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# A REVIEW ON THERMOSTABLE VACCINES

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**Abstract:** Vaccines are readily losing their efficacy when exposed to higher temperatures. But 3 vaccines are approved by World Health Organization for use at temperature up-to 40$^{o}$c those are Meningitis, Human Papilo Virus and Cholera vaccines. Vaccine for SARS–COV–2 is under clinical trial which is also thermostable vaccine. The Indian institute of sciences and biotech firm developed MYNVAX Vaccine by using genetic engineering.it is a domain of the S–protein of the SARS -COV–2 viruses called the Receptor binding domain, which attaches itself to the ACE- 2 receptor on the surface of target cells in the human respiratory tract. This makes the virus to enter the body and cause the infection. The pseudo viral assays done at the CSIR –Institute of microbial technology in India and the results from the live virus tests by CSIRO –Australia were very encouraging shows that effective neutralization of alpha, beta, gamma and delta SAR –COV–2 variants. This review of literature is to summarize the clinical trials, mode of action, storage conditions and efficacy levels of Thermo stable vaccines.

**Key words**: WHO, Thermostable, SAR –COV–2,

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**Introduction:** Vaccines usually contains dead or inactivated organisms or purified products derived from them. There are several types of vaccines that are being used .These represent the different strategies used to reduce the risk of illness while retaining the ability to induce a beneficial immune response. A vaccine is a biological preparation that gives active acquired immunity to a particular infectious disease. A vaccine generally contains a biological preparation from disease causing micro organism. And since the start of the 21$^{st}$ century, it is prepared synthetically that resembles it. This preparation is usually made up of weakened or killed forms of the microbes, its toxins, or its proteins. Vaccine stimulates the body's immune system to recognize the agent as a threat and starts manufacturing antibodies against it, so that it can further identity and destroy if any of the micro-organisms related to that agent that it should encounter in the future. Vaccines will be prophylactic (done or used in order to prevent a disease), or therapeutic (to fight a disease that has already occurred, such as cancer). The process of administering of vaccines is called vaccination.

Vaccination is the best technique of preventing infectious diseases, and its widespread immunity is responsible for the worldwide destruction of smallpox and the restriction of diseases such as polio, measles and tetanus from abundant of the world. The effectiveness of vaccination has been wide studied and verified; for example, vaccines that have tested effective include the influenza vaccine, the HPV vaccine and the chicken pox vaccine. The World Health Organization (WHO) reports that licenced vaccines are presently accessible for twenty-five different prevent able infections. The terms vaccine and vaccination are derived from Variolaevaccinae (smallpox of the cow), the term devised by Edward Jenner to denote cowpox. He used the phrase in 1798 for the long title of his Inquiry into the Variolaevaccinae notable as the cow pox, within which he described the protecting result of cow pox against small pox. In 1881,to honor Jenner, Louis Pasteur proposed that the terms should be extended to hide the new protective inoculations then being developed(1)

**TYPES OF VACCINES :**

1) INACTIVATED VACCINE:An inactivated vaccine is a vaccine consisting of virus particles, bacteria or other pathogens that have been grown in culture and then lose disease producing capacity. Examples include the IPV polio vaccine, hepatitis A vaccine, rabies vaccine and most influenza vaccine.

2) ATTENUATED VACCINE:Some vaccines contain live and attenuated micro -organisms. In the preparation of attenuated vaccine, the active virus is cultivated under conditions that will inhibit their virulent properties. Attenuated vaccines are some are viral and bacterial in nature. Examples include the viral diseases yellow fever, measles, mumps, and rubella and the bacterial disease typhoid. The live Mycrobacterium tuberculosis vaccine developed by Calmette and Gurein is not made of a contagious strain but contains a virulently modified strain called "BCG" used to elicit an immune response to the vaccine . The live attenuated vaccine containing strain Yersinia pestis EV is used for plague immunization. Vaccine produce more durable immunological responses . But they may not be safe for use in immune compromised individuals.

