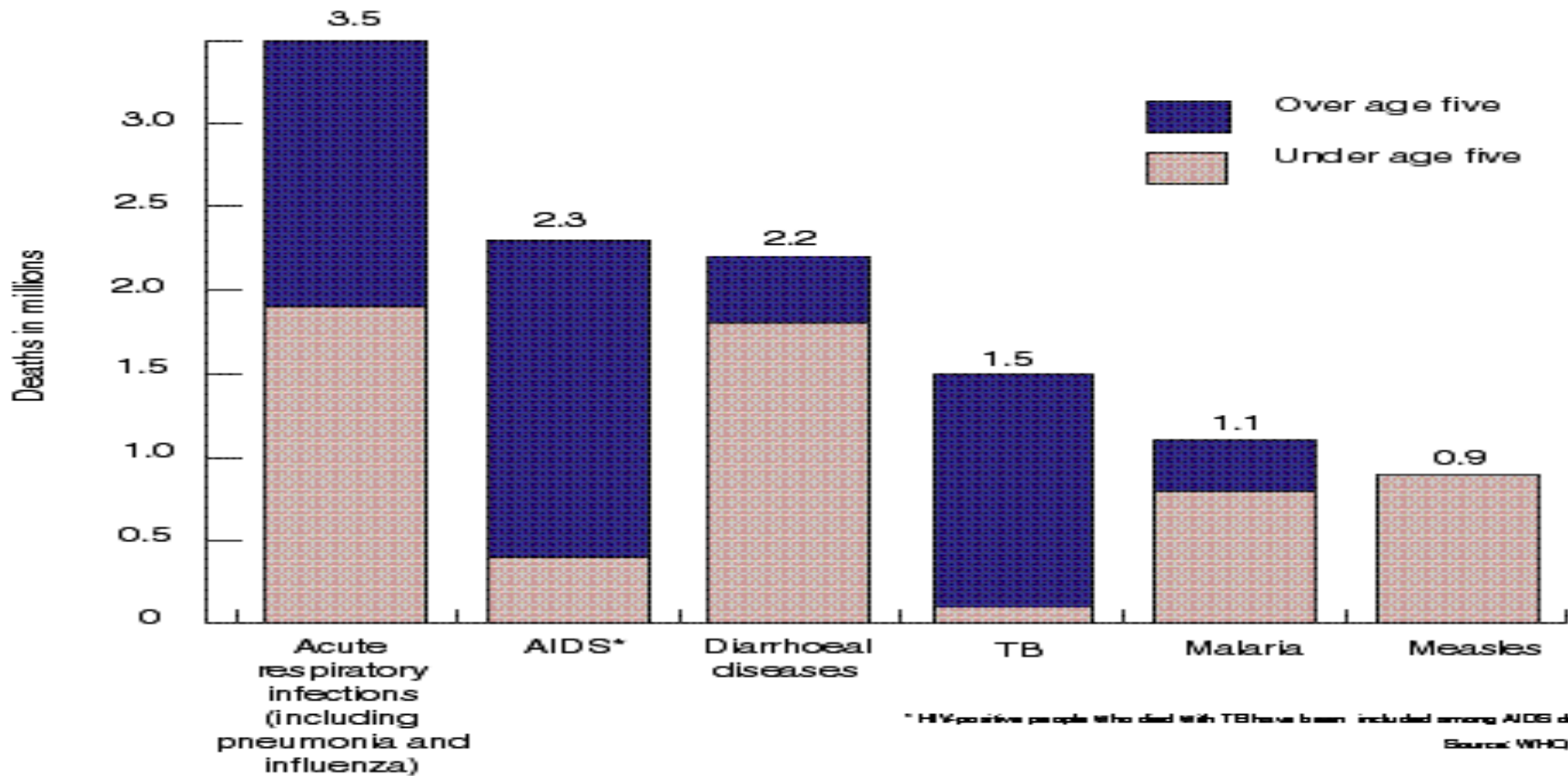
World Health Organization Reports

- **"Nearly nine million children under 14 years of age die every year from infectious disease. *And at least a third of them could be saved if existing vaccines were more widely used, but the rest only if suitable new vaccines were developed...*"**



Leading infectious killers

Millions of deaths, worldwide, all ages, 1998



Vaccines from Bench to Clinic



Discovery Phase

- Usually the result of experimentation in academic, pure research or biotech labs
- Basic research focuses on the biological mechanisms microbes use to cause disease and the characteristics of a microbe that might be used as a vaccine
- Data provide “Proof of Principal” and suggest commercialization of idea
- Academic labs incapable of further product development

