The status of refrigeration techniques for vaccine storage and transportation in low-income settings

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Abstract

Vaccines need to be continuously stored between 2°C to 8°C, from their production to administration to beneficiaries. Every year, more than 25% of vaccines are wasted. One of the main reasons for this wastage is the lack of cold chain continuity in low-income settings, where electricity is scarce. Recently, several advances have been made in cooling technologies to store and transport vaccines. The current paper presents a review of refrigeration technologies based on scientific publications, industry white papers and other grey literature. For each refrigeration method, we describe its working principle, the best performing devices available as well as the remaining research challenges in order to obtain a very high degree of performance enhancement. Finally, we comment on their applicability for vaccine transport and storage.

Keywords | cold chain; refrigeration technologies; passive refrigeration; active refrigeration; vaccine storage and transportation

1. Introduction

Each year, more than 1.5 million people die from a disease that could have been prevented with vaccination [1]. In order to maintain their full potency, vaccines need to be stored between 2°C and 8°C [2] and this requirement applies to the whole supply chain, or cold chain (illustrated in *Figure 1*), from manufacturing to beneficiaries. However, more than 25% of vaccines are annually wasted, primarily due to the inability to maintain the optimal temperature range along the cold chain [3].

According to the amount of vaccines to be carried, each stage of the cold chain (national, regional, villages) requires specific transport and storage equipment [4]. While the choice of transport is mainly influenced by road conditions [5], the choice of storage equipment depends on the availability of energy resources (mainly electricity), the duration of transportation or storage as well as the volume of vaccines [6, 7]. This cold chain involves logistical challenges [8], particularly in low-income settings where equipment might be defective, electricity supply unreliable, roads impassable and health workers not adequately trained [4, 9].

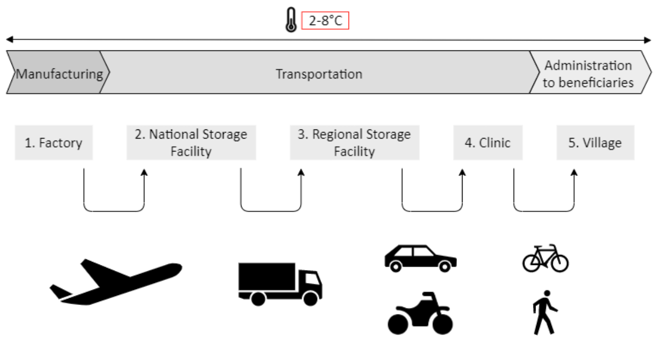

Figure 1 - **Cold Chain Process**: From manufacturing to administration to beneficiaries.

To ensure a safe and effective delivery of immunization, the World Health Organization (WHO) has developed the Performance, Quality and Safety (PQS) system [10]. This provides cold storage recommendations specific to each stage of the supply chain, and consists of a list of performance specifications and test procedures to prequalify cold chain equipment. To help procurement agencies make decisions, the PQS catalogue [11] lists prequalified cold chain equipment. The refrigeration equipment falls into two main categories: passive and active [12].

Passive refrigeration devices do not require any external source of energy during use. Such equipment consists of (i) long-term passive containers, which are used to store vaccines at health facilities where electricity is unreliable, (ii) vaccine carriers and (iii) cold boxes, the latter two being used rather to transport vaccines from the facility to the beneficiaries [5]. The performance of passive refrigeration equipment is mostly assessed by its cold life, i.e. the duration it is able to maintain an inner temperature range of 2-8°C.

Active refrigeration equipment requires access to energy in the form of heat or electricity during use. This approach is more appropriate for storage in health facilities than for transportation. When electricity is available 8 hours or more per day and power outages are shorter than 48 hours, on-grid equipment is recommended by the WHO [11]. On the contrary, when electricity is available less than 8 hours per day with recurrent power outages longer than 48 hours, devices able to generate their own power such as heat-driven or solar refrigerators are preferred. [13, 14]. The performance of an active refrigeration system is represented by its efficiency to convert input energy such as electricity or heat to cooling capacity (i.e. capacity to remove heat from a cold source). This measure is called the coefficient of performance (COP) and is computed as the ratio between cooling capacity (output) and supplied energy (input). [15].

The current review compares the main refrigeration methods, passive and active, for vaccine storage or transportation, their respective performance and technologies being currently developed or already available on the market. The research challenges to improve the performance (efficiency and/or cold life) of these refrigeration methods are also identified.

2. Passive refrigeration techniques

2.1 Passive Cooling Systems

2.1.1 Working principle

Passive refrigeration relies on the combination of an insulated container with coolant packs acting as thermal batteries to control vaccine temperature [5]. A container is efficiently thermally insulated when heat exchange between its interior and exterior is minimized. To achieve minimal heat exchanges, the materials used for the container need to resist temperature changes, i.e. to have low thermal conductivity. Both air and vacuum exhibit low thermal conductivity, having respectively a coefficient of 0.024W/mK and 0W/mK, therefore being very efficient thermal insulators. Various methods exist to build an insulated container, including vacuum flasks, cryogenic dewars and vacuum evaporation.

Vacuum flasks consist of two flasks placed one within the other, joined at the neck, with a near-vacuum gap, to reduce heat transfer, between the two recipients [14]. Based on the same principle, cryogenic dewars consist of two flasks separated with vacuum and multilayer insulation to reduce heat transfer even more. However, both these methods present some drawbacks. Creating the near-vacuum is highly energy-demanding, maintaining this state requires expensive materials, and leakages are difficult to detect and identify. As a consequence, the temperature inside the container can increase and affect the vaccine's potency, without the knowledge of the user. [14].

