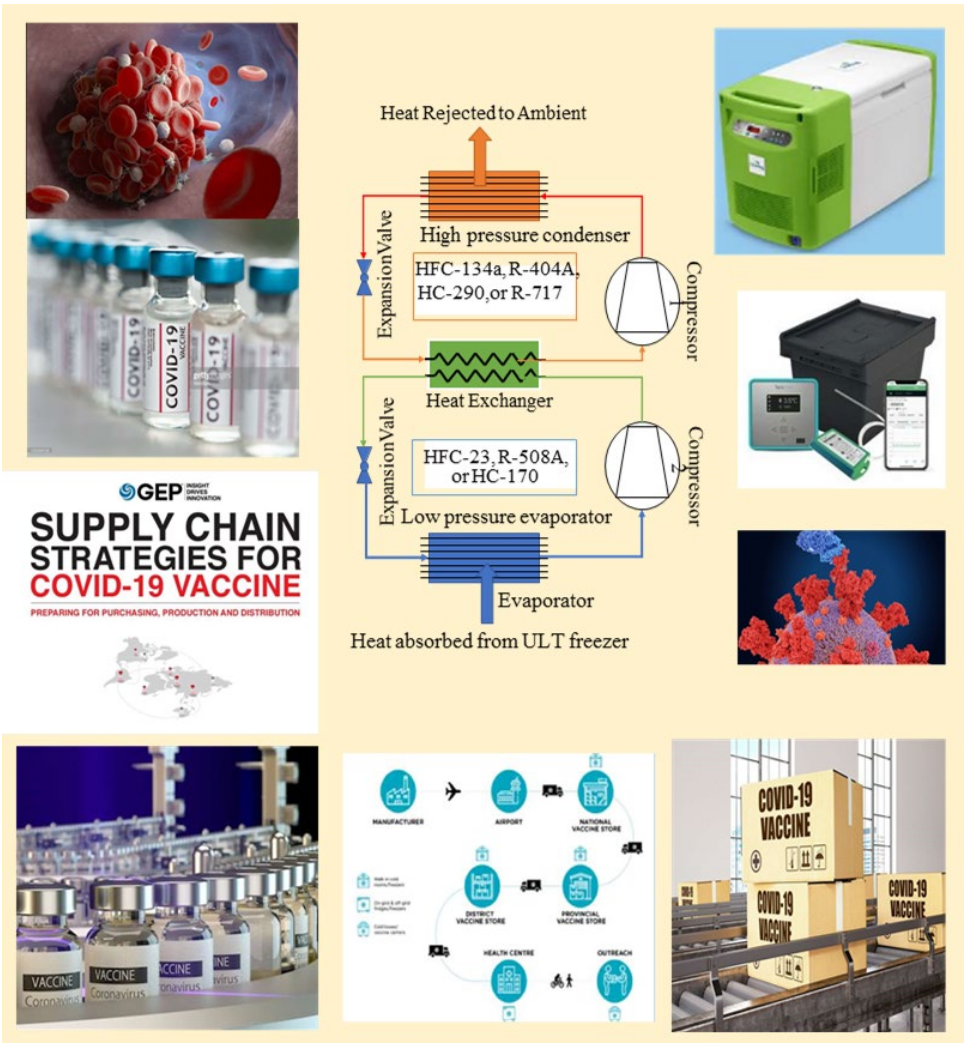
Montreal Protocol on Substances that Deplete the Ozone Layer



Report of the Refrigeration Technical Options Committee Vaccines Cold Chain Subcommittee

Addendum to the TEAP 2021 Progress Report

September 2021

UN environment
United Nations Environment Programme

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ISSUES RELATED TO VACCINE COLD CHAINS

The text of this report is composed in Times New Roman.

Co-ordination:	Omar Abdelaziz, RTOC co-chair
Composition of the report:	RTOC Subcommittee
Layout and formatting:	Omar Abdelaziz, Lambert Kuijpers
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Outline

Foreword

Publication of this note is directly related to the development and application of vaccines to the Covid-19 pandemic and to the vaccine cold chain in general. It is necessary to note that there are daily and year-round storages, transport, and logistics requirements for many medicines and vaccines for more epidemic infections than just Covid-19. One needs to be aware that at the moment, there are also other pandemics ongoing that get less attention, such as diabetes and HIV/AIDS. Insulin, for instance, is needed for diabetes disease, and it requires cold transport and storage, and it is also a delicate medicine that needs much care and attention during transport.

