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STORAGE CONDITIONS OF DIFFERENT TYPES OF VACCINES

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Abstract:

Vaccines are the biological preparations which are considered as the most economical and effective preventive step against the most contagious, non-contagious deadly infectious diseases. Vaccine contains a particle/agent that provides protection against infection by activating the immune system or on subsequent exposure to a pathogen. Due to the pandemics prone to the world from ancient times different types of vaccines are designed based on requirement and administered in to human body to teach immune system how to fight off with foreign particles or pathogens. This review includes the detailed information of the vaccines, importance of vaccines, stability and storage conditions of vaccines. Vaccines has its own stability issues which are caused by light, heat, radiation, changes in environment, reactions with container or with other components in the mixture which must be considered during development, storage, transport. A cold chain is a temperature-controlled supply chain used to maintain the vaccine stability problems during its storage. Any fluctuation in temperatures during manufacturing, transporting, it results in decrease in vaccine potency and increase in risk of vaccine preventable diseases.

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INTRODUCTION:

A biological preparation known as a vaccination offers either acquired immunity or adaptive immunity to a specific illness. The vaccine is the most cost-effective way to prevent numerous infectious diseases that result in morbidity or mortality. Vaccines are a diverse family of preparations that may contain proteins, polysaccharides, antitoxins, DNA recombinant antigens, inactivated viruses or live viruses. Their active ingredients are weekend bacteria. Additionally, they may include adjuvants, stabilizers, preservatives and other excipients, which all contribute to their quality, safety, and effectiveness.

Light, heat, radiation, alterations in the environment, reactivity with the container or other ingredients in the combination, and vaccine instability are all potential causes. stability, heavy water (D_{20}), the lyophilisation process, vaccine vials or tubes, freeze thawing cycles, production process, equipment and the cold chain utilized for vaccine maintenance and transportation are the elements that affect the storage of vaccines.

The capacity to maintain its chemical, physical, microbiological and bio pharmaceutical qualities within predetermined bounds for the course of its preservation period is known as stability. Stability studies may also be carried out after the product approval to confirm that it continues to function as it did before to approval and to assess the impact on product quality of consciously introduced manufacturing modifications. The aim of stability studies is to determine a re-test period or a shelf life as well as suggested storage settings and to offer information on how the quality of a vaccine changes over time under the effect of various environmental variables.

Most vaccines are poorly thermostable necessitating continuous storage between 2ºC and 8ºC from the time they are manufactured until they are given to a patient, to maintain a desired low temperature, a cold chain is a supply chain with temperature control. The procedure of sending vaccines to numerous locations around the world is frequently done via the cold chain technique. To maintain the ideal temperatures that assure the vaccination won't lose its efficacy this procedure is routinely utilized with vaccines. Recently, a controlled temperature chain (CTC) label was introduced to guarantee that vaccines can endure a temperature excursion up to 40ºC for up to 4 days. Most vaccinations need to be stored in the refrigerator from manufacturing to usage because of their thermosensitivity. Vaccine stability needs to be ensured to properly implement global vaccination programs (1).

Stability studies on vaccines are conducted

- To determine the storage period of intermediates.
- To determine or modify a modify a maximum shelf life.
- Minimum release specification for final product (2).

Classification of vaccines

1. Live attenuated vaccine

- BCG **(**Bacillus Calmette-Guerin)
- MMR **(**Measles, Mumps, Rubella)
- OPV **(**Oral Polio Vaccine)

2. Inactivated vaccine

- IPV **(**Inactivated Poliovirus Vaccine)

3. Subunit vaccine

- Protein vaccine - Hepatitis-B Vaccine
- Polysaccharide - Pneumococcal polysaccharide vaccine & Meningococcal polysaccharide vaccine
- Conjugated vaccine -HIB vaccine (HIB-Haemophilus Influenza Type B)

4. Toxoid vaccine

- Diphtheria tetanus and Pertussis vaccine

5. Viral vector vaccine

- RVSV-ZEBOV (EBOLA)