In the evaporative cooling method, also called vacuum evaporation, the gap between flasks consists of water at near-vacuum pressure. Lowering the pressure reduces the water temperature boiling point and allows the ambient temperature to provide the necessary energy to evaporate it. The evaporation draws energy from the surrounding environment and thus cools the inner flask. The evaporated water is either freed to the atmosphere from the device through a hole or goes to another compartment of the device. [16]. With the latter approach, water could be reused for several cycles of refrigeration but needs to be conditioned after each cycle by reducing its pressure.

The thermal batteries placed inside the container to control its temperature consist of packs filled with phase change material (PCM). PCM is a substance that releases or absorbs sufficient energy during phase transition to generate either a heating or cooling effect in the surroundings. When the PCM condenses or freezes, it releases a large amount of energy in the form of latent heat. When the PCM melts or evaporates, it absorbs energy from the environment. [17]. The coolant packs need to achieve a temperature range of 2-8°C [18] and thus when the packs are frozen, they need to be reconditioned (heated back to 2°C), before use in order to avoid freezing of the vaccines [13]. The WHO recommends water as a simple, cheap, safe and effective PCM to use, despite its freezing temperature of 0°C, which thus necessitates reconditioning to avoid freezing of the vaccines.

The WHO PQS system divides the passive refrigeration technologies into various categories depending on their vaccine storage capacity and adjusts its cold life requirements accordingly (see *Table 1*) [19]. The main difference between vaccine carriers and conventional cold boxes is their storage capacity (0.5-5 L for vaccine carriers, 5-25 L for cold boxes). Vaccine carriers are required to have a cold life of a minimum of 15 hours and are considered as being long range if above 30 hours. On the other hand, cold boxes need to have a cold life of at least 48 hours and are classified as long range above 96 hours. Additional categories of cold boxes offer either a large storage capacity, above 100L (>24 hours of cold life, >48 hours for long range), or long-term cold duration, above 35 days (capacity of >5L).

While passive refrigeration is appreciated for its low cost, low maintenance and light weight [7], it presents some limitations. Firstly, freezing and preparing the coolant packs requires access to active refrigeration, which involves adequate electrical power. Additionally, passive containers generally offer limited storage time (i.e., 15 hours - 35 days [11]), and are thus more appropriate for single day missions, or when substations are available, where coolant packs can be recharged and replaced by newly conditioned packs [3]. Finally, the use of such passive refrigeration poses a risk that the vaccine could freeze due to incorrect use of the coolant packs or use of the wrong type of container [5].

	Capacity	Short range	Long range
Vaccine carrier	0.5-5 L	> 15 h	> 30 h
Long-term cold box	5 L	-	> 35 d
Conventional cold box	5-25 L	> 48 h	> 96 h
Large storage capacity cold box	> 100 L	> 24 h	> 48 h

Table 1 - **Cold holdover requirements** for vaccine carriers and cold boxes, based on Specifications from WHO PQS Catalogue [19] (*h: hours, d: days, L: litres*).

2.1.2 Existing technologies

Even though vaccine carriers and cold boxes are already widespread on the market, their cold life could still be improved and the coolant packs-related constraints could be minimized. The three devices presented below were developed with the support and/or collaboration of the Bill & Melinda Gates Foundation.

The Indigo Cooler showed promising results [20]. It consists of a vacuum flask vaccine carrier with a 2 L inner storage capacity that can be worn like a backpack. Based on evaporative refrigeration, it does not require any electricity, ice or battery during use. The pressure inside the device is initially lowered so that water evaporates at 5°C. When exposed to a heat source, the water inside the walls of the device evaporates, keeping the vaccine compartment cool. Once all the water has evaporated and moved to another compartment, it needs to be pressurized again at a charging station so that the cycle can restart. This process allows the storage temperature range to be maintained for 5 days when the ambient temperature is 43°C. No evidence was found of the Indigo Cooler being available on the market or whether it has been PQS-prequalified by the WHO, despite field tests conducted at multiple locations [20].

As for long-term cold boxes, only one device has been prequalified by the WHO PQS programme, namely the Arktek Passive Vaccine Storage Device (PSD). The device is designed for stationary use, with a 5.4 L vaccine storage capacity. It relies on the principle of a vacuum flask with multilayer insulating materials (i.e. cryogenic dewar) and is not powered by electricity but requires ice packs to be renewed monthly. [3]. When the ambient temperature goes up to 43°C, the device ensures a temperature in the range of 0-10°C for at least 35 days. [21]. The Arktek PSD is currently sold to leading healthcare stakeholders (WHO, Médecins Sans Frontières, UNICEF, etc.) and its indicated price in the UNICEF Supply Catalogue is US$ 2,393 [22].

The Sure Chill company also developed a long-term cold box but based on Vacuum Insulated Panels and providing freeze protection. The device with a vaccine storage capacity of 7.8 L was field tested and able to maintain an internal temperature below 10°C for 33-42 days [23, 24]. It is currently undergoing a second phase of field pilot studies and is in the process of being scaled up. However, no evidence was found of WHO prequalification status.

2.1.3 Research challenges

In passive devices, due to the thickness of the insulation and the number of coolant packs, the effective volume of vaccines transported in the container is as low as 8% compared to its total volume [11]. This means that the volume of a passive device that actually holds the vaccines represents less than a tenth of the volume of the box. The main research efforts thus aim to improve the performance of passive containers and increase their storage capacity by focusing on heat retention. The objective is to develop a low-cost and high-performance insulation, which minimizes heat leakage while reducing the volume of the coolant packs. [25, 26].