3) TOXOID VACCINE: Toxic vaccines are made from inactivated toxic compounds and cause illness rather than the micro-organism. Examples of toxic-based vaccinate tetanus and diptheria. Toxoid vaccines are known for their efficacy. Not all toxoids are micro-organisms; for example:Crotalus atrox toxoid is used to vaccinate dogs against

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rattlesnake bites. A toxin is an inactivated toxin(usually an exotoxin) whose toxicity has been suppressed either by chemical heat treatment and either properties like immunogenicity are maintained.

4) ISUBUNIT VACCINE: Instead of introducing an inactivated or attenuated micro-organisms to an immune system, a subunit vaccine uses any fragment of virus to create immune response. One example is the subunit vaccine against hepatitis B virus, that is composed of only the surface proteins of the virus. Another example is eligible algae vaccines, such as the virus-like particle(VLP) vaccine against human pappilomavirus(HPV), which is composed of viral major capsid protein example is hemagglutinin and neuraminidase subunits of influenza virus. A subunit vaccine is being used for plague immunization.

5) CONJUGATE VACCINE:Some bacteria have a polysaccharide outer coat which is poorly immunogenetic. By linking these outer coasts to proteins(e.g., toxins) , the immune system can recognize the polysaccharide as if it was protein antigen. This approach is used in the Heamophilus influenzae type B vaccine.

6) HETEROTYPIC VACCINE: Heterologus vaccines are also known as "Jennerian vaccines", which are pathogens of other animals that either don't cause disease or cause mild disease in the organism being treated . The example is Jenner's use of cowpox to protect against smallpox . A current example is the use of BCG vaccine made from Mycobacterium hovies to protect against tuberculosis.

7) RNA: An mRNA vaccine (for RNAvaccine) is a novel type of vaccine which is composed of the nucliec acid RNA, packaged within a vector such as lipid nanoparticles. Among the COVID-19 vaccines are a number of RNA vaccines under development to combat the COVID-19 pandemic and some have received emergency use authorization. An RNA vaccine or mRNA (messenger RNA) vaccine is a type of vaccine that uses a copy of a natural chemical called messenger RNA(mRNA) to produce an immune response.The vaccine transfects molecules of synthetic RNA into immunity cells. Once inside the immune cells, the vaccine's RNA functions as mRNA, causing the cells to build the foreign protein that could normally be produced by a pathogen(such as a virus)or by a cancer cells. These protein molecules stimulate an adaptive immune response which teaches the body how to identify and destroy the corresponding pathogen or cancer cells The delivery of mRNA is achieved by a co-formulation of the molecule into lipid nanoparticles which protect the RNA strands and helps their absorption into the cells.(2)

**HISTORY OF VACCINES**: Here is a long list of the main developments in the twenty years :1944-45 :First flu vaccine campaign with a new shot developed ,1960:poliovirus,1963:Measles,1969:Rubella,1971:Measles,Mumps,Rubella(MMR),1976:Swine flu, vaccination in the US ends after it was as,1977:Vaccine against 14types of pneumococcal bacteria ,1980:Smallpox eradicated ,1986:Hepatitis B,1995:Hepatitis,2002:Polio eliminated in Europe ,2006:Human papillomavirus (HPV) The most common sexually transmitted infection ,2009:H1N1,Aug2020:Polio eradicated in Africa(3)

**Benefits of using vaccines out of the cold chain**: Warm vaccines also known as thermostable vaccines. "A thermostable or 'warm vaccine' is critical for remote or resource-limited locations with extremely hot climates which lack reliable cold storage supply chains, including regional communities. Vaccines that can withstand high temperatures are rare. Till date 3vaccines are approved by WHO for use at temperature up-to 40degrees they are meningitis, human papilo virus (HPV) and cholera.