Pre-clinical and Clinical Development

- Costs \$600 million-\$1 billion
- Can take 10 or more years
- Incentive-Profit
- Vaccines must be made employing “good manufacturing practice (GMP)”
- Cost and time needed to assure vaccine is safe and efficacious.
- Begins with submission of an “Investigational New Drug (IND)” application to the FDA
 - Description of vaccine, its method of manufacture, quality control testing done prior to administering to humans, data on safety and immunogenicity in animals, contains proposed clinical protocol

Phase 1

- Following submission of IND a candidate vaccine is tested in a small number (10-30) healthy human adult volunteers who are not at risk for the disease in question.
- Main goal is safety and to a lesser extent immunogenicity involving different doses and different immunization schedules.

Phase 2

- Involves a larger number of volunteers (50-500), usually a mixture of low-risk and higher risk individuals from the population where phase 3 studies will be done. Informed consent must be obtained from all participants.
- Main goal is to generate safety data as well as information for refining dosage and immunization schedule, vaccine formulations and lot consistency

Phase 3

- The randomized, controlled clinical trial aimed at providing scientific evidence about the clinical performance of vaccines.
- Involves 1000s of participants from high risk populations where individuals are randomized into test and control groups to be given vaccine or placebo in a blinded study to avoid bias.
- The goal of phase 3 trials is to determine vaccine safety and efficacy in a large study population sample leading to licensure application.



Vaccines: Points to Consider

- Vaccines have been the most effective public health tool resulting in reduced morbidity and mortality and an increase in the quality of life throughout the world.
- The US infant mortality rate was 20% about 100 years ago, and the childhood mortality rate before the age of five was another 20%.
- The use of vaccines has been so successful in disease eradication that the public has no understanding of many diseases or their effect on health and so don't see vaccination as a priority.
- There is also a large anti-vaccination movement of parents who are fearful because of bombardment with unsubstantiated facts about the dangers of vaccination.

Why Support Vaccination?

- We don't vaccinate just to protect our children. We also vaccinate to protect our grandchildren and their grandchildren. With one disease, smallpox, we "stopped the leak" in the boat by eradicating the disease. Our children don't have to get smallpox shots any more because the disease no longer exists. If we keep vaccinating now, parents in the future may be able to trust that diseases like polio and meningitis won't infect, cripple, or kill children.

Vaccine Controversies

- The public health benefits of vaccinations are exaggerated. Critics of vaccination policy point out that the mortality rates of some illnesses were already dramatically reduced before vaccines were introduced, and claim that further reductions cannot immediately be attributed to vaccines.
- Secondary and long-term effects on the immune system from introducing immunogens directly into the bloodstream are not fully understood.

Vaccine Controversies (cont)

- Vaccinations contain chemical components that are known to be toxic, such as formaldehyde, aluminum in various compounds, acetone, glyceride, ethylene glycol, and neomycin when injected in large enough quantities
- Thimerisol in MMR vaccines and association with autism

Public has Challenged the Safety of Several Vaccines



Anti-vaccine Lobbyists

- Not everybody believes that vaccines are good
- There are significant and influential followers

They can bring untold damage to immunization programs resulting in diseases and deaths

Recent examples:

- Northern Nigeria and polio (4-fold increase)
- MMR and measles in UK
- Hepatitis B in India

Current Vaccine Initiatives



Challenges in HIV Research

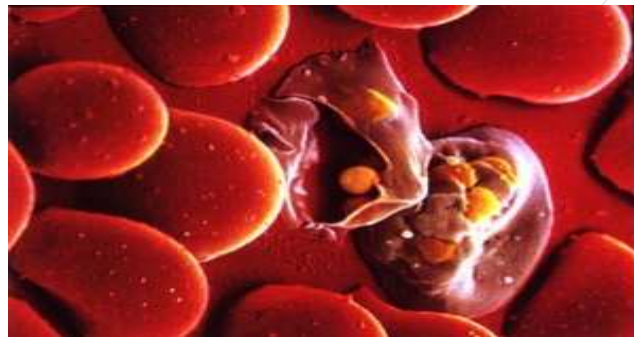


- Viral Genetic Diversity: HIV is not just one specific virus.
- Immune Protection: We don't know what immune responses are needed, or how strong they need to be.
- Neutralizing Antibody: Difficult to generate broadly neutralizing antibodies.
- Vaccine Testing: Slow process, very expensive