Thermal insulation| Super Insulated Materials (SIMs), such as Vacuum Insulated Panels (VIPs) and advanced porous material, have been recently developed as an alternative to conventional thermal insulation methods [27]. Vacuum Insulated Panels (VIPs) consist of a vacuum trapped in a polymer matrix comprising a core and an envelope. The choice of materials for these two components depends on the application (such as heat, ventilation and air conditioning, medicine, food storage) and the desired properties (such as conductivity, efficiency, cost, non-toxicity, incombustibility). Typically, the core materials include fumed silica, polyurethane (PUR) foam, glass fibre or even aerogel (see below), while the envelope is made of metal, polymer laminate or metalized multilayer. The envelope consists of three layers: the inner one serves as sealing of the core materials, the middle one as a barrier against water vapour and air transmission through the envelope and finally, the outer layer as a protection to enhance the panels' robustness. [28,29].

Due to their structure and composition, VIPs could reach high performance with thermal conductivity as low as 0.002-0.004 W/(mK) [28, 30]. However, thermal conductivity increases over time due to any gases or water vapour permeating through the envelope. Even though this challenge could be resolved either by developing materials that can better resist permeating gases and water vapour, the costs would still need to be reduced for an application in low-income settings [31]. Also, VIPs have been investigated especially in the field of building and construction and further research is required to assess their applicability for storage of vaccines, in particular as regards the potential influence of environmental moisture on their efficiency [32].

Aerogels consist of nanoporous materials with pore sizes around 20 nm and variable mass density. They are solids derived from gel where the liquid component is replaced with gas, and could for instance be used as a core material for VIPs. [33]. Aerogels show non-flammability, non-reactivity, low thermal conductivity at ambient pressure and adjustability in terms of size and shape. Despite these valuable properties, their cost of production remains high, they are humidity-sensitive and show a low tensile strength, making the materials fragile [31].

Phase Change Materials| PCMs have the potential to reduce the risk of freezing if the material is designed so that its freezing temperature is in the range required for vaccine storage (e.g. 5°C). Such alternatives to water PCM could be organic (e.g. paraffin, fatty acids or vegetable oils), inorganic (e.g. salt hydrates or metals) or eutectic types. Most of these PCMs come with issues that are not encountered when using water, such as environmental concerns about their disposal due to their non-biodegradability, potential toxicity (i.e. skin and eye irritation), or incompatibility with the container. [34, 35]. However, material exchange with the environment can be prevented by PCM encapsulation, allowing the risk of leakage to be reduced while increasing the surface area to improve heat transfer, and thus potentially reducing the volume of PCM required compared to vaccine volume [17].

Encapsulation involves creating macro-, micro- or nanocapsules made of PCM droplets coated with another material. Khan *et al.* [36] present a novel microencapsulation method based on wet instead of dry capsules, whereby paraffin wax PCM is encapsulated into poly(hydroxyethyl) methacrylate (PHEMA), resulting in improved thermal conductivity: from 0.1 W/(mK) (dry capsules) to 0.49 W/(mK) (wet capsules) at 25°C. Shchukina *et al.* [37] identify nanocapsules as promising to achieve an optimal size and high efficiency of thermal energy storage. The study also presents manufacturing techniques to reduce costs and allow wide-scale production of PCM nanocapsules. Despite these approaches, water remains the cheapest and most environmentally-friendly PCM to use.

3. Active refrigeration techniques

3.1 Vapour compression refrigeration

3.1.1 Working principle

The vapour compression technique, representing a market share of 80%, is the most common and widespread in refrigerators [38]. These mechanically-driven refrigeration systems are made of four components all connected with pipes: a compressor, a condenser, an expansion component and an evaporator (see *Figure 2*). Vapour compression relies on a refrigerant circulating in the system, undergoing phase transitions, triggered by the components of the system, and either absorbing or rejecting heat. [39].

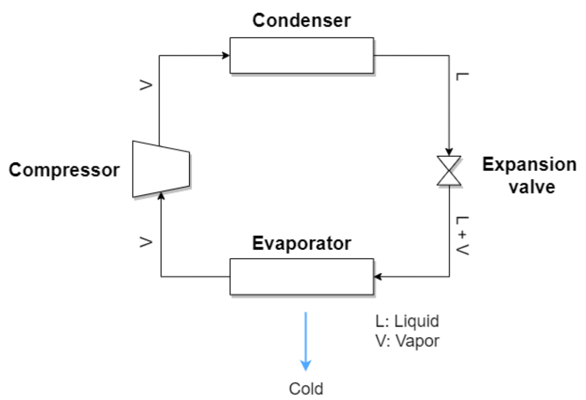

Figure 2 - **Vapour Compression Refrigeration** process.

The refrigeration cycle starts with the compressor receiving vapourized refrigerant from the evaporator. The compressor increases the pressure of the gas and, according to the ideal gas law (PV = nRT), its temperature as well. This superheated vapour is cooled down through the condenser where heat is rejected and triggers phase transition to saturated liquid. The liquid refrigerant's pressure and temperature are then reduced when going through the expansion valve. This creates a mixture of liquid and vapour which finally reaches the evaporator. The liquid then evaporates by absorbing heat from the cold chamber, thus ensuring a cool temperature. The saturated vapour returns to the compressor for the cycle to be continued. [40–42].

