

# Challenges Of Storage And Transport Of Covid-19 Vaccines - A Review

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## Abstract

A vaccine is a material administered to an individual to boost their immune system's resistance against infection. Diseases that can be prevented by vaccination can be controlled and eradicated with proper vaccine handling and storage. It is crucial to formulate and deliver stable, effective and safe vaccines. Since vaccines are intricate biological products so any kind of temperature fluctuation can result in reduction of their effectiveness. To prevent this, cold storage facility is set up; refrigerators, thermometers and storage protocols are in place. The main vaccines distributed for COVID in India are Covishield and Covaxin. In order to maintain a cold chain supply for these vaccines, they must be transported and stored at a regulated temperature in accordance with the manufacturer's guidelines. The end-to-end supply chain for COVID-19 vaccines must adhere to specific cold chain standards from manufacturing to distribution in warehouses and healthcare facilities. Audits for cold chains and temperature monitoring should be performed regularly on the vaccine lots to ensure proper distribution practices are adhered. The present study focuses on the good distribution practice and storage of vaccines.

**Keywords:** Vaccine, COVID-19, Good Distribution Practice, Storage, Cold Chain, Transport, Temperature.

## INTRODUCTION

A vaccine is a substance created from the causative organism of the disease that is used to promote the production of antibodies and provide immunization against diseases. Vaccines are temperature sensitive biological agents. Hence, they require proper storage and transport under a temperature-controlled environment. Pharmaceutical retail chains of today have a large number of participants who move the product from the maker to the patient. All stakeholders must adhere to the Good Distribution Practice (GDP) principle to guarantee that the quality is upheld during distribution. The majority of GDP processes are conducted at arm's length, away from the manufacturer's direct management along with the participation of various companies with varying levels of ability, expertise and size <sup>[1]</sup>. Storage and distribution may involve the intricate flow of goods across international borders, variations in documentation and handling specifications, and communication among numerous supply chain participants <sup>[5]</sup>. Every time vaccinations are exposed to temperatures outside of the optimal range, they risk losing their potency or perhaps becoming ruined as biological products <sup>[11]</sup>.

An acceptable cold chain configuration, adherence to standards, and effective logistic management are essential in order to maintain vaccines completely preserved from the manufacturing site to patient use. It is essential that the vaccinations are stored and transported at the proper temperatures to maintain their potency. In order to do this, cold storage facilities use freezers and refrigerators, while cold trucks and cold boxes are used for transportation <sup>[12]</sup>. The process used to ensure that vaccinations are handled, stored, and transported under optimal conditions, starting with the vaccine manufacturer and continuing until administration, is referred to as the "cold chain" <sup>[30]</sup>. By employing appropriate packaging materials, temperature changes during shipment must

be minimised. Vaccines are transported and supplied through refrigerated vehicles. Utilizing approved modes of transportation allows for the monitoring of storage and transit conditions.

The Good Distribution Practice (GDP) is a compilation of defined, regular working procedures that ensure the quality, safety, and efficacy of pharmaceutical goods are sustained during their entire journey through the pharmaceutical supply chain [3]. In accordance with the WHO Guidelines for Good Distribution Practices for Pharmaceutical Products, this area of quality assurance is responsible for monitoring and ensuring the quality of pharmaceuticals during logistical issues using appropriate controls [7]. The most widely used techniques to govern their activities are good manufacturing practice (GMP) and good distribution practice (GDP) [2]. Supply chain managers can handle the distribution of pharmaceuticals more successfully if they are aware of the quality risk connected with the product. The principles of Good Storage Practices (GSP) and Good Distribution Practices (GDP) ought to be incorporated into national rules and laws for the storage and shipment of medical supplies in a nation or region, as needed, as a way to establish minimal requirements [4].

### Good Distribution Practices:

Medication and medical equipment should be preserved in a precise manner and under particular conditions prior to being utilized or made available for sale, as well as during the time they are being transported from the manufacturer to the end user. This is known as good distribution practise (GDP), which is a quality system. All parties involved in the distribution of pharmaceutical products, from the maker's site to the agency responsible for discharging or providing the product to the patient or their agent, have a duty to ensure that the consistency of those products' quality and the dependability of the chain of distribution are maintained at all times. To set minimal requirements, national laws and policies regulating the supply of pharmaceuticals in a country or region should, if appropriate, incorporate the notions of GDP. GDP guidelines should be followed while dealing with goods that have been donated. Due diligence should be used by all stakeholders involved in the distribution process while conforming to the GDP principles, such as transparency and credible threat detection systems. To maintain the quality of distribution chain, every component of the GDP system is crucial [10].