Status of HIV Vaccine Development

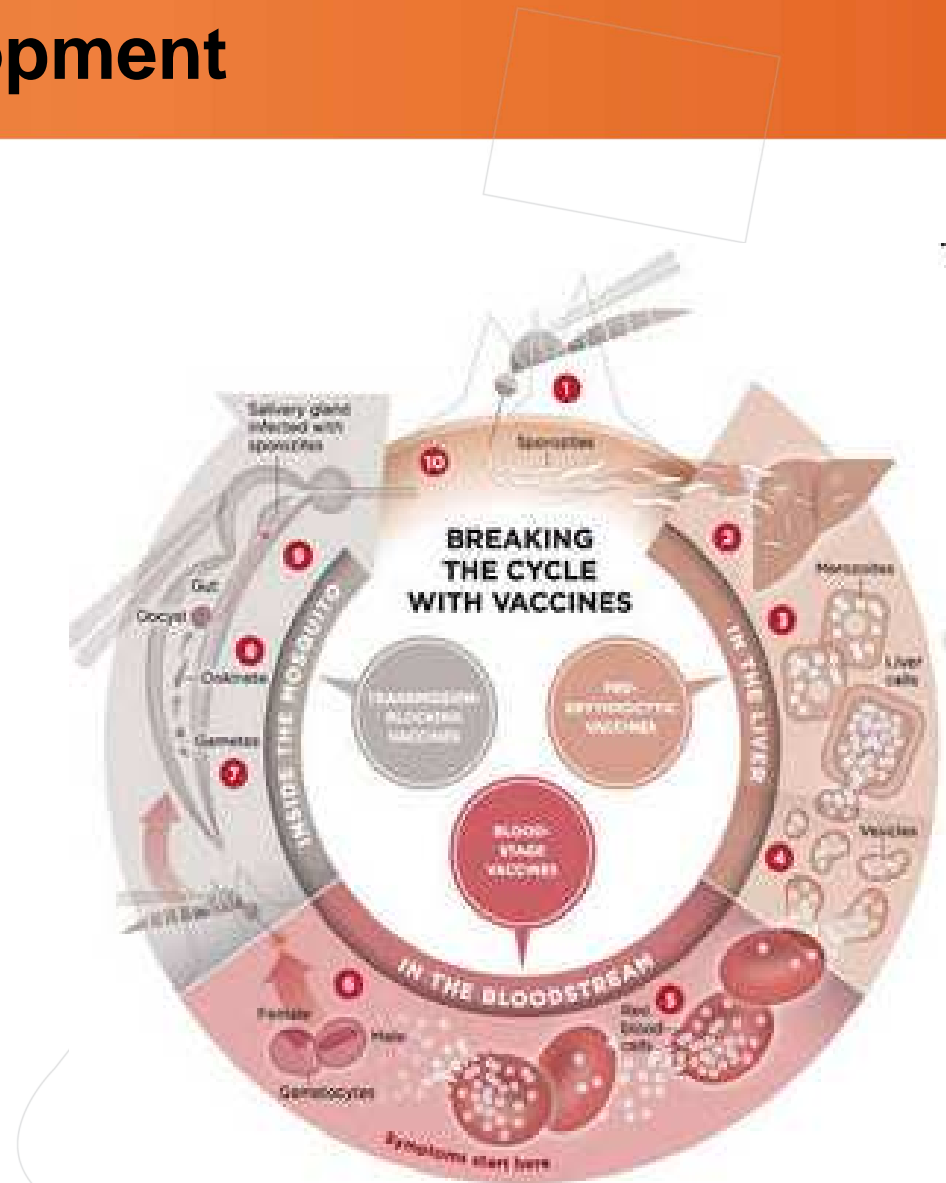
- Over 60 Phase I/II trials of 30 candidate vaccines
 - United States, Thailand, South Africa, Brazil
- One Phase III trial
 - VaxGen gp120 protein subunit vaccine

Malaria Vaccines in Progress



Malaria Vaccine Development

- More than a dozen vaccine candidates are now in clinical development, and one, GlaxoSmithKline Biologicals' RTS,S, is in Phase III clinical testing—the first malaria vaccine candidate to advance to third stage of testing



Phase III trial in Malaria



Kisumu, Kenya

- Phase III trial of the world's most clinically advanced malaria vaccine candidate was launched in Kisumu, Kenya, in July 2009 and may reach the market in 2015.

Malaria Vaccine Development

- The vaccine candidate—GlaxoSmithKline Biological' (GSK Bio) RTS,S—is the first of the current generation of malaria vaccines to warrant Phase III testing on this scale. The vaccine has a promising safety profile, was more than 50% effective in reducing episodes of clinical malaria in children 5 to 17 months old in earlier testing, and can be administered together with the package of vaccinations routinely given to African children.