- It will not needed to be refrigerated at temperature below 0ºc.
- Heat tolerant vaccines can be transported to remote and villages for tens of millions of jabs without depending on the cold chain.
- It can be particularly helpful for mass vaccination.
- Storing and keeping vaccines does not requires walk in freezers, ice-lined refrigerators, refrigerated trucks, coolant packs such as dry ice and cold boxes.
- Vaccines can easily lose potency when exposed to higher temperatures and it cannot be seen in warm vaccines.
- The new formulation can remain stable at 37°c.
- These vaccines can be deployed quickly in hard- to-reach communities, and reduce pressures on healthcare workers.

The "warm" or a heat-stable vaccines can be stored at 100C for 90 minutes, at 70C for about 16 hours, and at 37C for more than a month and more. The 'warm' vaccine formulations developed by scientists at Indian institute of science (iisc) and biotech firm Mynvax result in antibodies that neutralise all current SARS-CoV-2 variants of concern, an independent evaluation of the formulations done by CSIRO(common wealth scientific and industrial research organization), Australia.

The published study was led by Prof Raghavan Varadarajan from IISc and Times of India first reported about the vaccine in November 2020.(4)

Coronaviruses are large, enveloped, positive -strand RNA viruses that can cause diseases ranging from the common

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cold to severe acute respiratory syndrome(SARS). The virus causing coronavirus disease 2019(COVID-19) is a novel **β** -coronavirus which is now named as SARS -Cov-2(3). This virus has four essential structural proteins including the small envelope(E) glycoprotein, membrane(M) protein , nucleocapsid(N) protein , and spike(S) glycoprotien , and also three accessory(non-structural) proteins including papain- like protease (PLpro) and 3Chemotrypsin-like(3CLpro, also known as the main protease-Mpro), which are responsible for cleavage of viral polypeptide into functional units; and RNA-dependent RNA polymerase(RdRp), which is critical for viral replication and transcriptionconverting enzyme II (ACE_2) receptor, which is found in virtually all human organs in varying degrees. In general, S protein, PLpro, 3CLpro, RdRp and ACE-2 are the most attractive targets for the development of new antiviral drugs against COVID-19. Although thus disease is asymptotic to mild in most people(approximately 80%) in the most severe cases, it can lead to pneumonia, acute respiratory distress syndrome, sepsis and septic shock, multi-organ failure , and even death . Despite global entertainment measures to fight the current pandemic, the incidence of covid-19 has continued to rise , with over 73.9, million confirmed -cases and over 1.6 million deaths worldwide as of 17 December 2020 COVID-19 poses a serious threat to global public health and a broadly effective therapeutic strategy could provide a key means of overcoming this crisis . Unfortunately there is currently no known effective treatment for COVID-19. Thus, drug repurposing(i.e , testing the efficacy of existing drugs used previously to treat other diseases) is a basic goal in order to develop a fast therapeutic approach for patients with COVID-19

Mynvax vaccine completed animal trails and entering into the human trials .ln animals trials it shows strong immune response in mice protected hamster from the virus.(5)

The IISc-Mynvax vaccine has been designed by genetically engineering a domain of the S-Protein of the SARS-CoV-2 virus, called the Receptor Binding Domain (RBD), which attaches itself to the Ace2 receptor on the surface of target cells in the human respiratory tract. This enables the virus to enter the body and cause the infection

S-Protein of the virus is about 1,300 amino-acids long but the vaccine focuses only on a string of 200 amino acids.

SARS-CoV2 variants are shown by the pseudo-viral assays done at the CSIR-IMTech in India, and also that the results from the live virus tests by CSIRO were very encouraging.

CSIRO played a key role in evaluating the formulations against all current SARS-CoV-2 variants of concern. “CSIRO scientists at the Australian Centre for Disease Preparedness in Geelong contributed to the study by assessing vaccinated mice sera (blood samples) for efficacy against key coronavirus variants, including the Delta variant currently spreading globally including in Sydney.

Mynvax vaccine data shows that all formulations tested result in antibodies capable of consistent and effective neutralisation of the Alpha, Beta, Gamma and Delta SARS-CoV-2 variants of concern.

In addition to IISc and CSIRO, the study included researchers from the University of York in the UK, CSIR-Institute of Genomics and Integrative Biology (CSIR-IGIB), New Delhi, Translational Health Science and Technology Institute, Faridabad, and CSIR-Institute of Microbial Technology, Chandigarh.

