REVIEW ARTICLE

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Cryogenic Storage and Transportation of Vaccines

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Abstract

Vaccines are mankind's most powerful weapons against any kind of communicable disease caused by viruses, bacteria, etc. The vaccines are involved in the boosting of the immune system against particular microorganisms. The major problems for the vaccines are temperature maintenance and transportation. The rise in temperature can deteriorate the vaccine and cause it to lose its activity. During the transport of such vaccines, which are highly degradable due to slight temperature changes, extreme caution is exercised. Vaccine stabilization methods are designed to minimize potency loss during manufacture, storage, distribution, and clinical usage. This problem can be solved by using cryogenics, which is an emerging technology used in various fields to store food preparations, biological cell cultures, transportation of vaccines, aerospace sectors, and agriculture areas. In cryogenics, the temperatures are kept very low by using cryogens like oxygen, nitrogen, helium and hydrogen. In general, vaccines like COVID are going to be stored at the possible lowest temperatures like 2-8°C, where as the Ebola vaccine is –60°C to –80°C. The employment of cryogenics can even achieve the temperature –273°C i.e., the absolute zero.

Keywords: Cryogens; Vaccines; Sensitivity; Storage; Transport; Cold chain supply.

INTRODUCTION

The word cryogenics was derived from the two Greek words "kryos" and "genic", meaning frost production. Cryogenics was started in the year 1845 by Michael Faraday, who succeeded in the liquefication of the gas by using ether and dry ice. Another stepping stone in the cryogenics development was laid down in 1883 by obtaining temperatures of –183°C to –196°C by using oxygen and nitrogen. James Dewar succeeded in liquefying H_2, thus reaching the lowest temperature of –259°C. Liquid N_2, O_2, He, Kr, CH_4, CO_2 are termed cryogens[1]. Cryogenics has many established applications in space science, automobiles, metallurgical, industrial, and pharmaceutical sectors. Other applications of cryogenics include fast freezing of foods and preservation of biological materials[2] such as livestock semen, human blood, tissue and embryos, and grinding of foods. Cooling of the superconducting magnets is used in magnetic resonance imaging (MRI) and nuclear magnetic resonance (NMR) machines, mass spectrometers, and the beam steering magnets used in particle accelerators and magnetic separation in pigment industries[3]. Most of the vaccines are thermo

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labile, i.e., their nature is altered with a change in temperature. Extensive care should be taken during the transportation of the vaccine vials until they are administered so that the vaccine's potency doesn't diminish. Thus, in order to ensure the biological stability and shelf life of these vaccines during their storage and transportation, they are frozen at very low temperatures[4]. Cryogenic systems have been successfully used since the early 1900s for storing and transporting oxygen, blood, food, vaccines, and so on. Cryogenic systems play a vital role in the storage and transportation of vaccines worldwide. Vaccines are composed of antigens, preservatives, adjuvant, buffers, stabilizers, antibiotics, and other chemicals. Due to this chemical composition, the vaccine's stability depends on the temperature. Deviations from the vaccine's ambient temperature leads to an irreversible loss of its optimal potency and stability. The administration of the denatured vaccine creates an insufficient immune response in the body and sometimes leads to severe health complications.[5]

History of Vaccines and it's Transport[6]

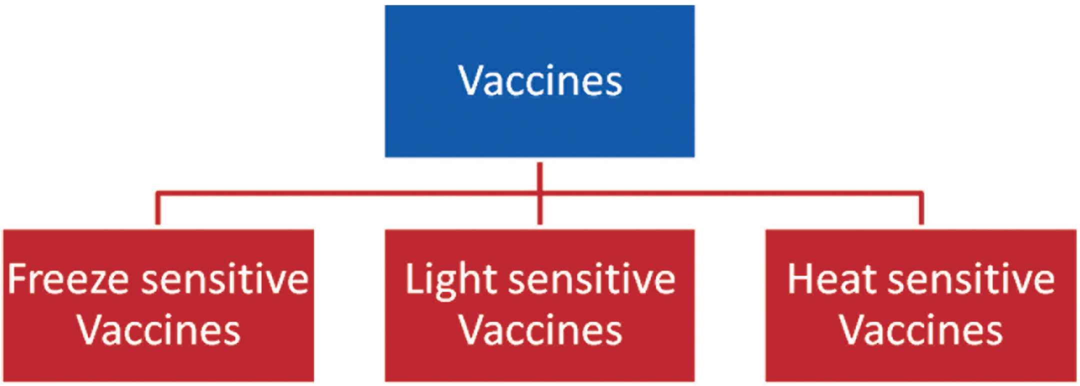
Most of the vaccines are heat sensitive and some are freezing sensitive. A few are light sensitive. Previously, cool kits were used to transport the vaccines to different regions. Nowadays, the transport is done by using cold chain transport. A cold chain is a temperature controlled supply chain that includes all vaccine related equipment and procedures. The cold chain begins with the cold storage unit at the manufacturing plant, extends to the transport and delivery of the vaccine and correct storage at the provider facility, and ends with the administration of the vaccine to the patient.