Vapour compression refrigeration (VCR) presents a high performance coefficient of (COP = 3.5-5.79 [43, 44]) and other advantages such as a wide operating temperature range (typically -153 °C to 27°C [45]). This refrigeration system requires reliable access to electricity necessary to drive the mechanical work of the compressor. However, it could also be designed for discontinuous power supply when combined with thermal storage or solar energy. [39]. Some additional disadvantages and challenges also arise with VCR technology, such as its high initial cost, the use of environmentally hazardous refrigerants, its high energy consumption and the bulk of the compressor, as it is very difficult to minimize the size of the compressor without losing significant efficiency [46].

3.1.2 Existing technologies

A well-established and widespread VCR system consists of ILRs (see *Figure 3*) [6]. Such devices rely on a simple vapour compression system with ice lining surrounding the vaccine compartment. The lining could be made of ice, cold water-filled or frozen ice packs. Solar or on-grid electricity makes it possible to keep vaccines at the appropriate temperature, as well as to store backup thermal energy in the lining. In the event of a power cut, the lining maintains a temperature below 10°C for at least 20 hours. Most ILRs are appropriate for settings with at least 8 hours of electricity per day. Enhanced ILRs could combine chilled water and ice and allow longer cold holdover, over 10 days, when fully frozen. [11].

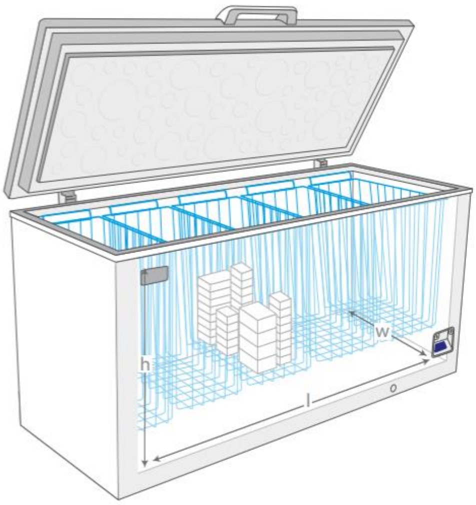

Figure 3 - **Typical Ice-Lined Refrigerators**, by [47].

Solar-assisted VCRs have been developed based on the principle of thermal energy storage similar to that of ILRs. For instance, SunDanzer, a US-based company, offers devices that are solar powered with no battery, but lined with PCM. As a WHO prequalified system, they can maintain the appropriate temperature range for 4 days in an ambient temperature of 43°C, even in the absence of energy supply. SunDanzer devices for medical applications exist in two sizes: either 15 L or 55 L, costing US$ 2,495 and US$ 3,599, respectively. [48].

Sure Chill, a UK-based company, developed an alternative approach to conventional ILRs but also relying on thermal energy storage. The vaccines compartment of Sure Chill devices is surrounded with water maintained at 4°C, the temperature at which water is most dense. Ice is stored above it in an additional compartment and maintained in this phase using electricity. The water around the vaccines circulates in a continuous cycle: as the water far from the ice storage compartment warms up, its density decreases. This warmer water rises up close to the ice compartment, where it is cooled down again to 4°C and sinks below the vaccines compartment. When there is no electricity, this cycle continues until the ice in the upper compartment fully melts. Sure Chill is a WHO-prequalified, energy-efficient and environmentally-friendly solution that can be used either on-grid or off-grid with solar panels. Many models exist with different cold holdovers (2-12 days) and volumes (27-225 L) for various applications (global health, home appliances, agri-food, etc.). [49]. Prices in the UNICEF Supply Catalogue vary from US$ 1,250 for the 27 L on-grid refrigerator, to US$ 5,625 for the 58 L solar direct driven refrigerator combined with freezer [50].

3.1.3 Research challenges

Despite its high performance, VCR suffers from drawbacks related to environmentally-harmful refrigerants and its energy consumption. The research challenges are thus to develop environmentally-friendly working fluids and to reduce energy consumption.

Refrigerants| Historically refrigerants tend to be environmentally-harmful substances, depleting the ozone layer and/or contributing to the greenhouse effect, such as halogenated refrigerants, hydrochlorofluorocarbon (HCFC) and chlorofluorocarbon (CFC)-based refrigerants [41]. The latest generation of refrigerants limits its impact on the environment by relying on natural substances: hydrofluoroolefin (HFO)-based solutions, associated blends, ammonia, carbon dioxide, hydrocarbons and water [51]. Even though natural, some of these refrigerants exhibit drawbacks related to potential flammability, toxicity or power requirements. Blends, however, consist of a mix of multiple refrigerants whose properties, as a result, vary according to their composition. Zhao *et al.* [44] identified R717 (ammonia) and its blends to be the most appropriate fluids (COP = 1.43-5.79) to substitute the common and efficient, but ozone-depleting, HCFC refrigerant R22 (COP = 1.38-5.56).

Recently, studies have presented the potential of combining nanoparticles with refrigerants to improve the efficiency of VCR and to reduce its energy consumption [52]. Performance of such a system could be increased from 3.5% to 7.2% compared to pure refrigerant, while energy consumption could be reduced from 9.6% to 25%. The range of these improvements depends on the refrigerants used (HFC, HCFC, hydrocarbon etc.), the type of nanoparticles (Al_2O_3, ZnO, TiO_2 etc.) and the concentration of nanoparticles [53]. For instance, Adelekan *et al.* [54] tested the combination of TiO_2 nanoparticles with R600a (isobutane) refrigerant with different concentrations of nanoparticles and of refrigerant. The nanorefrigerant that reached the highest COP value (4.99) comprised 0.1g of TiO_2 for 40g of R600a.