It is also important to emphasize that two thirds of the world population, mostly living in A5 countries, are not connected to a reliable electrical grid that can supply continuously, without instability and shortage, low or medium temperature refrigeration systems. This is fundamental for the vaccine storage, preserving its properties for an extended period of time. However, Covid-19 is an issue that deserves all attention at this moment.

European Community (EC) President von der Leyen[1] highlighted that fighting the current Covid-19 pandemic requires reaching out far beyond any single country or region. She mentioned that there is a need for global solutions that ensure that vaccines are distributed at scale to avoid virus mutations that can undermine the remarkable progress made to fight this unprecedented pandemic. That restoring and sustaining the global economy requires global solutions for vaccine production, storage, and distribution. Furthermore, that it is important that the world work together to be prepared for any future outbreaks; hence, any solutions should consider future needs.

WHO Director General, Tedros Adhanom Ghebreyesus in his statement last December 2020, said: *With vaccines now being introduced, it's really important that they are distributed equitably around the world.*

For that, vaccine cold chain plays an important role. This chain involving cold rooms, freezers, refrigerators, cold boxes, and carriers are fundamental for keeping vaccines at the right temperature during the journey from the manufacturing line to immunization programs and clinics and health centres.

The Montreal Protocol (MP) parties over the years, through their Ozone Units and representatives, have been directly involved with refrigeration technologies, and have been following their challenges and issues due to the replacement of refrigerant, but also others, directly or indirectly related to the issue of the use of refrigerants. The RTOC, as the main supporting body of the MP for the Refrigeration and Air Conditioning (RAC) sector, intends to offer its contribution to the parties to understand the importance of the vaccine's cold chain, which was expanded by Covid-19. In this way, this Technical Note addresses several aspects of the present vaccine cold chain issue, gathering the most relevant and recent information related to refrigeration equipment and technology, use of refrigerant, energy consumption during the production, distribution, and storage of vaccines.

1. Introduction

A safe and efficient vaccine distribution to remote places is crucial to protect the health of the global population and to support the UN sustainable development goals (SDGs) #3 Good health and well-being, #16 Peace, justice, and strong institutions, and #17 partnerships for the goals. Furthermore, the use of energy efficient and environmentally friendly refrigeration and cooling technologies and methods will further support SDGs #9 Industry, innovation, and infrastructure, #11 Sustainable cities and communities, #12 Responsible consumption and production, and #13 Climate action. Covid-19 is a serious virus that may result in sustained illness 'long covid' [2], as such, prevention is one of the most effective ways to combating this pandemic. Furthermore, variants will continue to evolve, and the epidemic would continue to pose serious risk globally. In addition, the percentage of unvaccinated population remains too high in many countries. According to recent findings, Covid-19 continues to be an issue despite the high vaccination levels, mainly due to recent virus mutation. [3]

Many vaccines require a proper "vaccine cold chain", a challenge that has been particularly highlighted by the current, still ongoing Covid-19 pandemic. The SARS-CoV-2 virus outbreak can be considered as a turning point in establishing reliable and extended vaccine cold chains, including for ultra-low temperatures. An ultra-low-temperature vaccine cold chain (or part of the cold chain) is an exceptional challenge since most other vaccines (and medicines) can be stored at higher temperatures (-20 C to +8 C). Where this challenge was flagged by the two 'low temperature' vaccine producers at an early stage, it has been addressed by the global refrigeration industry manufacturing low temperature equipment by rapidly increasing the existing production capacity of equipment to produce cold at ultra-low temperatures. The technology that has been widely adopted to meet the ultra-low-temperature requirements relies on the vapor compression cycle technology and/or the direct use of dry CO_2 ice. In principle, even when certain other technologies than vapour compression can be used for low temperature storage, the observation is that no new technologies have so far been applied. The Covid-19 pandemic has led to an incredible number of studies on the cause of the disease, how to address specific symptoms, and how the available vaccines could be used and adapted, in particular in case of virus mutations that would lead to higher chances for getting infected. That also includes prescriptions for how to store the vaccines currently available, which would require ultra-low temperatures in the first parts of the cold chain for some of them. The last few months have shown that there is a constant adjustment of requirements for storage and handling of certain vaccines (apart from how to administer them), where it is difficult to forecast what will be the situation in a few months' time. Not to even mention what would be the situation in a year from now, with all kinds of unexpected innovative developments where it concerns storage and handling of any Covid-19 vaccines and possibly others.