Unlike drugs, virtually all vaccines need to be transported at cold temperatures (usually between 2 and 8 degrees Celsius) prior to use. If they are exposed to higher temperatures, many vaccines lose potency. Re-cooling does not help. Thus we need cold chain of handling before use. It would therefore be extremely useful if we can make and transport a vaccine at room temperature, with no cold chain needed.(6)

**Active domain**

The COVID virus has, on its surface, a protein called the spike which is about 1,300-amino-acids long. Within this, a sequence that is about 250 amino acids long, called the receptor binding domain (RBD), attaches itself to the “host” cell surface and starts the process of infection. The group decided to synthesis in the laboratory, not the full length spike protein, but a 200-amino-acid fragment of the RBD, and study its structure, (three-dimensional architecture, or the shape which allows it to fit snugly to the host cell surface — a “lock and key” fit), thermal stability (can it work at temperatures higher than the normal lab conditions), and so forth. Happily, the authors found that this fragment, when freeze dried (or “lyophilized”), is highly stable, can withstand transient exposure to temperatures as high as 100 degrees Celsius and can be stored for over a month at 37 degrees Celsius, suggesting a cold-chain should not be required for this molecule.

**Clues from structure**

On an aside, for the past 70 years, India has been a pioneer in the field of how the structure or architecture of a protein offers clues to its function . For example how the triple helical structure of collagen, experimentally discovered by the late G. N. Ramachandran in 1954, explains why it is found in the skin and tendons, offering them rope-like strength. Prof. Ramachandran also suggested, given a protein sequence, how we may predict the ways it may fold into a 3-dimensional architecture. This, in turn, has led biochemists to synthesise proteins with changes in their amino acid sequence that function the way they want it to.

The authors have done exactly this by carefully choosing the sequence of the RBD fragment to be expressed, and demonstrating that the resulting protein is thermo-tolerant. This exemplifies the power of protein structural analysis and “genetic engineering”.

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**ADVT**

The RBD protein was produced in large amounts in mammalian cells as well as in a yeast called Pichia pastoris, which is a highly cost-effective, inexpensive, host. However, when they compared the two proteins, they found that the yeast-expressed protein was more heterogeneous and did not yield the desired antibodies when tested in animals. They also tried expressing the identical RBD fragment in the usual model bacterial system, E.coli, but the protein was non-functional.

**Adjuvants and trials**

Now that we have a thermo-tolerant RBD, can it be tried as a vaccine candidate, generating antibodies that will block the receptor-binding motif of the spike protein and prevent infection? Generally, immunologists add what is called an adjuvant which, when co-injected along with the vaccine material (cells or molecules), stimulates the immune system and enhances the ability of the vaccine to work. Aluminums salts are often used.

The authors chose to use guinea pigs in their initial immunization's, since these are thought to be better models than mice for respiratory illnesses. As adjuvant, they used a generic version of the MF59 adjuvant which has an excellent safety record in humans, and they injected the RBD formulation in guinea pigs. After two doses, tests showed substantial levels of the desired receptor-blocking antibodies in the animals. So, it works.

They point out that numerous other groups have used the entire full length spike protein, or new RNA-based approaches to express antigens, including the RBD. However, unlike all the COVID-19 vaccine formulations currently in clinical trials which require a cold chain, this particular thermo-tolerant RBD fragment, (and possibly other RBD formulations), can be stored at room temperature for extended periods.

The researchers are now testing the ability of the formulation to protect animals from challenge with infectious virus and will simultaneously carry out safety and toxicity assessments prior to testing in human clinical trials. We wish the group all success.