### Good Storage Practices:

For a pharmacist, one of their most crucial duties is drug storage. Therefore, appropriate strategies must be created and put into practice to warrant that these obligations are satisfied. The medications must be safeguarded to reduce the likelihood of deterioration and contamination. Throughout the term of storage and usage, the stability of the product remains within the prescribed range [6]. Good Storage Practice is a component of quality control that makes sure pharmaceutical items are stored with adequate control to retain their quality [4]. Corporations and humanitarian sectors have acknowledged Good Pharmaceutical Storage and distribution methods as essential business operations enhancing comparative benefit in healthcare settings [8]. A crucial function is played by the storage in order to assure that the potency of medicinal products is maintained, avoid degradation, spoiling, and degeneration, and maintain its durability. Stockpiling is a key factor in maintaining the quality and safety of products throughout their lifespan. Good Distribution and Storage Practices ensure that the items are certified in accordance with the relevant laws [5].

### Good Transportation Practices:

The examination of excellent practices for transporting pharmaceuticals brings to light the necessity of creating a systematic strategy through good transportation practices (GTP). The World Health Organization (WHO) published a technical paper that outlines best storage practices for holding pharmaceutical items and materials until they are used. This guidance document's goal is to outline the extraordinary steps deemed necessary for the handling and transportation of medications. The pharmaceutical sector lacks standardised regulatory advice specifically for GTP. The GTP can be used to emphasise the benefit of preserving pharmaceutical quality during distribution operations [9]. The quality of pharmaceutical items is also at danger from the possibility of freezing or warming as a result of temperature swings during transit and their effects on the products [13]. Given the specific storage needs, the GTP provision should be able to guarantee that the pharmaceutical product range is split into market categories based on product features and sensitivity criteria [2].

## VACCINE STORAGE

Every time vaccinations are subjected to temperatures beyond their optimal range (2°C to 8°C), they risk losing their usefulness or perhaps becoming wrecked as biological products. The ideal temperature for frozen vaccines is -15°C. Additionally some vaccines need to be shielded from light. The loss of efficacy, which cannot be halted, may accelerate when items are stored beyond the acceptable temperature range, both during shipment and storage [30]. An adequate cold chain setup, adherence to regulations, and effective operational planning is needed to keep vaccines completely conserved from the manufacturing unit to patient use [12].

As stated in the Guidelines for Good Distribution Practice of Medicinal Products for Human Use, it must be made sure "that temperature conditions are kept within acceptable ranges during transport." The use of refrigerators and thermometers, temperature monitoring, storage protocols, and responsibility distribution are only a few of the structural and operational requirements for adhering to best practices for keeping vaccines at prescribed temperatures [15]. In studies examining vaccine storage techniques, checklists are frequently used as a self-administered tool or by 3rd parties conducting visual inspections along with surveys [16-25]. As a result of their reduced bias, these checklists are now accepted practices in quality management [26]. Every single cold storage facility for vaccines needs to have standby equipment and 100 percent spare refrigeration capacity. The first preliminary and basic steps for vaccine stockpiles are set by the World Health Organization (WHO) [27]. A refrigerant, R-134A fluid is utilised in chilly rooms at +4°C. However, 20°C cold rooms are not the right setting for it. An alternate refrigerant that can be used for this is R-404A. The R-134A refrigerant is used in cooling system for the cold storage of the AstraZeneca-Oxford Covishield, CoronaVac, and Janssen COVID-19 vaccines [28].

## VACCINE SUPPLY CHAIN FOR COLD STORAGE

For vaccine supplies to be viable for immunisation programmes, temperature control in vaccine storage facilities and supply systems is a crucial concern [58-60]. The term "cold chain" describes the procedure used handling, storage and transport of vaccines in ideal circumstances beginning with the vaccine maker and continuing until administration [32].