6. Messenger RNA vaccine

- Covid-19 vaccine

Table 1: Vaccination chart

Vaccination schedule	Vaccine type	Protection
At birth	BCG, Hepatitis B (1st dose)	Tuberculosis, Hepatitis-B.
6 Weeks	DTP, IPV (1st dose), Hepatitis-B (2nddose), Hib (1stdose), Rotavirus (1stdose), PCV (1st dose).	Diphtheria, tetanus, pertussis, Hepatitis-B, Influenza, Polio, Rotavirus.
10 Weeks	DTP(2nddose), rotavirus(2nddose), IPV(2nddose), PCV(2nddose), HIB (2nd dose).	Diphtheria, Tetanus, Pertussis, Hepatitis-B, Influenza Polio, Rotavirus.
14 Weeks	DTP(3rddose), PCV (3rd dose), IPV(3rddose), Rotavirus (3rd dose).	Diphtheria, Tetanus, Pertussis, Polio.
6 Months	OPV(1stdose), Hepatitis-B(3rddose).	Polio, Hepatitis-B.
9 Months	MMR	Measles, Mumps, Rubella.

History

The first vaccines were developed in 18th century. Many other vaccines were also developed in 19thcentury. In 20th century vaccines were made based on immune markers. Because of Molecular biology, it is possible now to develop vaccines which were not possible earlier. Immunization is a proven intervention and one of the most cost-effective ways to ensure child survival. The first and foremost important vaccine i.e., smallpox was developed in 1798. The history of vaccines and immunization were the first attempt to prevent disease in society. Smallpox has a long history and is believed to commenced about 3,000 years ago in India or Egypt. A summary of the creation of human vaccinations diluted from live eliminated whole creatures purified polysaccharides or proteins.

18th century

- ✓ Smallpox(1798)

19th century

- ✓ Rabies (1885)
- ✓ Typhoid (1896)
- ✓ Cholera (1896)
- ✓ Plague (1897)

First half of the early 20th century

- ✓ Tuberculosis (1927)
- ✓ Tetanus toxoid (1926)
- ✓ Diphtheria toxoid (1923)
- ✓ Yellow fever (1935)
- ✓ Influenza (1936)
- ✓ Rickettsia (1938)

Middle of the 20th century

- ✓ Oral polio (1963)
- ✓ Polio (injected) (1955)
- ✓ Secreted proteins from anthrax (1970)
- ✓ Antigen for Hepatitis B surface the recombinant (1986)
- ✓ Measles (1963)
- ✓ Rabies (Cell Culture) (1980)
- ✓ Meningitis Polysaccharide (1974)
- ✓ Lyme OspA (1998)
- ✓ Japanese encephalitis (1992)
- ✓ Recombinant toxin B from cholera and Pneumococcus polysaccharide (1993)
- ✓ Rubella Encephalitis from ticks (1981)
- ✓ Type B Haemophilus influenzae Multisaccharide (1985)
- ✓ Hepatitis-A (1996)
- ✓ Type B conjugate of H. influenzae (1987)
- ✓ Varicella (1995)
- ✓ Group C meningococcal conjugate (1999)
- ✓ Acellular pertussis (1996)
- ✓ Reassortants of the rota virus (1999)
- ✓ Hepatitis-B (produced from plasma) (1981)
- ✓ Attenuated cholera (1994)
- ✓ Cold adapted influenza (1999)

Century 21

- ✓ Rotavirus (new and attenuated Reassortants) (2006)
- ✓ Japanese encephalitis (2009)
- ✓ Conjugates of pneumococci (heptavalent) (2000)
- ✓ Human papilloma virus Recombinant (quadrivalent) (2006)
- ✓ Zoster (2009)
- ✓ Cholera (WC only) (2009)
- ✓ Conjugates for meningococcus (Quadrivalent) (2005)
- ✓ Human papilloma virus recombinant (bivalent) (2009)
- ✓ Conjugates of pneumococci (13-valent) (2010)
- ✓ Proteins of the meningococcal group B (2013)

Jenner's use of an animal poxvirus to prevent smallpox was based on the premise that an agent that is virulent in animals may be less virulent in people. This concept was important in the evolution of Bacillus Calmette-Guérin. But is considerably more apparent in the choice of rotavirus strains from rhesus and bovine the development of human rotavirus vaccinations. Robert Koch (1843-1910) first identified the tubercle bacillus that causes tuberculosis in humans in 1882.The first BCG clinical experiment was a newborn infant from a family with a history of tuberculosis, and it happened in France as well in 1921. Hilary Koprowski and colleagues created rabies and oral polio vaccines by passing them through chicken embryos or mice. Enders, Weller, and Robbins shown that several viruses, including polio and measles, could be cultivated in cell culture, and this technology was eagerly adopted by vaccine manufacturers. Albert Sabin's oral polio vaccine, as well as measles, rubella, mumps, and varicella vaccinations, were all made feasible via cell-culture passage *in vitro*.