**Mechanism**

The vaccine formulations use a part of the viral spike protein called the receptor-binding domain (RBD). The spike protein allows the virus to connect with the host cell to infect it. The vaccine is different from other vaccines as it does not use the entire spike protein, rather it only uses a specific part of the RBD — a string of 200 amino acids.(7)

**HUMAN PAPILLOMA VIRUS**

**Clinical trials :**

Only two HPV vaccination projects were initiated in India. One was a post-licensure observational study for operational feasibility of school-based and community-based vaccination in Khammam district (Andhra Pradesh, Gardasil®) and Vadodara (Gujarat, Cervarix™), conducted by the State Governments in collaboration with Indian Council of Medical Research and PATH (a US based non-profit non-governmental organization). The other was a multicentric clinical trial to investigate immunogenic efficacy of two doses (6 months apart) compared with conventional three doses (at 0-2-6 months) of Gardasil®, which if found successful would have resulted in 33% cost reduction(8).Clinical trials have shown that HPV vaccines are highly effective in preventing cervical infection with the types of HPV they target when given before first exposure to the virus that is, before individuals begin to engage in sexual activity. HPV vaccines have also been found to reduce infections in other tissues that HPV infects, including the anus and oral region (9).Trials and real-world data from population-based studies have now demonstrated that the vaccines greatly reduce the risk of precancers and cancers of the cervix, vagina, and vulva in vaccinated women (10,11). A clinical trial of Gardasil in men indicated that it can prevent anal cell changes caused by persistent infection The trials that led to approval of Gardasil 9 found it to be nearly 100% effective in preventing cervical, vulvar, and vaginal infections and precancers caused by all seven cancer-causing HPV types (16, 18, 31, 33, 45, 52, and 58) that it targets (12-15)

**Mechanism of action :**

Mechanism of action of the human papillomavirus (HPV) on cell cycle regulation. To progress from G1 to S cell cycle phase, cells have to pass the G1 restriction point that is under the control of the retinoblastoma protein (pRb). pRb binds and represses E2F transcriptional factors. Mitogenic signalling through CyclinD1/CDK4 or CyclinD1/CDK6 phosphorylates pRb, promoting E2F release. CyclinE/CDK2 completes pRb phosphorylation, allowing S-phase entry. HPV affects the cell cycle by using two viral oncoproteins, E6 and E7. The E6 protein binds p53 and promotes its degradation, whereas E7 protein binds and inactivates pRb. These viral oncoproteins determine cell cycle entry and inhibition of p53- mediated apoptosis. HPV-dependent inhibition of pRb promotes p16 accumulation. p16 represents a surrogate marker of HPV-positive HNSCC(16)

**Efficacy:**

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Results of multiple phase II and III studies are available for both vaccines. The USFDA recommended surrogate clinical end point for cervical cancer (development of CIN grade 2 or worse) has been used as the primary outcome measure in most HPV vaccine studies.[10] Published analyses have included variable study populations [Table 3].(17)Since obtaining cervical specimens from girls or young adolescents is considered unethical, clinical efficacy in younger girls (9–14 years) is extrapolated from immunobridging studies comparing vaccine immunogenicity in them with older females (15–26 years). Both vaccines have shown high efficacy rates for various clinical end points including condyloma, low- and high-grade CIN and AIS, as well as VaIN and VIN, associated with vaccine-related HPV types. The characteristics of three large phase III trials of Gardasil® (FUTURE I and II study) and Cervarix™ (PATRICIA study) conducted in young women and the prophylactic efficacies from these trials are summarized in Table 4. While the efficacy for prevention of HPV-16/18 related CIN-2/3 ranged from 90.4% to 98%, the overall HPV vaccine type-related CIN efficacy has ranged from 89.2% to 100%.The quadrivalent vaccine also demonstrated 91% to 100% efficacy against HPV-6/11/16/18-related VIN-2/VIN-3 or VaIN-2/VaIN-3 and 96% to 100% efficacy against HPV6/11/16/18-associated condyloma.[13,14] High efficacy rates have been reported in the ATP analyses of most studies. However, efficacy has been lower in the MITT and ITT analyses [Table 4]. This may reflect, at least in part, lesser protection with single dose compared with three doses. More importantly, the lower efficacy in ITT (which includes women already exposed to vaccine-related HPV) clearly suggests that women naive to vaccine-related HPV types are likely to benefit the most with prophylactic vaccination.[10] Further analyses of the findings of FUTURE I/II and PATRICIA trials over longer follow-up periods have reinforced the efficacy of both HPV vaccines.[18-20]