Vaccine manufacture in India came into light in the early 19th century with the preparation of small pox vaccination. In the late 19th century, subsequent improvisations of the vaccine took place. With the outbreak of diseases such as cholera, plague, influenza, and typhoid at the turn of the twentieth century, the government of India began to impose special vaccination efforts.

With the improvement of the health system, trained vaccinators, cold chain equipment, and system eradication of small pox, the eradication of small pox was successful in 1977. This led to the launch of a National Immunization Programme in India called the Expanded Programme of Immunization (EPI) in 1978.[7]

The launch of the Universal Immunization Programme (UIP) on November 19, 1985 has led to the establishment of a reliable cold chain system and has improved the manufacture of cold chain equipment. The responsibility for the maintenance of the cold chain was regulated by UNICEF and commercial agencies till March 1991, when it was taken up by the States and Union territories.[8]

Types of Vaccines and their storage:[9]



Freeze Sensitive vaccines

Vaccines for Hepatitis A and B, meningitis, and typhoid are susceptible to freezing temperatures. Freeze sensitive vaccines should not be exposed to sub zero temperatures. These vaccines are kept at temperatures ranging from +2 to +8 degrees Celsius above zero degrees Celsius. The preservation of these vaccines is made easier in tropical countries by the use of freezers, whereas it is more difficult in cold countries due to sub-zero temperatures. To avoid deterioration, heaters are maintained to raise the temperature levels.

Light sensitive vaccines

The vaccines like BCG, Tubersol and others are sensitive to sunlight, ultraviolet light or fluorescent light. These kinds of vaccines are stored in amber ampoules to prevent light exposure. These vaccines are kept in cryogenics for transport and to ensure vaccine efficacy.

Heat sensitive vaccines

The heat-sensitive vaccines are very liable to heat due to their protein-based subunit. Even a very minute heat exposure can deteriorate the vaccine efficacy. This kind of problem occurs in current countries. Vaccines like polio are quite heat sensitive and shouldn't be exposed to more than +8 °C. These kinds of vaccines are maintained by using freezers and cryogenic chambers.

Steps Maintained in the Cryogenic Transportation and Storage of Vaccines[10]

1. **Sample comprehension:** Prior to vaccine transport and storage, we must understand the type of vaccine and its specifications for deterioration, tolerance temperature, and target storage temperature.
2. **Protocol and valid cold chain assets**: Based on the information, a validated protocol is verified with various preliminary tests done on the vaccines by exposing them to the temperature changes along with the asset. Various measures were analysed, like temperature uniformity, temperature measurement, and fluctuations, and they had been examined along with the chamber they were placed in.
3. **Temperature Maintenance**: This is the crucial step in the storage of the vaccines. Very effective temperature regulation systems have been used to detect even the minute changes in the temperatures during the storage. This system is involved in the passage of the coolant into the cryogenic chamber to maintain the temperature.
4. **Securing the cold chain:** a proper appropriate manufacturer is dependable for the storage of vaccines with proper scientific evidence, and products can be safely stored and efficiently transported at the conditions required to ensure stability, pharmaceutical activity, and efficacy are maintained along the way.

Cryogenic transportation Components[11]

The components of the cryogenic containers help to maintain the required temperature to protect the vaccines from deterioration. The components include the insulating containers, cryogens, and temperature monitoring devices. Temperature, vibrations, and shock can alter the quaternary structure of the molecules composing the vaccine. To ensure the prevention of such hazards and to maintain the efficacy of the vaccine, cryogenic transportation is carried out. The outermost vessel containers are made of carbon steel and the innermost vessel is made of stainless steel, which can withstand very low temperatures. These two vessels are insulated with different insulating materials to bind them together. Currently, the insulating containers being used are thermal shippers, Ult freezers, Arktek, Vaccine Freezers, Vaccine Refrigerators, Cold Boxes, and high density vaccine containers. These containers ranged from very large tanks to very small ones, depending on their usage.

Cryogens or coolants or PCMs (Phase Changing Materials): These are the crucial components for the maintenance of very low temperatures ranging from 0 to –195°C, which protects the vaccines. Other than dry ice, coolants like Pulse E-75, Plusice E-65, hydrogen, helium, nitrogen, etc., are widely used.

Temperature monitoring devices: These are used to maintain and manage the temperature along with the flow of the coolants present in it. Devices like vaccine vial monitors,integrated digital thermometers,stem thermometers, cold chain monitor cards (for international vaccine shipments), electronic shipping indicators (for international vaccine shipments)are used for this purpose.