Reassortment has resulted in the development of three important vaccines: live and inactivated influenza vaccines, as well as one of two rotavirus vaccines. Rotavirus vaccines have also been created through reassortment. The first, created by Kapikian et al., consisted of one animal rotavirus and three Reassortants, each of which included 10 rotavirus RNA segments and one coding for the VP7 surface protein of human rotaviruses.

Salmon and Smith in the United States and the Pasteur Institute group in France created the first inactivated vaccines almost simultaneously. Wright and Semple in England and Pfeiffer and Kolle in Germany were the first to use inactivated typhoid vaccinations. Haffkine used inactivated plague bacilli to vaccinate humans against plague. In the 20th century, viruses were also subjected to chemical inactivation. The first inactivated viral vaccine to be successful was the influenza shot, and results from its Salk's successful use of the vaccine made it possible. Provost and colleagues created the hepatitis A vaccination using chemical inactivation as well. The meningococcal polysaccharide vaccine was created by Artenstein, Gottschlich, and colleagues and was the first vaccination to incorporate capsular polysaccharides. This vaccination protected military recruits from an epidemic and an endemic disease. Avery and Goebel had demonstrated the usefulness of polysaccharide protein conjugation in 1929. However, until Schneerson, Robbins, and associates made use of this insight, a conjugated type B H. influenza vaccine.

The creation of vaccines has been significantly impacted by the genetic engineering revolution that began at the turn of the 20th century. The history of vaccination campaigns reveals that in a heterogeneous society like India where health is a state responsibility, systematic scientific rigor is needed to improve coverage with all antigens. Throughout the world, vaccination technology advanced in the late 19th century. Typhoid conjugate vaccine Typebar-TCV, a fourth-generation typhoid vaccine, was introduced in India in August 2013.Beginning in December 2011, the Haemophilus influenzae type b (Hib) vaccine has been made available in the states of Kerala and Tamil Nadu. In 1957, the Pasteur Institute of India created the influenza vaccine and in 1970, it created the BPL inactivated rabies vaccine. The composition of future vaccines is expected to be more complex than it has been in the past, but the principles revealed by past achievements will still be crucial as vaccination is expanded to additional diseases and to all age groups (3-5).

Types of vaccines

Oral Polio Vaccine (OPV):

Polio virus causes polio (Poliomyelitis). Polio is an infectious disease which passes from person to person and can cause paralysis by infecting the central nervous system and motor neurons. Polio has no known treatment, but it can be avoided with a reliable immunization by administering a vaccine.

Dr. Albert Sabin first developed OPV. Generally, OPV administered to the children in the form of oral drops contains three strains of live weakened polio virus. Oral polio vaccines are the most important vaccine used to suppress polio. Ten cycles of freezing and

thawing did not result in any viral loss. The importance of maintaining a cold chain was underlined in order to distribute effective OPV in the field and ensure the success of the described immunization program in India.

If kept at -20^0 C or lower temperature, polio vaccine is known to maintain its efficacy for a lengthy period of time. One of the most thermolabile viruses is the Polio virus. Most economically developing countries lack suitable storage facilities for oral polio vaccination. The shelf life of oral polio vaccine is 6 months (6).

Hepatitis-B:
Hepatitis-B is caused by hepatitis D virus (HBV) that cause inflammation and damage to liver so Hepatitis-B vaccine is used to prevent Hepatitis-B infection. The first dose is recommended within 24 hours of birth with either two or three more doses given after that. It is also known as first anti-cancer vaccine because it prevents the leading cause of liver cancer. It is given by intramuscular route it can be spread from one person to another person by infected blood semen or other body fluids contact.