The cold chain starts with the cold storage unit at the manufacturing site, continues through distribution and transportation of the vaccine, includes proper storage at the facility of the provider, and ends with the administration of the vaccine to the patient. Cold chain requires building extensive infrastructure and is very expensive to maintain. The complexity of the cold chain is illustrated in documents, such as the CDC Vaccine Storage and Handling Toolkit [60]. Utilizing the cold storage approach is essential since vaccinations must generally be stored in a cool environment. The choice of cold storage is crucial since vaccination properties and efficacy are extremely sensitive to temperature variations [40]. Focus should be on providing cold chain management for temperature-sensitive pharmaceuticals during the pharmaceutical goods' storage and distribution to ensure that the quality and virtue of the yield will not be jeopardised [33].

In conjunction with the cold chain maintenance standard process, which should be observed continuously, the supply chain cycle should be given rigorous temperature and humidity monitoring throughout its stages [13]. Improper transit storage that exposes vaccinations to temperatures beyond the approved ranges can reduce their effectiveness [14]. In order to keep the vaccine's properties intact, refrigeration for the cold chain is essential. The current cold storage method uses a lot of energy and has a lot of moving elements that cause friction. The greater environmental concern comes from the gases used in conventional refrigeration, which have a high potential to cause global warming. The expansion of cold storage facilities results in increased energy use and environmental pollution due to the use of hazardous refrigerants [30]. Achieving control or eradication of illnesses like polio and measles has been hampered by supply chain concerns.

Following are some suggestions to assist decision-makers in comprehending and addressing vaccination supply chains [55]: - The obligation to raise awareness of supply chain issues. To boost dialogue between supply chain specialists and decision-makers in the vaccine industry. To create computer simulation models of supply chains at the international and national levels to act as virtual testing grounds for various policies, interventions, and technological advancements. To create a need for financing, new policy changes, the release of new vaccines,

etc. connected to vaccinations, the supply chain's mapping and modelling. To help with the design and development of new technology, create target product profiles (TPPs) using supply chain models and other analysis. To create a record of vaccination choices and how supply chain concerns and modifications influenced these choices. To make and distribute a manual on how to handle and improve a country's supply chain when making vaccine judgments [29].

## REFRIGERATED TRANSPORT AND DISTRIBUTION

Extreme temperatures, especially when storing and transporting vaccines, can cause biological components to lose their efficacy swiftly [30]. When ensuring the appropriate storage conditions for pharmaceuticals during transport, it is crucial to adhere closely to the manufacturer's instructions. The route should also be picked according to the degree of risk associated in order to complete the required temperature controls at the proper location. Products that must be transported between 2–8 °C consistently undergo temperature-monitored transit since the GDP guideline came into force in 2013 [7].

Strengthening GDP standards is crucial before ensuring product efficacy, security, and excellence, especially for controlling the cold chain of items up to consumers (polyclinic and the private ownership) [31]. A vaccine supply chain's cold chain capacity requirement, in particular, call for training for the store staff on good storage practices.

Both established and developing nations' cold chains, including India, are affected by the ubiquitous issue of freezing during transportation [32, 33]. The primary factor in transportation-related freezing is a lack of properly conditioned ice packs [34, 35]. The cold storage and refrigerated shipping of the Covid-19 vaccine in India is the main obstacle in its dissemination [36]. To maintain the range allowed by the manufacturer's criteria, vaccinations are kept in a buffer. It is not advised to keep vaccinations or thermometer probes in cabinets on the floor, adjacent to walls, indoors, or beside the outlet of cold air from the freezer since the temperatures inside the storage facility and the temperature of the vaccination are likely to differ significantly from each other [57]. Consequently, the thermometer probe must be inserted into a vial of glycol or another thermal buffer substance that is equivalent in size. To obtain a refrigerator management quality signal, the components mentioned in and according to the SOPs must be successfully accomplished [41-46].

In a study using VAERS [52] data, the ideal vaccination package configuration to use in a refrigerated transit from pharmaceutical distributors to multiple healthcare clinics, hospitals, and pharmacies were recognized. According to the study's findings, the quantity of coolant packs, how they are arranged atop, and the dimensions of the storage container all significantly affect how much cold is kept, how hot it stays during storage, and how long it stays that way. The temperature within the vials shouldn't fall below 2°C, therefore adding another layer of plastic wrap can be helpful [53].