Equipments for the cold chain transport[12,14]

Based on their way of maintaining the low temperatures, the equipment used for cold chain transport are grouped as:

(1) Active equipment

(2) Passive equipment

1. **Active Equipment:** These are the equipment used in the manufacturing, storage and preservation purpose. These are fixed and utilized by the research labs, manufacturing units, storage materials etc. The examples or this kind are Ult freezers, cryogenic chambers, refrigerators. They require electric supply

for freezing process i.e, active freezing takes place. Stirling ultra low temperature freezer that consumes less energy compared to other freezers shown in the fig. 1.

1. **Passive equipment:** Mostly used in last mile transport and uses dry ice and PCMs for freezing. Eg. Cold boxes, vaccine carriers. High density vaccine container has long cold life than the regular vaccine carriers.

Transportation of Vaccine[13]

The transportation of vaccines take place from the manufacturing industry to the central storage unit in thermal shippers (–90°C to –60°C) by means of Pharma Cargo or by means of other vehicles. The thermal shippers use dry ice and they are labeled as 'UN1845'. These should be shifted to the central storage unit within stipulated time of environmental contact. The central storage unit maintains the vaccine at -80°C to-60°C using Ult freezers that works using electricity. From the central storage vaccine sare transported to subnational stores or service points by means of vaccine carriers, arktek or cold boxes that uses coolant packs. They maintain a temperature range from +2°C to +8°C.

According to the vaccine's condition it is stored and transported at different temperatures up to a certain in time.

Originating temperature environment	Maximum time at room temperature (up 25°C) during storage or transfer		Time required to stay in frozen environment after room exposure during transfer
	Unopened vial cartons	Opened vial cartons	
From ULT freezer (–80°C to –60°C)	Upto 5 minutes	Upto 3 minutes	At least 2 hours before they can be removed again
From thermal shipping container (–90°C to –60°C)	Upto 5 minutes	Upto 3 minutes	At least 2 hours before they can be removed again
From freezer (–25°C to –15°C)	Upto 3 minutes	Upto 1 minutes	Removed from freezer and move to +2-8°C within 2 weeks.

CONCLUSION

A new era is being heralded in by cryogenics, not just in the transportation of vaccines but also in the study, preservation, and production of food products. The majority of vaccinations are delivered by cold chain delivery using the right methods. To stop degradation, the majority of vaccinations are kept in storage between 2°C to 8°C. With the most recent breakthroughs of the deterioration of vaccines due to temperature variation, there are more firms producing cryogenic chambers and containers. Since then, the significance of these cryogenics has significantly increased. As the vaccines travel across the nations, they are exposed to various climatic conditions With the use of cryogenic technology, this can be avoided. India has also shows its interest on the supply of cryogenic refrigerators to keep the vaccines viable.

REFERENCES

1. "Cryogenics" The Gale Encyclopedia of Science. Encyclopedia.com. 16. 2022 https://www.encyclopedia.com.
2. Goswami TK. Role of cryogenics in food processing and preservation. International Journal of Food Engineering. 2010, 13;6(1).
3. Rehman W, Farhan M, Rehman F. A Review of Cryogenics Applications for Power and Energy. InASME Power Conference 2020, (Vol. 83747, p. V001T10A016). American Society of Mechanical Engineers.
4. Anifandis G, Taylor TH, Messini CI, Chatzimeletiou K, Daponte A, Ioannou D, Tempest HG. The Impact of SARS-CoV-2 on Sperm Cryostorage, Theoretical or Real Risk?. Medicina. 2021, 8;57(9):946.
5. Jha AR. Cryogenic technology and applications. Elsevier; 2011, 1.
6. Lahariya C. A brief history of vaccines & vaccination in India. The Indian journal of medical research. 2014,139(4):491.
7. Sokhey J, Kim-Farley RJ, Bhargava I. The expanded programme on immunization: a decade of progress in India. Annals of tropical paediatrics. 1989, 9(1):24-9.
8. Arora S. National Immunization Schedule India: A Review. Res Rev J Immunol. 2017,7(3):6-10.
9. World Health Organization. Temperature sensitivity of vaccines. World Health Organization; 2006.
10. World Health Organization. Operational guidance on establishing an ultra-cold chain system in support of the Pfizer-Bio NTech COVID-19 vaccine rollout, 1 February 2022. World Health Organization; 2022.
11. Storage CV, Toolkit H. Atlanta: US Department of Health and human Services. Center for Disease Control and Prevention. 2014.
12. 12. Matthias DM, Robertson J, Garrison MM, Newland S, Nelson C. Freezing temperatures in the vaccine cold chain: a systematic literature review. Vaccine. 2007 May 16;25(20):3980-6.
13. 13. Bown CP, Bollyky TJ. How COVID–19 vaccine supply chains emerged in the midst of a pandemic. The World Economy. 2022 Feb;45(2):468.
14. Lin Q, Zhao Q, Lev B. Cold chain transportation decision in the vaccine supply chain. European Journal of Operational Research. 2020 May 16;283(1):182-95.