This RTOC technical note focuses on the current (June 2021) situation, where it relates to the specific needs for refrigeration and cooling of vaccines (and Covid-19 vaccines in particular) in the distribution chain. It will therefore also deal with refrigerant options and technologies, for vaccine storage and transport with a link to the issues posed by specifics of the distribution chains. This implies the consideration of energy consumption issues, the availability of refrigeration means and the link to the distribution chain, particularly in Article 5 countries. Of course, the distribution chain needs to be addressed in tandem, but that is not a major issue for this note. The latest IPCC report [4] has created an emergency perception with many and several questions are raised about the energy consumption and choice of working fluids. Also, the available and stable electric grid to supply the cooling is in question.

For the drafting of the RTOC technical note, the RTOC co-chairs created a RTOC Subcommittee including RTOC members. The Subcommittee members are presented below

Omar Abdelaziz	American University in Cairo
Bassam Elassaad	Consultant, Lebanon
Jitendra Bhambure	Consultant, India
Lambert Kuijpers	Consultant, Netherlands
Petter Neksa	SINTEF, Norway
Alexander Pachai	Johnson Controls Intl., Denmark
Roberto Peixoto	Maua Institute of Technology- IMT, Sao Paulo, Brazil
Fabio Polonara	Università Politecnica delle Marche
Natarajan (Rajan) Rajendran	Emerson Climate Technologies

After that, a first draft was finalised by the end of May and was sent to the whole RTOC Committee for review. After that, it was sent for information to the Technology and Economic Assessment Panel and then submitted to the Ozone Secretariat for placing it on its website.

Chapter 2 gives a first overview of temperature requirements for the Covid-19 vaccines, with some specific information on storage issues at the manufacture site and at distribution centres. Chapter 3 deals with the transportation of vaccines and its logistics. Chapter 4 then focuses on the major issue for this note, the storage of vaccines at low, medium, and higher temperature, and the refrigerants and technologies currently involved. In chapter 5, energy efficiency considerations are presented. Chapter 6 elaborates on availability issues and chapter 7 deals with specific linkages to the cold chain.

2. Temperature Requirements for the Vaccine Cold Chain

The challenge that the refrigeration sector must face, through adequate technologies, is directly related to fulfilling the requirements for different vaccines storage and transport temperature conditions, at the production site, during transport and at national distribution centres.

2.1 Temperatures for the Critical Vaccines

In principle, in the case of ultra-low temperatures, cold chains can be maintained by the application of passive (open) type cooling technologies, such as the cooling by CO_2 dry-ice (sublimating at -78°C[i]). The dry-ice or water ice is produced centrally[ii] and packed around the containers containing the vaccine to be cooled. Active cooling using a hermetic or closed type of refrigeration system is a feasible alternative, providing cooling via refrigeration equipment, based on a vapor compression system, such as plug-in refrigerators. This equipment is designed to provide adequate cooling capacity to satisfy the cold chain temperature required by conditions for the different vaccines. The operation of any equipment of this type requires a relatively stable electrical power, as it must operate at relatively constant temperature levels.

Table 2.1 Storage temperature and storage period for different Covid-19 vaccines

Covid-19 Vaccine Manufacturer	Storage temperature (°C)	Storage period	Product Name
Pfizer/BioNTech†	2 to 8°C -25 to -20°C -60 to -80°C	31 days 2 weeks 6 months	Comirnaty[5], BNT162[6]
Moderna	Room temperature 2 to 8°C -20°C	12 hours 30 days 6 months	mRNA-1273[7]
AstraZeneca/Oxford	2 to 8°C	6 months	ChAdOx1[8]
Johnson&Johnson/Janssen Pharma.	Room temperature 2 to 8°C -25 to -15°C	2 hours 3 months 24 months	Ad26.COV2-S[9], [10]
Sinovac Biotech	2 to 8°C	3 years	CoronaVac[11]
Bavarian Nordic & consortium	2 to 8°C	NA	ABNCoV2[12]
Baharat biotech	2 to 8°C	NA	COVAXIN BBV152[13]–[15]
CureVac/GSK	5°C	NA	CVnCoV[16]
Gamaleya Institute	2 to 8°C	NA	Sputnik V[17]
Medicago GSK	2 to 8°C	NA	Phase 3 test[18], [19]
Novavax	2 to 8°C	NA	NVX-CoV2373[20]
Sanofi/GSK	2 to 8°C -20°C	NA	MRT5500[21]
Sinopharm	2 to 8°C	NA	BBIBP-CorV[22]

† Discrepancy in the storage temperature and storage period listed is based on the data available on the original reference.