Utilizing packing materials appropriate for the contents, such as disposable insulated containers and pre-cooled packaging materials, may help limit temperature anomalies during shipment [54]. The safest technique is to deliver vaccines straight to the medical institutions with cold storage that is ready to use [42-49]. However, using a mobile refrigerator with a temperature tracking system to convey the vaccine is advised.

## COVID-19 VACCINES SUPPLIED IN INDIA

The first case of COVID-19, an infectious disease brought on by a new coronavirus strain (SARS-CoV-2), was discovered in Wuhan, China, in December 2019. Pharmaceutical companies' main priorities are to offer enough COVID-19 vaccines to meet demand, as well as to show that their vaccine have acceptable safety profiles and produce positive immune responses in all special interest groups [60]. The Government of India started what is widely acknowledged to be the largest vaccination campaign across the nation, mostly relying on two vaccines developed by Indian vaccine manufacturers [61]. On January 16, 2021, India's government began offering free COVID-19 vaccinations, and as part of what is anticipated to be the world's largest immunisation campaign, they are asked all of their residents to get vaccinated. India was the site of the development of 4 of the 8 COVID-19 vaccines that were being tested in different phases of clinical trials. India has the capacity to produce and supply 3 billion doses of COVID-19 vaccine yearly, accounting for nearly 60% of the world's total vaccine production

<sup>[38]</sup>. Bharat Biotech has created India's first indigenous COVID-19 vaccine (Covaxin). Together with the Indian Council of Medical Research, the National Institute of Virology developed this inactivated vaccine (BBV152).

The Serum Institute of India's Covishield, Zydus Cadila's ZyCoV-D, and Dr. Reddy's Lab's Sputnik V are further prominent COVID-19 vaccine contenders <sup>[39]</sup>. The Oxford-AstraZeneca vaccine known as Covishield and the indigenous Covaxin vaccine made by Bharat Biotech have both been given approval for limited emergency usage by India's medicines authority.

The Indian government moved swiftly to boost the nation's capacity for vaccine production and has developed a sophisticated digital system to manage and analyse every facet of vaccine administration <sup>[36]</sup>. They have appointed the National Expert Group on Vaccine Administration (NEGVAC) for COVID-19 to offer guidance on every aspect of the COVID-19 vaccine's administration in India. Technological attributes have also been crucial in helping to keep communities safe and informed, provide medical professionals with creative ways to carry out their tasks and give the government agencies real-time data on the impact that the virus has caused <sup>[62]</sup>. India has succeeded in expanding its medical manufacturing operations to a global scale and claiming the label of global pharmacy <sup>[37]</sup>.

### Covishield:

It is produced by the Serum Institute of India using the same viral vector-based technology that is employed in the production of the Ebola vaccine and utilises the same Astra Zeneca vaccine's patent-based technology. L-histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80, ethanol, sucrose, sodium chloride, and disodium edetate dihydrate are all ingredients in Covishield. It also contains an inactivated adenovirus with portions of the corona virus. The second dose of Covishield must be delivered 4-6 weeks following the first dose, as per the Drug Controller General (India) approval provided for the drug.

**Covaxin:**The same business that produces hepatitis-A, tetanus and flu vaccines, Bharat Biotech Limited, is the manufacturer of this whole-Virion attenuated corona virus vaccine. In addition to other chemicals, Covaxin also contains inactivated Corona Virus, Aluminium Hydroxide Gel, TLR 7/8 agonist, 2-Phenoxyethanol, and Phosphate Buffered Saline. Two doses of Covaxin are to be given at intervals of day 0 and day 28, respectively. Prior to any Phase III data, Covaxin was authorised for use in emergencies back in January. The results have been released, and Bharat Biotech has disclosed interim Phase III data for its Covid-19 injection, demonstrating that it is 78 percent effective in preventing mild, moderate, and severe coronavirus infections and is effective against the majority of variations. There are some negative effects associated with Covaxin, however they are generally of mild to moderate type. There haven't been any other major adverse reactions to vaccinations documented. (Table 1).