While the environmental impact remains a challenge and priority in the development of refrigerants [51, 55], blended refrigerants with their adjustable properties allow greenhouse potency, flammability and performance stability after multiple cycles to be balanced [56]. However, the choice of refrigerants influences many factors in the vapour compression system, from the design of the refrigeration equipment (compressor type, power requirement etc.), process efficiency and the final cost of the system. [41, 51, 56].

Energy consumption| Most of the energy supplied to vapour compression systems serves to drive the compressor [57]. In addition, thermodynamic losses occurring during both compression and expansion phases contribute to the system's energy consumption. Various approaches exist to reduce energy consumption and losses, thus increasing performance, and a promising avenue relies on expansion energy recovery. For instance, Zhang *et al.* [58] showed a gain of about 25-30% of the compressor input power with CO_2 as refrigerant by using an expander. Also, the performance of such systems increases up to 30% for CO_2-based systems and up to 10% for non CO_2-based systems [59]. However, expanders are not yet commercially available and most studies conducted on expanders are based on numerical analysis.

3.2 Sorption refrigeration: Absorption and Adsorption

3.2.1 Working principle

The principle of sorption refrigeration is similar to conventional VCR, where a thermal compressor replaces the mechanical compressor. Similarly to a mechanical compressor using electricity to generate a superheated and pressurized refrigerant, a thermal compressor uses external heat to achieve the same refrigerant conditions [39]. Sorption refrigeration includes absorption and adsorption-based systems. Absorption is a process in which a fluid (absorbate) is dissolved into a liquid or solid (absorbent). Adsorption is a process in which atoms, ions or molecules (adsorbates) from a substance adhere to a surface of the adsorbent. [60]. The coupling of an absorbate/adsorbate and an absorbent/adsorbent is called a working pair.

Absorption| The working fluid of an absorption refrigeration system consists of a liquid mixture of absorbate and absorbent [60]. In addition, the system is made of a generator, a condenser, an expansion valve, an evaporator, an absorber and a heating pump (see *Figure 4*). Heat – typically between 75°C and 120°C – is applied to the generator in which a refrigerant-saturated liquid is located. The refrigerant becomes a high-pressure and high-temperature gas that further liquefies in the condenser and is depressurized through the expansion valve. The evaporator then extracts heat from the liquid refrigerant, the gaseous refrigerant is absorbed again by the liquid absorbent and the cycle starts again. [39, 61]. Absorption refrigeration might require an additional device called a rectifier to purify the refrigerant vapour when the boiling points of the refrigerant/absorbate and the absorbent are close. [62].

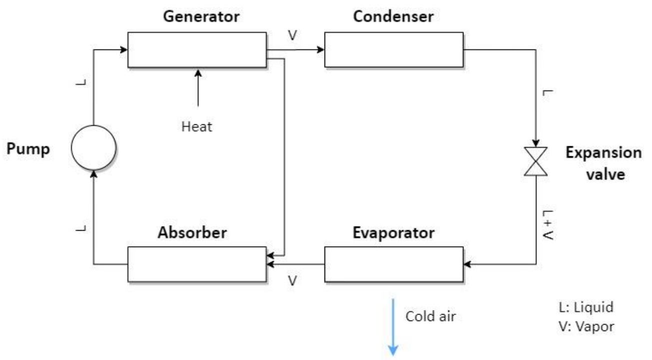

Figure 4 – **Simple absorption process**.

The most common working pairs used for absorption refrigeration consists of water combined with salts, acids and bases in solutions such as lithium bromide (LiBr), or with ammonia (NH_3) [63]. When water is combined with lithium bromide, it acts as the refrigerant/absorbate. Despite lithium bromide's corrosiveness, the working pair provides a high degree of safety and appropriate properties in terms of volatility ratio, stability and latent heat. However, water freezes below 0°C and thus limits its range of application temperatures. When water is combined with ammonia, it acts as the absorbent. Ammonia is completely soluble in water, which allows crystallization to be avoided. However, ammonia is toxic, flammable and incompatible with a variety of materials. [64].

Absorption coolers are environmentally friendly, require a low-grade heat (75-120°C) and have fewer moving parts than traditional VCR. They are more technically mature than adsorption cooling systems [65]. However, they have a high upfront cost, are usually bulky and have a low COP, of up to 1.1 [61].

Adsorption| Adsorption refrigeration operates very similarly to absorption systems. They consist of an adsorber, a condenser, an expansion valve and an evaporator (see *Figure 5)* [15]. At the beginning of the cycle, heat – typically between 50 and 100°C [60] – is applied to the adsorbent bed saturated with refrigerant/adsorbate: the pressure of the adsorbate increases. In a similar way to the traditional VCR, the refrigerant vapour flows to the condenser where it undergoes phase transition to liquid. The liquid refrigerant flows to the expansion valve, where its pressure and temperature are decreased. The refrigerant finally goes through the evaporator and absorbs heat from its environment. The cycle can then start again with the adsorption of the refrigerant by the adsorbent bed. [66].

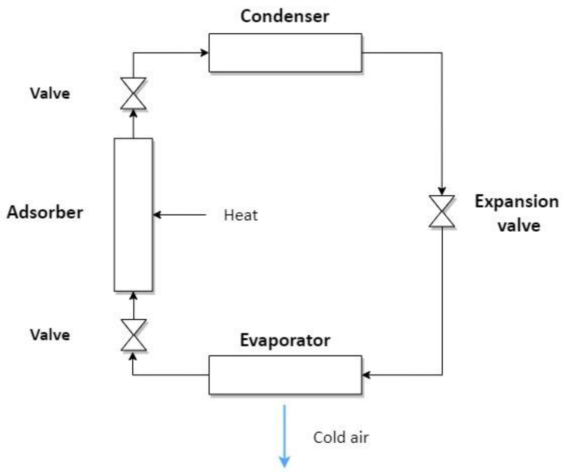

Figure 5 – **Simple adsorption process**.