Table 2.1 provides the most recent summary of current storage temperature requirements for Covid-19 vaccines from different manufacturers for different storage periods. Most vaccines may be safely

[i] Carbon dioxide in its solid form is known as "dry ice," and under common conditions it sublimates, turning directly into gas. The freezing (or sublimation) point of carbon dioxide is -78.5 degrees Celsius,

[ii] Dry ice sublimation process requires ventilation to avoid elevated levels of CO_2 in the surrounding air. CO_2 pellets are delivered from a factory/supplier (mostly a chemical industry manufacturing other products where large amounts of CO_2 are released) in bags or in large boxes.

stored in equipment providing medium temperature refrigeration (2 to 8°C). However, one of the vaccines requires Ultra Low Temperature (ULT) conditions for long-term storage.

2.2 Storage throughout the Vaccine Lifecycle

The various aspects of storage at the manufacturer as well as the temperature level requirements for storage and distribution of vaccines are presented below.

2.2.1 Storage at the manufacturer

ULT is defined in this note as providing temperatures between -60°C and -80°C. When stored in dry ice with no water in the air the sublimation temperature will be around -78°C, but in real conditions, water vapor in the air will result in frost (water ice formation) and the sublimation temperature will be increased to about -65°C or slightly higher. Cold stores for -80°C are built at pharmaceutical production facilities for various processes.

2.2.2 Storage at distribution centres

Special distribution centres for pharmaceutical products are already in place for moderate temperatures. In these distribution centres the vaccines are placed in commercial/industrial fridges and chest freezers that are normally kept at either the -20°C or +5°C range depending on product requirements. These are standard types of equipment and are supplied by many international suppliers. Predominantly they use either HFC-134a or HC-600a for smaller systems (up to 200 litres) and HC-290 for larger systems. In these systems, temperatures are constantly monitored. An unwanted temperature level increase triggers an alarm to ensure proper action by the distribution centre operators.

3. Vaccine Cold Transportation

Proper cold transportation is required to ensure that vaccines are effective at the point of use. It is important to note that in these systems, temperatures are constantly monitored. If the safe temperature is exceeded during transport, a flag is raised in the transport log, and the product will be treated depending on what precisely the log records present.

3.1 Containers

Both normal temperature and special ULT refrigerated transport containers are available from several manufacturers.[23]–[25]Containers can be supplied with either passive cooling using dry ice to keep the contents cold -or cool- during transport or with active cooling if one is able to connect to an electric power supply. This supply would use the power grid while on the ground or a battery package while onboard a ship or during air transport. These containers are equipped with continuous remote controls and monitoring equipment and can provide accurate and reliable temperature control. They are typically used for pharmaceuticals, biological samples, and high-grade food products.

3.2 Portable ULT refrigerators

Small vaccine batches may be transported using portable ULT refrigerators.[26] This equipment is either 12V DC or battery powered and is operated by using the reliable reversed Stirling Engine cycle, with non-fluorinated refrigerants. It can operate over a wide range of temperatures from -20 to -86°C. They are equipped with wireless temperature logging allowing for remote monitoring.

3.3 Dry ice

For vaccines' shipments at ultra-low temperature, dry ice (i.e., CO_2 ice) can be used. Dry ice is produced by expanding liquid CO_2 from a pressurized vessel to produce CO_2 snow that is subsequently compressed to form bricks or pellets for commercial use. Dry ice sublimates (transition from solid to gas) at -78.5°C at atmospheric pressure. However, the sublimation temperature is affected by the condensation/frosting of water vapor over the dry ice surfaces. A shielding towards open air is therefore necessary. The minimum temperatures recorded in humid air have been at -35°C[27]. This phenomenon can be alleviated by reducing the surface /volume ratio (using bricks instead of pellets). In practice, CO_2 cannot be used to lower the temperature, it can only be used to maintain that temperature.