**Table 1:** Vaccines and its preservation parameters

S. No.	Name of the vaccine	Vaccine Type	Manufacturer/Developer	Country	Storage Conditions
1.	<b>Novavax</b>	Protein Subunit	Novavax, Inc	Australia	2° to 8°C
2.	<b>Medicago</b>	Plant based virus-like particle	Medicago, Inc	Canada	2° to 8°C
3.	<b>Convidecia</b>	Non-Replicating Viral Vector	CanSino BIO	China	2° to 8°C
4.	<b>Sputnik Light</b>	Vector of a Non-Replicating Virus	Gamaleya Research Institute	Egypt	2° to 8°C
5.	<b>Covishield</b>	Vector of a Non-Replicating Virus	AstraZeneca	France	2° to 8°C

6.	<b>CoronaVac</b>	Inactivated	Sinovac Biotech	Hong Kong	2° to 8°C
7.	<b>Covaxin</b>	Inactivated	Bharat Biotech	India	2° to 8°C
8.	<b>Comirnaty</b>	mRNA	Pfizer, Inc., and BioNTech	Italy	-70°C
9.	<b>Sputnik V</b>	Vector of a Non-Replicating Virus	Gamaleya Research Institute	Russia	-18° to -22°C
10.	<b>Janssen</b>	Vector of a Non-Replicating Virus	Janssen Pharmaceutical Companies (J&J)	South Korea	2° to 8°C
11.	<b>Vero Cells</b>	Inactivated	G42 Healthcare (Hayat-Vax)	Sri Lanka	2° to 8°C
12.	<b>Spikevax</b>	mRNA	Moderna, NIAID	United Kingdom	-50°C to -15°C
13.	<b>Abdala</b>	Protein subunit	Centre for Genetic Engineering and Biotechnology in Cuba.	Vietnam	2° to 8°C

### Cold-Chain Technology:

All equipment used in the cold storage facilities must adhere to a number of performance requirements outlined by the WHO EPI programme, UNICEF, or national regulation. To transport or preserve vaccinations, only validated techniques should be utilised. For storing vaccines, the following tools are advised: Cold rooms, Refrigerators, Freezers; etc. Equipment like these is frequently used to transport immunizations: Cold boxes, Vaccine carriers.

### Vaccine Cold Boxes:

Immunizations and fillers are transported and/or temporarily kept at a cool temperature using frigid boxes, which are sealed containers that can be lined with ice packs (from two to seven days). Monthly vaccine supplies are purchased from local stores and delivered to the hospital via freezers. In addition to acting as carriers for vaccines, they are also used for outreach initiatives, mobile sessions, and vaccine storage when the refrigerator is malfunctioning or defrosting. Variables in cool box models affect how many vaccinations they can hold.

### Monitor for Vaccine Vials:

It contains a chemical that gradually darkens when exposed to heat. This indication's backdrop, which has a pre-printed baseline colour and is imprinted as a tiny box on a series of concentric background, is wider than the backdrop itself. There are additional options for changing the colour of the pre-printed background square. The VVM can then be configured to roughly match the time-temperature susceptibility graph of the component. This prevents significant vaccine waste and ensures that heat-compromised vaccine is "tagged" to be thrown away. It also makes it possible to remedy small breaches in the cold chain.

### Retention of Cold Chain:

Every time a vaccination is exposed to a temperature above the advised range, some of its effectiveness is lost. Continual exposure to hot spells causes a build-up of irreversible decrease of potency. There are various reasons why it's crucial to keep vaccines effective: - A quality product must be utilised. It's crucial to handle resources carefully. Vaccines are costly and occasionally hard to get by. Revaccinating someone who has already had an unsuccessful vaccination is unpleasant from a professional standpoint and could damage the public's trust in vaccinations and/or the healthcare system<sup>[30]</sup>.

## CHALLENGES DURING VACCINE TRANSPORTATION

Due to nationwide lockdowns and containment area protocols, there were several intrusions in delivering routine healthcare services. During that period of time, the Healthcare Professionals faced many challenges due to mobility restrictions as well as lack of transportation facilities [59]. A strong experimental investigation could help solve problems with regulating the cold chain during storage and transit. Strengthening GDP standards is necessary before ensuring product quality, safety, and efficacy, especially for controlling the cold chain items up to ultimate consumers (polyclinics and the private ownerships) [56]. Additionally, cold chain inspection (CCI), which consists of substantial inspection and temperature measurement, should be carried out in conjunction with vaccine lot release. This includes correct documentation, assessment of the lot summary protocol (LSP), and other steps. The staff at the shop should be given instructions on how to determine the number of vials, vaccine volumes, and the requirement for coolant-packs in the cold chain, how to use vaccine cold boxes, and how much dry storage space is required for commodities linked to immunizations [12]. Compliance with proper distribution practices is difficult because of a scarcity of refrigerated vehicles, distribution fleets that aren't large enough to handle the growth in EPI services, and inadequate road infrastructure.