Vaccines are stored and handled at 2-8^{0}C. Storage of vaccines beyond the recommended temperature may reduce potency. It is one of the most heat stable children's vaccines, which maintains stability up to 4 years

Unpunctured vials can be stored for a total 12 hours prior to first use between 8-25^0 C. Based on temperature and number of vials the amount of time required to thaw vaccine differentiated temperature above 45^0 C can inactivate vaccines. These vaccines are never frozen because freezing can decrease effectiveness by forming aggregates and aluminium sedimentation (7).

Pneumococcal vaccine:
These are the vaccines which are administered to prevent the illness caused by streptococcus pneumonia bacteria. These vaccines protect from some types of bacterial infections like meningitis (infection to brain and spinal cord) and sepsis (a life-threatening reaction to and infection). Conjugated vaccines and polysaccharide vaccines are the two types of pneumococcal vaccine. Polysaccharide vaccine administered intramuscularly or subcutaneously. Conjugated vaccines given intramuscular but preferred site for conjugated vaccine in infants and young children if vastus lateral muscle in anterolateral thigh.

Based on age and medical status different vaccines are recommended usually 4 doses of pneumococcal vaccine are administered to infants at age 2, 4, 6, 12 to 15 months respectively. These vaccines are stored between 2-8^{0}C. Freezing of vaccine or exposing to freezing temperature results in stability of vaccine. Time out of refrigeration should not exceed 96 hours.(8)

rVSV-ZEBOV:
Ebola is caused by different strains of Ebola viruses which belongs to the family filoviridae genus. Ebola viruses, that are found initially in sub-Saharan Africa. The Zaire Kik wit 1995 Ebola virus (ZEBOV) glycoprotein (ZEBOV-GP) gene was substituted for the rVSV-ZEBOV, a live attenuated recombinant virus. As a result, the virus develops a VSV backbone with ZEBOV-GP covering its surface. In west Africa clinical trials of the live attenuated vesicular stomatitis virus vectored Ebola vaccine rVSV-ZEBOV is undertaking presently.

At -70^0 C or less, this vaccine can be preserved. For 24 hours at 25^0 C and for 1 week at 4^0 C, it is reliable. Since damage from unintentional heating or freezing can result in efficacy loss for certain vaccine routinely employed in national immunization programs, maintaining the cold chain of vaccine delivery is crucial. As the temperature (i.e., >25^{0}C) increases the stability of the vaccine decreases. The rVSV-ZEBOV vaccine is stable after thawing, opening and keeping the vaccine vial in a refrigerator for at least a week (9).

MMR (measles, mumps, rubella):
The causative organism of measles is single stranded enveloped RNA virus with one serotype belongs to the genus morbilli virus. Measles is an acute disease which is convoluted by the middle ear infection or bronchopneumonia. Mumps is a condition brought on by a virus that carries the rubella virus gene. Mumps is critical condition which majorly seen in children and young adults. By this infection glandular and nerve tissue are damaged. Rubella is caused by the rubella (roo-BELL-uh) virus which mainly affects the foetus. Rubella is a moderate mild febrile illness with a skin rash, accompanied by certain symptoms, and is very common in children.

According to WHO, Measles is the most sensitive vaccine to environmental conditions like temperature. At temperatures between -70^0 C and -20^0 C, the MMR vaccine is perfectly stable. At 20 to 25^0 C, restored vaccine loses 50% of its potency in an hour, while at 37^0 C, it loses practically all of its potency in an hour. Rubella monovalent freeze-dried vaccine and the

bivalent rubella component, low rates of vaccine degradation have been seen with the trivalent MMR vaccines or the measles-mumps-rubella vaccine (10).

BCG (Bacillus Calmette-Guerin):
A live attenuated vaccine called BCG is used to prevent primary tuberculosis which is caused by bacteria caused by mycobacterium tuberculosis these bacteria generally infect the lungs but it can also infect other parts of the body like kidney, spine and brain. It is a life attenuated vaccine which is administered as an intradermal injection usually on the upper left arm which leaves a small scar.