If sublimated CO_2 escapes from the refrigerated box and pools in the space where the box/boxes are stored, this may create a toxic atmosphere, and high concentrations of CO_2 can/will displace the normal air at atmospheric conditions. Therefore, the vaccine manufacturer normally indicates how many times the storage boxes can be opened for refilling.

To monitor the temperature in the boxes there are loggers placed inside the box that monitor in minutes-intervals the inside box temperature. If the temperature exceeds a critical value longer than a specified time, the box/batch will be discarded. There are several types of containers for transport using dry ice as refrigerant. One may find (1) containers with a polyethylene external structure (they

can be palletized) and polyurethane foam as insulant material, (2) containers with polystyrene material without any surface protection and (3) cardboard boxes. Boxes are available in different sizes and can hold up to 5000 vaccine glasses in one lot; these boxes have an internal volume of 57 or 120 litres. Dry ice does not produce liquid (except for small quantities of water condensate).

3.4 Last mile transport

As shown in Table 2.1, the last part of storage requires only modest cooling (2 to 8°C). This could be done using insulated boxes that have compartments filled with water ice. It is important to maintain the vaccine storage chamber dry to avoid any moisture damage. Furthermore, recent advances in phase change materials (PCMs) that can be tailored to provide optimized thermal storage capacity at the required temperature level can provide further solutions. They can be designed to change phase (liquid to solid and vice versa) between 2 and 8 °C and are then operated to increase the thermal storage capacity per unit mass/volume compared with water ice.

4. Vaccine Cold Storage Equipment

Vaccine cold storage temperatures, sizes and technologies applied differ throughout the entire vaccine cold chain. At the national, regional, or district level, stationary vaccine cooling/freezing may use insulated walk-in coolers or freezers with mono-blocks or split equipment. Furthermore, for emergency applications, cold and/or freezer containers can be used. At point-of-use level, vaccine cooling/freezing may be performed using vaccine refrigerators (2 to 8°C) or freezers (-22 to -20°C); this also with solar direct drive (SDD) vaccine laboratory refrigerators, freezers or ULT freezers. Different refrigerants and technologies are usually required for the diverse storage temperatures needed. As mentioned in section 2, vaccines require strict and stable temperature during storage. Temperature monitoring devices can be found in the Performance Quality and Safety (PQS) catalogue of the WHO.[28]

4.1 Ultra- low temperature applications (-60 to -80°C)

4.1.1 Equipment based on vapor compression

Freezers for ultra-low temperatures are relatively common globally, mostly for laboratory purposes and for storage such as for vaccines. The estimated number of units produced globally every year is about 60,000 units per year, based on market estimates for freezers between 300 and 800 litres[29], [30], and the number is expected to grow steadily. Optionally, for safety, these systems can be supplied with either CO_2 or liquid nitrogen in an open-type back-up system. This is normal in critical units for emissions and for vaccines[iii]. For walk-in freezers, the general advice is to apply multiple circuits (for split systems) or multiple mono-blocks to provide the adequate level of redundancies in case of failure. This implies emissions from servicing or improper handling at end of life in the range of 3-10 tonnes of HFC-23 per year. The Kigali Amendment schedules will emphasise avoiding the use of this very high GWP refrigerant. Furthermore, atmospheric measurements that show emissions of HFC-23 in the order of 16,000 tonnes per year that may originate from HCFC-22 manufacture and feedstock [31] use will also emphasise the fact that HFC-23 should be avoided as much as possible. It can be expected that this will automatically lead to the preferred use of hydrocarbon-based cascade cycles or not-in-kind methods, such as the air cycle.

Ultra-low temperatures are normally produced using cascade configurations that use a cycle with a certain refrigerant to produce the ultra-low temperature and a second cycle (using a different refrigerant) that pumps heat from the low temperature/bottom cycle to the ambient. Often, high GWP refrigerants such as HFC-23 and R-508A are used in the cold cascade stage and R404A or HFC-134a are applied in the high temperature part of the cycle, as shown in Figure 4-1. Typical local storage (cascade) units, with a capacity around 15 kWh/day, have a total charge of about 600g of refrigerant. Increasingly, cascade systems using HC refrigerants are being used. Generally, HC-290 or HC-600a will then be used at the high stage, with HC-170 (or sometimes HC-1150) at the low stage. Some systems are also available using a mixture of HCs with an auto-cascade cycle. With flammable

[iii] In these systems, the CO_2 is expanded from the high-pressure tank to ambient pressure – thereby reducing its temperature and producing the cooling effect; the expanded gas is then vented safely to atmosphere. Open liquid nitrogen systems allow nitrogen to evaporate at ambient pressure to produce the cooling effect.

refrigerants, the system charge can be limited more than it would be with non-flammable refrigerants. HFC-23 is a controlled substance scheduled for phase-down under the Kigali Amendment to the Montreal Protocol, which will significantly limit its use (due to its GWP of 14800[32]). Sales of this fluid have fallen drastically according to the latest EEA report[33]. With limited global data available on recent production of HFC-23 this can only be mentioned with a degree of uncertainty.