## CONCLUSION

The novel coronavirus responsible for the current pandemic, which was accompanied by high morbidity and mortality worldwide [50]. Therefore, in order to end the current health catastrophe, mankind was searching for a reliable and potent vaccine. Although not always sterilising, the majority of SARS-CoV-2 vaccinations may have disease-preventing or disease-attenuating effects [51]. When exposed to extreme temperatures, vaccines lose their efficacy. Hence, they require cold chain and temperature-controlled storage and transport. To ensure the quality, safety and efficacy of the vaccines, GDP standards should be maintained. GSP and GTP guidelines should also be referred to for vaccine storage and transport. The effectiveness and characteristics of vaccines can be compromised by temperature fluctuations, thus choosing the right method of cold storage is crucial. The main vaccines used in India are Covishield and Covaxin. Several cold chain equipment's were used for the transportation of these vaccines.

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## REFERENCES

1. Soulsby C, Kennedy A, 2022. A new route to Pharma GDP Compliance and Standardisation. *Pharm Technol* 46, Pages - 40-44.
2. Kumar N, Jha A, 2019. Application of principles of supply chain management to the pharmaceutical good transportation practices. *Int J Pharm Healthc Mark.* 13, Pages - 306-330.
3. European Commission, 2013. Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use. *Official Journal of the European Union.* 343, 1-14.
4. WHO Drug Information, 2019. Good Storage and Distribution Practices for Medical Products. World Health Organization, 33.
5. Bhaskaran J, Venkatesh M P, 2019. Good Storage and Distribution practices for Pharmaceuticals in European Union, *J Pharm Sci Res.* 11, Pages - 2992-2997.
6. Bajaj S, Singla D, Sakhuja N, 2012. Stability testing of pharmaceutical products. *J Appl Pharm Sci.* 02, Pages - 129-138.
7. Rost J, Langhein S, Bartel D, et al, 2021. Good manufacturing practice- and good distribution practice-compliant cold storage and refrigerated transport of allergen products: what is important? *Allergo J Int.* 31, Pages - 36-42.
8. Imran A, 2017. Assessment of Good Storage Practices and Good Distribution of Pharmaceuticals in Punjab. *Pak J Health Sci Q.* 1, Pages - 9-12.
9. Kumar N, Jha A, 2017. Temperature excursion management: A novel approach of quality system in pharmaceutical industry. *Saudi Pharm J.* 25, Pages - 176-183.
10. Hadjihamza F, Pandova E, Bozinova V, 2016. Good Distribution Practice for medicinal products. *Maced Pharm Bull.* 62, Pages - 447-448.
11. Vangroenweghe F, 2017. Good Vaccination Practice: It all starts with a good vaccine storage temperature. *Porc Health Manag.* 3, Page - 24.
12. Anderson R, Perrier T, Pervaiz F, et al, 2014. Supporting immunization programs with improved vaccine cold chain information systems. *IEEE GHTC.* Pages - 215-222.
13. Lloyd J, Cheyne J, 2017. The origins of the vaccine cold chain and a glimpse of the future. *Vaccine.* 35, Pages - 2115-2120.
14. Sykes C, 2018. Time- and Temperature-Controlled Transport: Supply Chain Challenges and Solutions. *Phys Ther.* 43, Pages - 154-157.
15. Salisbury D, Ramsay M, Noakes K, 2013. Immunisation against infectious disease. *Diabetes Manag (Lond).* 1, Pages - 1-15.