The adsorption capacity of a working pair is assessed as the maximal amount of adsorbate (grammes) that can be taken up by the adsorbent (grammes), i.e. $g_{adsorbate}/g_{adsorbent}$: the higher the ratio, the longer the refrigeration period, since the adsorbent takes in more refrigerant fluid. [67]. The adsorbent is a porous solid element which should thus exhibit a high capacity for adsorption with temperature variation [68]. While common adsorbents consist of activated carbon, silica-gel and zeolites, common adsorbates consist of ammonia, methanol and water [66].

Activated carbon-methanol systems provide the largest adsorption capacity (0.259 $g_{methanol}/g_{activated\ carbon}$), compared with silica gel-water (0.116 $g_{water}/g_{silica\ gel}$) and zeolite-water (0.236 $g_{water}/g_{zeolite}$) ones [67].

Adsorption coolers have limited moving parts, use no harmful refrigerants, require even lower grade heat (50-100°C) and, due to the absence of moving parts, are suitable for applications where there is a lot of vibration, a feature desirable in rough road conditions [69]. However, the technology has not yet reached technical maturity and research needs to be conducted to improve efficiency, as this is still low, with a COP of up to 0.6 [70].

Both sorption systems work in an intermittent manner as described above. A continuous cooling effect requires at least the combination of two adsorption/absorption systems operating alternately: while one of the cycles undergoes sorption, the other undergoes desorption and then the roles are reversed. [39, 70]. Moreover, adsorption and absorption principles could also be coupled with other systems. Such hybrid devices could offer higher performance or a cost reduction when coupled with solar systems, thermal energy storage devices or even waste heat recovery [60, 62, 71]. In addition to reducing long-term costs, powering sorption systems with waste heat recovery or renewable energy to drive the desorption phase could also reduce its environmental impact [73].

3.2.2 Existing technologies

Commercially available sorption technologies are found in various fields but not in vaccine storage and transportation. For application in the air-conditioning of homes and buildings for example, SolabCool, a Netherlands-based company, offers a solar adsorption system based on silica gel and water [74], while Purix provides a solar absorption system based on the working pair water (H2O)/lithium bromide (LiBr) [75]. Nevertheless, some technologies are applied in a wider range of applications, such as *FreeCold* developed by ColdInnov, which offers an absorption refrigeration system for cold rooms, milk tanks, refrigerators and freezers [76].

ISOBAR cooling technology [77] is an absorption-based vaccine box showing 88 hours of cooling under WHO PQS test conditions (theoretically even 130 hours). It uses ammonia and water as a working pair that can be pressurized or charged electrically or thermally. In 2019, Enersion Inc. filed a patent [78] for a cold storage adsorption-based container in which the top of an insulated vacuum chamber is covered with an adsorbent material which adsorbs water vapour from melting ice. They compared the performance of cold boxes without adsorbents, with silica gel adsorbent or with zeolite adsorbent: the cold box with silica gel provided a cold hold-over time below 15°C of 187 hours which is by 7.6 times greater than the cold box without absorbent.

The WHO PQS system encompasses requirements for absorption systems but adsorption solutions are not mentioned. Indeed, absorption technology is more mature and showed its efficiency in various applications [64] while adsorption still faces significant technical challenges. Despite the potential of sorption technologies in vaccine storage, none has yet been prequalified by the WHO for safe vaccine storage [12].

3.2.3 Research challenges

In order to bring drastic improvement to the efficiency of these systems, the main research challenge is to develop working pairs that have considerable heat and mass transfer properties. [70, 71]. Indeed, the heat and mass transfer that occurs in sorption refrigeration greatly influences the performance of the system and represents its main technical limitation [66].

Regarding absorption, the most widely used and efficient working pairs – NH3/H2O and H2O/LiBr – are based on volatile solutions and require a vapour purification process to ensure the quality of the refrigerant [79]. Alternatives, showing potential even though requiring further investigations, have emerged, with ternary and quaternary salt mixtures as refrigerants [61]. For instance, LiNO3 or NaSCN show potential in replacing water in the ammonia (NH3)/water (H2O) pair with a 10% higher COP. The option of using CO_2 as refrigerant was also recently investigated but the COP (around 0.21) is lower than with conventional working pairs. Besides, it requires the development of specific absorbents and raises concerns about its high operating pressures. [71].

Regarding adsorption, the research focus is on adsorbents: composite adsorbents to enhance refrigerant uptake, creating an adsorbent coating over the heat transfer metal surfaces to decrease thermal resistance, or using Metal-Organic Frameworks (MOFs) [66]. MOF materials consist of highly crystalline porous materials offering robust and stable structures with tunable characteristics regarding their architecture and functionalization. Rezk *et al.* [80] identified one specific MOF, HKUST-1, to increase the water uptake by 93.2% compared to silica gel performance. Commercially available refrigerants used for VCR could also be employed as adsorbate to achieve a higher adsorption capacity (up to 2 g_{ref}/g_{ads}) [81, 82]. However, even if this reduces problems related to material compatibility and leakages, such refrigerants have environmental drawbacks, as seen in *Section 3.2.1*. A trade-off needs to be found between system efficiency, costs and environmental impact.