Lately, three new blends have been developed as an alternative to HFC-23 and have been assigned ASHRAE numbers R-469A in 2019, and R-472A and R-473A in 2021. The GWP of these alternatives are still higher than the ones of the HC alternatives, but much lower than the GWP of HFC-23, and they are classified as A1 refrigerants. Whether other proprietary blends could be available locally remains a question.

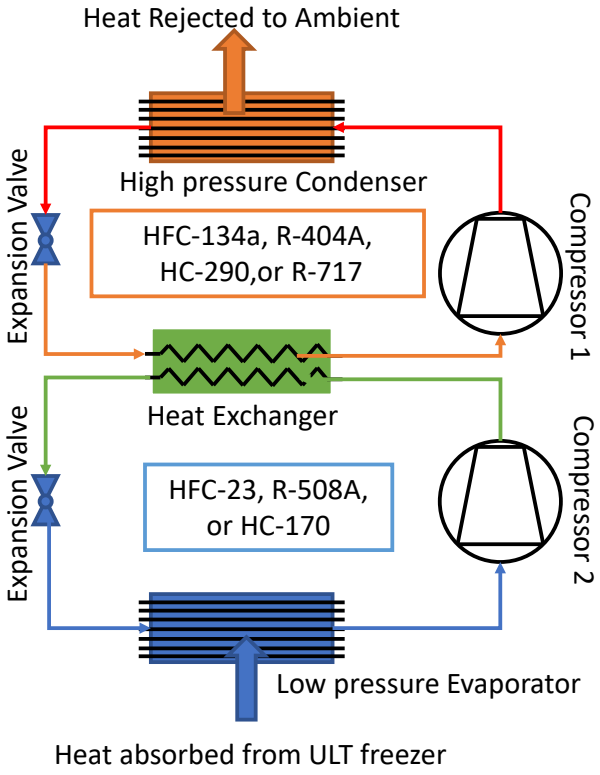

Figure 4-1 Cascade refrigeration system for ultra-low temperature with common primary and secondary refrigerants

Cascade cycles using HC-170 in the low stage and HC-290 or R-717 in the high stage have been in operation for many years now. In laboratory systems, freezers for research have been using HC-170 in the ultra-low temperature stage and HC-290 in the high stage as a standard since the middle of the 1990's. These systems are considered highly reliable and very efficient. Table 4.1 summarizes the different refrigerants used in ULT applications for the low and high stages of the cascade cycle.

Table 4.1 Refrigerants used in the low temperature stage of cascade cycles.

Refrigerant Family	Refrigerant Number	Refrigerant Composition (Mass %)	Safety Class	Bubble Point	Dew Point	Glide (K)	GWP
HFC based	23	HFC-23	A1	-82.0	-82.0	0.0	14800
	508A	HFC23-116 (39.0/61.0)	A1	-87.4	-87.4	0.0	11600
	508B	HFC23-116 (46.0/54.0)	A1	-87.0	-87.0	0.0	11700
low GWP blends	469A	R-744/32/125 (35.0/32.5/32.5)	A1	-78.5	-61.5	17.0	1357
	472A	R-744/32/134a (69.0/12.0/19.0)	A1	-84.3	-61.5	22.8	353
	473A	R-1132a/23/744/125 (20.0/10.0/60.0/10.0)	A1	-87.6	-83.0	4.6	1830
HC	170	HC-170	A3	-87.6	-88.6	0.0	1.4
	1150	HC-1150	A3	-103.8	-103.8	0.0	4
	50	HC-50	A3	-161	-161	0.0	30
R-729 (Air)	Conventional	N_2/O_2 (80.0/20.0)	A1	-194.6	-192.1	2.5	0
	Dry air	$N_2/Ar/O_2$ (75.57/0.012/23.16)	A1	-194.3	-191.5	2.83	0

Source: RTOC, 2018

In addition, a room-to-room two-temperature configuration can be devised to develop efficient ULT freezing solutions. A large external cold room is designed to operate at -20°C and this large room can

house a mix of ULT and low temperature storage spaces. The ULT space would be equipped with a dedicated vapor compression cycle-based type of equipment that rejects its heat to the -20°C space.