16. Yuan L, Daniels S, Naus M, et al, 1995. Vaccine storage and handling. Knowledge and practice in primary care physicians' offices. *Can Fam Physician*. 41, Pages - 1169-76.
17. Gazmararian J, Oster N, Green D, et al, 2002. Vaccine storage practices in primary care physician offices. *Am J Prev Med*. 23, Pages - 246-253.
18. Lewis P, Reimer R, Dixon A, 2001. Evaluating the efficacy of vaccine storage in the general practice setting. *Aust N Z J Public Health*. 25, Pages - 547-550.
19. Lee S, Lim H, Kim O, et al, 2012. Vaccine Storage Practices and the Effects of Education in Some Private Medical Institutions. *J Prev Med Public Health*. 45, Pages - 78-89.
20. Bell K, Hogue C, Manning C, et al, 2001. Risk Factors for Improper Vaccine Storage and Handling in Private Provider Offices. *Pediatrics*. 107, Pages - e100-e100.
21. Grasso M, Ripabelli G, Sammarco ML, et al, 1999. Vaccine storage in the community: a study in central Italy. *Bull World Health Organ*. 77, Pages - 352-355.
22. Haworth E, Booy R, Stirzaker L, et al, 1993. Is the cold chain for vaccines maintained in general practice? *Br Med J*. 307, Pages - 242-244.
23. Bishai DM, Bhatt S, Miller LT, et al, 1992. Vaccine storage practices in paediatric offices. *Paediatrics*. 89, Pages - 193-196.
24. Bailey H, Kurinczuk J, Kusel M, 1999. Plant A. Barriers to immunisation in general practice. *Aust N Z J Public Health*. 23, Pages - 6-10.
25. Thakker Y, Woods S, 1992. Storage of vaccines in the community: weak link in the cold chain? *Br Med J*. 304, Pages - 756-758.
26. Thielmann A, Puth M, Weltermann B, 2019. Visual inspection of vaccine storage conditions in general practices: A study of 75 vaccine refrigerators. *PLoS ONE*. 14, Pages - 1-13.
27. Nelson CM, Wibisono H, Purwanto H, et al, 2004. Hepatitis B vaccine freezing in the Indonesian cold chain: evidence and solutions. *Bull World Health Organ*. 82, Pages - 99-105.
28. Santos A, Gaspar P, de Souza H, 2022. Evaluating the Energy Efficiency and Environmental Impact of COVID-19 Vaccines Coolers through New Optimization Indexes: Comparison between Refrigeration Systems Using HFC or Natural Refrigerants. *Processes*. 10, Pages - 1-14.
29. Saif A, Elhedhli S, 2016. Cold supply chain design with environmental considerations: A simulation-optimization approach. *Eur J Oper Res*. 251, Pages - 274-287.
30. Kausar S, Afzal H, Brajesh K, et al, 2013. An Overview: Storage of Pharmaceutical Product. *World J Pharm Pharm Sci*. 2, Pages - 2499-2515.
31. Baheti BB, Panchal CV, Bhusnure OG, et al, 2013. Pharmaceutical cold chain compliance. *World J Pharm Res*. 2, Pages - 1441-1451.
32. Hanson C, George A, Sawadogo A, et al, 2017. Is freezing in the vaccine cold chain an ongoing issue? A literature review. *Vaccine*. 35, Pages - 2127-2133.
33. Murhekar M, Dutta S, Kapoor A, et al, 2013. Frequent exposure to suboptimal temperatures in vaccine cold-chain system in India: results of temperature monitoring in 10 states. *Bull World Health Organ*. 91, Pages - 906-913.
34. Matthias D M, Robertson J, Garrison M M, et al, 2007. Freezing temperatures in the vaccine cold chain: A systematic literature review. *Vaccine*. 25, Pages - 3980-3986.
35. Nelson C, Froes P, Dyck A, et al, 2007. Monitoring temperatures in the vaccine cold chain in Bolivia. *Vaccine*. 25, Pages - 433-437.
36. Kumar V, Pandi-Perumal S, Trakht I, et al, 2021. Strategy for COVID-19 vaccination in India: the country with the second highest population and number of cases. *Vaccines*. 6, Pages - 1-7.
37. Thakur J S, Kaur H, 2021. Vaccine Distribution for COVID-19 and equity issues in India. *Int J Non-Commun Dis*. 6, Pages - 98-101.
38. Sharun K, Dhama K, 2021. India's role in COVID-19 vaccine diplomacy. *J Travel Med*. 28, Pages - 1-4
39. Chakraborty C, Sharma A, Bhattacharya M, et al, 2021. The current second wave and COVID-19 vaccination status in India. *Brain Behav Immun*. 96, Pages - 1-4.
40. Hatchett R, 2017. The medicines refrigerator and the importance of the cold chain in the safe storage of medicines. *Nurs Stand*. 32, Pages - 53-63.
41. Thielmann A, Puth M, Kersting C, et al, 2019. Vaccine cold chain in general practices: A prospective study in 75 refrigerators (Keep Cool study). *PLoS ONE*. 14, Pages - 1-13.
42. Grol R, Grimshaw J, 2003. From best evidence to best practice: effective implementation of change in patients' care. *Lancet*. 362, Pages - 1225-30.
43. Chojnacki M, Miller W, Ripple D, et al, 2009. Thermal Analysis of Refrigeration Systems Used for Vaccine Storage. *J Res Natl Inst Stand Technol*. 7656, Pages - 1-41.
44. Gensichen J, Korff M, Peitz M, et al, 2009. Case management for depression by health care assistants in small primary care practices: a cluster randomized trial. *Ann Intern Med*. 151, Pages - 369-78.
45. Wutoh R, Boren SA, Balas EA, 2004. eLearning: a review of Internet-based continuing medical education. *J Contin Educ Health Prof*. 24, Pages - 20-30.
46. Kreuter MW, Wray RJ, 2003. Tailored and targeted health communication: strategies for enhancing information relevance. *Am J Health Behav*. 27, Pages - 227-32.
47. Yauba S, Joelle S, Jude N, et al, 2017. Temperature Monitoring in the Vaccine Cold Chain in Cameroon. *Vaccines*. 09, Pages - 1-6.
48. Lim J, Norman B, Rajgopal J, 2019. Redesign of vaccine distribution networks. *Int Trans Oper Res*. 29, Pages - 200-225.
49. Haidari L, Connor D, Wateska A, et al, 2013. Augmenting Transport versus Increasing Cold Storage to Improve Vaccine Supply Chains. *PLoS ONE*. 8, Pages - 1-7.