3.3 Thermoelectric refrigeration

3.3.1 Working principle

The thermoelectric effect relies on heat transfer due to DC current going through an electrical junction [83]. While electrical junctions are made of two materials, conductors or semiconductors, semiconductors which form p-n type junctions exhibit a very strong thermoelectric effect. At an atomic level, a p-n type junction is composed of a thermocouple of an electron carrier (n-type) and a hole carrier (p-type), both semiconductor materials connected via metallic contact pads. Depending on the direction of the DC current, the thermoelectric module achieves either heating or cooling. For cooling purposes, the current flows from the n-type semiconductor material to the p-type, driving the electrons to pass from a lower energy state to a higher one. [39, 84].

The performance and efficiency of these thermocouples are evaluated using a dimensionless quantity (ZT): the higher the value, the higher the efficiency [85]. Known as the figure of merit, ZT is computed as equal to S2σT/κ where σ is the electrical conductivity, S is the Seebeck coefficient, T is the absolute temperature, and κ is the thermal conductivity [86]. Thermoelectric devices start being efficient when their ZT value is above 1 [87]. The best thermoelectric materials have a high electrical conductivity and low thermal conductivity (i.e. high thermal insulation) and induce an electrical voltage in response to temperature difference across a material, represented by a high Seebeck coefficient.

The advantages of a thermoelectric cooling system are its compactness, light weight, low noise, proportional control capability, as well as the absence of moving parts and harmful refrigerants [84]. However, thermoelectric systems rely on batteries which require regular replacement and maintenance [88]. Also, the efficiency of these devices on the market remains very low (COP = 0.1-0.15) due to the lack of appropriate and low-cost materials [89].

3.3.2 Existing technologies

While thermoelectric devices are mostly available in the market for niche applications [83], several prototypes have been built and studied for vaccine storage. For instance, Ohara *et al.* [90] present the prototype of a small thermoelectric vaccine storage and transportation device, based on a modeling approach computing the optimum current and geometry. The system is made of an insulated inner chamber of 0.83 L, with storage capacity of 55 vaccine vials of 2 mL each, and walled with aluminum combined with a thermoelectric module, a heat pipe and two heat sinks. Once the device is activated, the temperature in the chamber decreases from 21°C to 3.4°C with a power consumption of 15.4 W.

A few years later, Gastelo-Raque *et al.* [91] developed a thermoelectric refrigerator system combined with batteries and photovoltaic panels for rural areas with limited access to electricity. The device stores up to 5 L of vaccines between 4°C and 6°C with an autonomy of 72 hours based on a rechargeable battery. More recently, Reid. *et al.* [92] presented a proof-of-concept for a thermoelectric chip combined with an aluminium block for storage of the vaccine vials. In contrast to most other designs tested at room temperature, this one is assessed with an ambient temperature of 37°C and provides an autonomy of 10 hours with a single battery charge.

Alternatively, the *Arktek Solar Direct Drive* is an enhanced version of the *Arktek PSD* (see *Section 2.1*), including a thermoelectric module. Li *et al.* [93] replaced two of the 8 ice blocks required by the *Arktek PSD* with an active Peltier-based cooling system, connected to a small solar panel. The refreezing of warm ice packs took 4 days while the temperature inside the main compartment was continuously between 3 and 5°C. A holdover time of 8 days was measured for this system in a controlled environment of 43°C during the day and 25°C during the night-time. However, this result is poor compared to the 35 days of the *Arktek PSD*, as a passive refrigerator with 8 packs and no thermoelectric module. [93].

Currently, no thermoelectric device has been prequalified by the WHO. In addition to their low autonomy and efficiency compared to vapour compression alternatives and passive systems, the development of low-cost materials with high figure of merit (ZT) remains a significant technical barrier.

3.3.3 Research challenges

Bismuth telluride (Bi2Te3) based alloys (ZT≈1.0) are the most used for applications around room temperature [84]. Most of the current research regarding thermoelectric refrigeration focuses on improving the ZT value of the materials while reducing their costs. Zolriasatein *et al.* [94] showed that the grinding process of a material could influence its thermoelectric properties: as they added stearic acid during the grinding, the figure of merit of the material was enhanced by 15%. Hinterleitner *et al.* [95] developed a new material, made from a thin layer of iron, vanadium, tungsten and aluminium applied to a silicon crystal, which ensures a ZT value between 5 and 6 at 300°C. However, these materials are very far from commercial application and ZT measurements are very complex and difficult to replicate [87].

3.4 Others

Other refrigeration approaches, including magnetic and thermoacoustic cooling, present potential for vaccine storage and transportation. However, no prototype or device based on these principles has been found for such an application.

Magnetic refrigeration is based on the magnetocaloric effect during which a material's temperature changes according to an applied magnetic field. An increase/decrease in the magnetic field applied to a magnetocaloric material magnetizes/demagnetizes it and heats/cools it up/down. [85]. The advantages of a magnetic cooling system are the absence of harmful refrigerants, its theoretical high efficiency, low noise and easy maintenance. Jacobs *et al.* [96] propose a magnetic refrigerator based on neodymium (rare earth) that provides cooling power over a temperature span of 12 °C with a COP greater than 2. However, such a device relies on rare-earth materials (e.g. gadolinium, neodymium) which are expensive and may constrain the application of magnetic refrigeration. [97]. Also, miniaturization represents another challenge, once commercial models of large-scale applications are available, that of integrating magnetic refrigeration in an active vaccine carrier.

Thermoacoustic refrigeration relies on the oscillations of sound waves to transfer heat. While the expansion of sound waves reduces the surrounding pressure and absorbs heat, their compression increases pressure and releases heat. [98]. Thermoacoustic refrigeration is environmentally friendly and does not involve moving parts, which facilitates its production and maintenance. [99]. Shivakumara *et al.* [100] developed a thermoacoustic refrigerator achieving a COP value of 1.66 and using helium as working fluid. However, thermoacoustic technologies are immature and present low cooling capacity, large physical size and heat exchanger inefficiencies [85].