**Storage conditions :**

- Store refrigerated at (36 to 46°F).
- Do not freeze.
- Discard if the vaccine has been frozen.
- Protect from light.(21,22)

## MENINGITIS

Meningitis is inflammation of the layers of tissue that cover the brain and spinal cord (meninges) and of the fluid-filled space between the meninges (subarachnoid space). Meningitis can be caused by bacteria, viruses, or fungi, by disorders that are not infections, or by drugs(23)

**Clinical trials:** MenAfriVac, which was approved for use outside of the cold chain in October 2012, was used to , vaccinate 155,596 people, aged 1 to 29, in 150 communities in northern Benin in December 2012. The World Health Organization (WHO) says no cases of meningitis A were reported by the vaccinated population in 2013. The findings were recently published in the journal Vaccine. MenAfriVac was first introduced in 2011 in a mass vaccination campaign in Africa's meningitis belt, which stretches from Senegal to Ethiopia. To date, more than 150 million doses of MenAfriVac have been used to vaccinate people across 12 African countries.But it was not until the Benin trial that the vaccine was administered outside of the cold chain.Michel Zaffran, coordinator of WHO's Expanded Programme on Immunization (EPI), said that it has been known since the early 1970s that a number of vaccines are relatively heat stable(24)

**Efficacy** :"African meningitis belt", a region south of the Sahara between Senegal and Ethiopia. However, the efficacy of this vaccine over time and requirements in terms of booster vaccinations remain unknow

**Storage conditions**: MenAfriVac can be stored for up to four days at up to 40 degrees Celsius without any loss of potency, efficacy or safety(25)

## CHOLERA VACCINES:

Cholera is an acute diarrheal illness caused by infection of the Intestine with Vibrio cholera bacteria.Cholera is spread through contaminated food or water. It is not Usually spread directly from person to person, but it can be spread Through contact with the feces of an infected person. Cholera Causes severe diarrhea and vomiting. If it isn't treated quickly, it Can lead to dehydration and even death. Cholera is an easily preventable disease that has no place in the 21st Century,"(26)

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Cholera vaccines are vaccines that are effective at preventing Cholera. For the first six months after vaccination they provide about 85 Percent protection, which decreases to 50 percent or 62 percent.During the first year. After two years the level of protection Decreases to less than 50 percent. Cholera vaccines should be stored between 2° and 8°C (35° and 46°F). Keep from freezing.The vaccine may be kept for single period of time of up to 14 days at temperature of up to 40°C.The approval is of great significance to regions where the vaccine is Used, including India, as it eliminates the challenges of maintaining The vaccine cold chain (between +2°C and +8°C to maintain vaccine Potency) during transport.The WHO's approval will help us make Shanchol available to Populations living in remote, hard-to-reach areas of India and Other parts of the world, especially ones with erratic electricity Supply. "The WHO approval for use of Shanchol in controlled temperature Chain (CTC) was granted after a review of its stability data. Used for Prevention and control of cholera in outbreak, endemic settings During humanitarian crises, Shantha Biotechnics' Shanchol cholera Vaccine is the second "mass campaign" vaccine and first cholera Vaccine worldwide to receive such a stamp of approval for storage And distribution outside the traditional cold chain. "Cholera is an easily preventable disease that has no place in the 21st Century," This important development will make it easier to deliver vaccines To the remote areas where it is desperately needed, saving lives And contributing to the global effort to finally consign this disease to the history books.The storage label change takes us a few steps closer to our vision Of a world where no lives are lost to preventable infectious Diseases, as it has the potential to significantly change cholera Control efforts for the better, not only in India but also in other Parts of the world where the vaccine is needed the most. It is Indeed a great news as it will help increase vaccine access and Decrease the cost of conducting vaccination campaigns worldwide.(27)

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