BCG vaccine stability viability decreases by 43% when kept at room temperature (30 to 33.5^0C). However, it doesn't lose potency when kept in the refrigerator. Vaccines in the form of Powder can be frozen for long term, but the vaccine which is diluted and reconstituted should not be frozen. BCG vaccine can be harmed by freezing and thawing. Proper cold chain treatment is important to maintain the stability of the vaccine (11).

HIB (Haemophilus influenzae type B):
Haemophilus influenzae type B virus causes mild illness, such as an ear infection/bronchitis, pneumonia, meningitis, infection of bloodstream. It mainly affects the children usually who are under 5 years of age but it can also affect adults with certain medical condition persons. Generally, it is administered through an intramuscular route. In 3 doses, 1st dose at 2 months of age, 2^{nd} dose between 6-12 months and 3rd dose between 12-15 months. HIB is a conjugated vaccine.

HIB vaccines are stored by refrigerating the vaccine between 2-8^0 C. Vaccines which are frozen or exposed to freezing temperature can lose their efficacy and potency by forming aggregates (12).

DTP (Diphtheria, tetanus and pertussis):
DTP is a severe infection caused by the 3 bacterial strains called Corynebacterium diphtheriae, Bordetella pertussis, clostridium tetani. Diphtheriae bacterial strain infect the mucous membrane of the nose and throat. Pertussis is most commonly known as whooping cough, which is a highly contagious respiratory disease. Clostridium tetani bacterial strain live in soil, saliva, dust and manure in the form of spores, when they enter the body through a deep cut burn or wounds, they mainly affect the nervous system which causes serious illness.

DTP is a combination vaccine. These combination vaccines are created to cure and prevent the occurrence of multiple diseases. Individual vaccines such as diphtheria, tetanus, pertussis was combined and developed into a single product called DTP.

Complex interactions of various components present in the vaccine create stability problems. Among the 3 components the diphtheria and tetanus components remain unchanged in terms of stability but the pertussis components lose its potency during prolonged storage of vaccines. These vaccines are stored between 2^0 C and 8^0 C. When these vaccines are exposed to inappropriate conditions it causes instability. Freezing of vaccine or exposing the vaccine to freezing temperature decreases the stability of vaccine thus resulting loss of potency of vaccine (13).

COVID-19:
The severe acute respiratory syndrome corona virus 2 (SARS-COV 2) is the virus which is associated with the outbreak initiated in Wuhan, China. Officially, the illness promoted by the virus is known as covid 19. It is an RNA virus which belongs to family coronaviridae. World-wide 7 types of corona virus have been discovered, one of those which affected the world during 2020. SARS-COV 2 virus affects lower respiratory tracts of humans which results in inflammatory pneumonia. It is mainly transmitted through the respiratory droplets of the infected person when they come contact with healthy individuals.

Different types of vaccines are developed in order to prevent and treat the covid 19 in span of 2-3 years to overcome the emergency situation arise in the world. In India two types of vaccines were developed and started administration of 2 types of vaccines called Covaxin and Covishield.

Covaxin:
Bharat biotech developed the Covaxin, India's first indigenous covid vaccine which contains RNA encapsulated in a protein capsid. It is available in multi dose vials which are stable at 2-6^0C temperature range. Covaxin does not require sub-zero storage or reconstitution because stability can be achieved by ordinary refrigeration.

Covishield:
Covishield is developed by oxford-AstraZeneca and manufactured by serum institute of India. It has 90% effectiveness in treating the Covid-19. It is an adenovirus vector-based vaccine. The efficacy of Covishield may be decreased, if the structure of spike(s) protein changes in the future. The storage temperature of vaccine is 2-8^0C with shelf life of 9

months. It is often administered intramuscularly [14,15].

CONCLUSION:

The world's most secure means of protecting children from deadly diseases is vaccination i.e., vaccine. Among the most significant developments in global health and development are vaccines. Different types of vaccines can generate particularly potent immunological reactions in the body, because they employ a particular portion of the germ. Since many biological preparations are unstable when stored the safety and effectiveness of the biological therapeutic product may be decreased. Because vaccinations are temperature sensitive, all vaccines now need to be kept in a cold chain. Innovative methods to address current issues in vaccine development include viral like particles and nano particle vaccines, DNA/RNA vaccines and rational vaccine design.

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