4. Discussion

Maintaining the cold chain is essential for vaccine storage. The requirements and technical challenges vary according to the level of the vaccine supply chain. For motionless storage and where electricity is reliable, large refrigerators are mainly used and might be combined with freezers for coolant packs. Such technology offers a large storage capacity but is energy-demanding and uses refrigerants that can be harmful for the environment. However, various active refrigeration techniques could be further investigated to overcome these challenges despite their initial high costs and lower efficiencies (see *Table 2* for the Overall Assessment).

For smaller capacity applications, cold boxes and vaccine carriers are employed and mostly based on passive refrigeration techniques. Vacuum flasks are the conventional approach, but creating near-vacuums is highly energy-demanding, while the materials required are expensive and leakages are difficult to identify. Evaporative cooling allows several cold cycles to be undertaken, but requires reduction of the pressure at each cycle to be recharged, and super-insulated materials provide a structure and composition with low thermal conductivity. These materials are still being investigated for an application to vaccine storage. The use of ice packs incurs a risk of freezing and the constraint of conditioning, which requires external energy input.

The main limitations for passive refrigeration devices are their cold holdover time and their use of coolant packs, of which they require a high number in relation to the quantity of vaccine. An ideal vaccine carrier or cold box, which is essential for last mile delivery, should show high efficiency in ensuring a storage temperature between 2 to 8°C for a long duration, while maximizing vaccine storage volume. It should be portable and robust with low recharging constraints. An option to improve the characteristics of these small capacity technologies would be to combine passive and active refrigeration approaches, when active refrigeration technologies can be miniaturized.

Among active refrigeration techniques, vapour compression is the most widespread on the refrigeration market due to its high efficiency (COP = 3.5-5.79). However, it is energy-demanding and bulky due to its compressor and potentially environmentally harmful due to its refrigerant. While energy efficiency could be improved by focusing on reducing thermodynamic losses or combination with renewable energy, different kinds of refrigerants, such as natural, HFO-based or blends, could also be developed and optimized. Most alternatives to VCR with a potential for lower environmental impact are still not able to compete due to their high initial costs and lower efficiency.

Sorption technologies relying on environmentally friendly refrigerants are driven by reduced amounts of thermal energy and require few if any moving parts, which tends to improve their durability. However, their performance is highly influenced by the materials used as working pairs. While absorption refrigeration shows better performance (COP = 0.7-1.15) than adsorption (COP = 0.4-0.6), the efficiency of both approaches remains below VCR.

Thermoelectric technologies offer compactness, light weight, low noise, absence of refrigerants or moving parts, but require more efficient materials to reach better performance than currently the case (COP = 0.4-0.7). With more efficient materials, this technology could be the best candidate for vaccine carriers.

Technology	State of Development		Performance	Advantages	Disadvantages	Research challenges
	Prototype	Market*				
Passive Refrigeration	-	CB, VC	up to 35 days	- Low cost - Low maintenance	- Coolant packs: Preparation and conditioning, risk of freezing - Low volume ratio vaccines/coolant packs	- Insulation materials with low thermal conductivity - PCM with low density and low thermal conductivity
Vapour Compression	-	R	COP 3.5-5.79	- High COP - Wide operating temperature range - Low volume of refrigerant	- High initial costs - Environmentally hazardous refrigerants - Energy-demanding - Bulky compressor	- Environmentally friendly refrigerant - Reduction of power requirement and thermodynamic losses
Absorption	VC	R	COP 0.7-1.15	- Environmentally friendly - Low-grade heat (75-120°C) - Few moving parts	- High initial costs - Low COP - Bulky	- Cost reduction - Increase energy efficiency
Adsorption	CB	R	COP 0.4-0.6	- Environmentally friendly - Low-grade heat (50-100°C) - Very few moving parts - Robust to vibration	- Low COP - No technical maturity	- Heat and mass transfer efficient working pairs
Thermoelectric	-	R, CB, VC	COP 0.4-0.7	- Compactness, light weight - No moving part - Environmentally friendly	- Low COP - Use of battery	- Low-cost material with high figure of merit ZT
Magnetic	P	-	COP > 2	- Environmentally friendly - Low noise - Easy maintenance	- Expensive rare-earth materials	- Low-cost and rare-earth free materials with high MCE - Miniaturization
Thermoacoustic	P	-	COP 1.66	- Environmentally friendly - No moving parts	- Low efficiency - Large physical size	- Gap between theoretical and experimental COP

Table 2 – **Overall assessment** of the various refrigeration techniques

* R: Refrigerator, CB: Cold Box, VC: Vaccine Carrier, P: prototype for non-vaccine application

5. Conclusion

Disruption of the cold chain generates avoidable wastage of vaccines and innovative refrigeration systems could be part of the solution. This study provides an overview of the various refrigeration techniques – mechanical compression, sorption and thermoelectric - with the potential to improve the outcomes of the cold chain, by considering their respective working principle, commercialized products and research gaps. In these COVID times, with the upcoming new vaccines, which need to be kept at -80°C, passive heat retention technologies such as PCMs and insulation are as important as the refrigerant methods in order to maintain a cold environment. The review highlights the necessity for the development of low-cost, low-energy demanding robust refrigeration systems and state-of-the-art insulation especially for low-income settings. Most of the research gaps relate to the development of efficient and low-cost materials.

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