50. Devi L, Sardar M, Sharma M, et al, 2022. Impact of ChAdOx1 nCoV-19 (Covishield™) Vaccination: How Long Will It Persist? *Int J Microbiol.* 2022, Pages - 1-7.
51. Pal M, Gutama K P, 2021. Efficacy of the Vaccines, Their Safety, and Immune Responses against SARS-CoV-2 Infections. *Am J Microbiol Res.* 9, Pages - 103-106.
52. Hibbs B, Miller E, Shi J, et al, 2018. Safety of vaccines that have been kept outside of recommended temperatures: Reports to the Vaccine Adverse Event Reporting System (VAERS). 2008–2012. *Vaccine.* 36, Pages - 553-558.
53. Ng C, Lean Y, Yeoh S, et al, 2020. Cold chain time- and temperature-controlled transport of vaccines: a simulated experimental study. *Clin Exp Vaccine Res.* 9, Pages - 8-14.
54. Matthias D, Robertson J, Garrison M, et al, 2007. Freezing temperatures in the vaccine cold chain: A systematic literature review. *Vaccine.* 25, Pages - 3980-3986.
55. Lee B, Haidari L, 2017. The importance of vaccine supply chains to everyone in the vaccine world. *Vaccine.* 35, Pages - 4475-4479.
56. Pambudi N, Sarifudin A, Gandidi I, et al, 2022. Vaccine cold chain management and cold storage technology to address the challenges of vaccination programs. *Energy Rep.* 8, Pages - 955-972.
57. Long A, Hayney M, 2013. Best practices essential for storage and temperature monitoring of refrigerated vaccines. *J Am Pharm Assoc.* 53, Pages - 660-661.
58. Patel K, Nayak B, Rana S, et al, 2022. Enablers and barriers towards ensuring routine immunization services during the COVID-19 pandemic: findings from a qualitative study across five different states in India. *Trans R Soc Trop Med Hyg.* 116, Pages - 814-821.
59. Fahrni M, Ismail I, Refi D, et al, 2022. Management of COVID-19 vaccines cold chain logistics: a scoping review. *J. Pharm. Policy Pract.* 15, Pages - 1-16.
60. Raina SK, Kumar R, 2021. "Covishield and Covaxin" - India's contribution to global COVID-19 pandemic. *J Family Med Prim Care.* 10, Pages - 2433-2435.