4.1.2 Equipment based on non-vapor compression

Air cycle systems have been proposed for larger cold stores at ULT temperature levels. The advantage of this type of system is that one does not have to use evaporators; therefore, there are no defrost problems, associated with evaporators. There are a couple of suppliers of these systems serving the market at present. At ULT levels, the efficiency of the air cycle is of a comparable magnitude as the one of the traditional vapor compression cascade cycle.

One of the options available on the market suggests a container frame with an anteroom and the storage located in the middle of the container. The air cycle is then placed at the other end of the frame.[34] The air cycle uses both a compressor and expander mounted on the same motor shaft, and an internal heat exchanger that contributes to reaching the low temperatures. The heat is eventually released to the ambient before the air goes back again through the internal heat exchanger and expander to the cold store.

Units operating using the reversed Stirling Cycle are also available on the market.[35] They can achieve an ULT of -86°C using hydrocarbon refrigerants without any need of a lubricating oil. They could be used for hub style or centralized storage facilities.

Alternatively, if an adequate electric grid is not present or not reliable, gas driven absorption systems (based on an ammonia/water solution) may be an option. This in turn requires stable supplies of fuel gas either from a pipeline, gas tank, or from supplies on a truck or other means of transport.

In remote areas, an option for transport and short-term storage of vaccines is the use of solar power-driven fridges. These systems are currently available in the market, where their development has been driven by several institutions (WHO, UN agencies etc.) [36], [37]. For isolated communities where knowledge about infections is difficult to collect, this technology may be less relevant.

4.2 Low and medium temperature applications (-22 to -20°C and 2 to 8°C)

There is a large number of freezers and refrigerators available on the market. Many of the older type units still use CFCs and HFCFs.[38] The main difference between domestic and professional equipment that is applied to achieve similar temperatures is the requirement for inside temperature logging and monitoring. The selection of refrigerants is not the main issue here, since the equipment will be using certain refrigerants that have either been procured locally or been imported (i.e., HFC-134a, hydrocarbons such as HC-600a or HC-290, or R-744).

Table 4.2 Refrigerants used for low to medium temperatures and in the high stage of cascade cycles

Refrigerant Family	Refrigerant Number	Refrigerant Composition (Mass %)	Safety Class	Bubble Point	Dew Point	Glide (K)	GWP
HFC	R404A	HFC-125/143a/134a (44.0/52.0/4.0)	A1	-46.6	-45.8	0.8	4200

	HFC134a	HFC-134a	A1	-26	-26	0	1360
HFO	R454C	HFO-1234yf/HFC-32 (78.5/21.5)	A2L	-46	-37.8	8.2	150
	R455A	HFO-1234yf/HFC-32/CO_2 (75.5/21.5/3.0)	A2L	-51.6	-39.1	12.5	150
HC	HC-600a	HC-600a	A3	-12	-12	0	<1
	HC-290	HC-290	A3	-42	-42	0	<1
CO_2	R-744 (CO_2)		A1	-78.5*	-78.5*	0	1

Source: RTOC, 2018
** Sublimation point*

5. Energy efficiency aspects for equipment used for vaccine storage

There is limited information on energy performance testing, MEPS and energy labels for laboratory refrigerators or freezers.[38] In [39], this note estimates the COP based on simple thermodynamic cycle calculations to be 0.62 for ULT applications (-70°C), 1.46 to 1.68 (-25 to -18°C), and 2.65 for medium temperature refrigeration applications (2°C). The TEWI estimates for vaccine cold storage over 10 years, assuming different temperature levels for the different vaccines, are shown in Figure 5-1. With the current world population of about 7.9 billion and the need for two Covid-19 vaccine doses in two semi-annual phases, this is assumed to require up to 70,000 refrigerators. The ten-year TEWI would vary from 1.5 to 5.8 Mt CO_2-eq. for ULT vaccines, 0.3 to 1.5 Mt CO_2-eq. for low temperature vaccines, and 0.2 to 0.6 Mt CO_2-eq. for normal temperature vaccines[39].

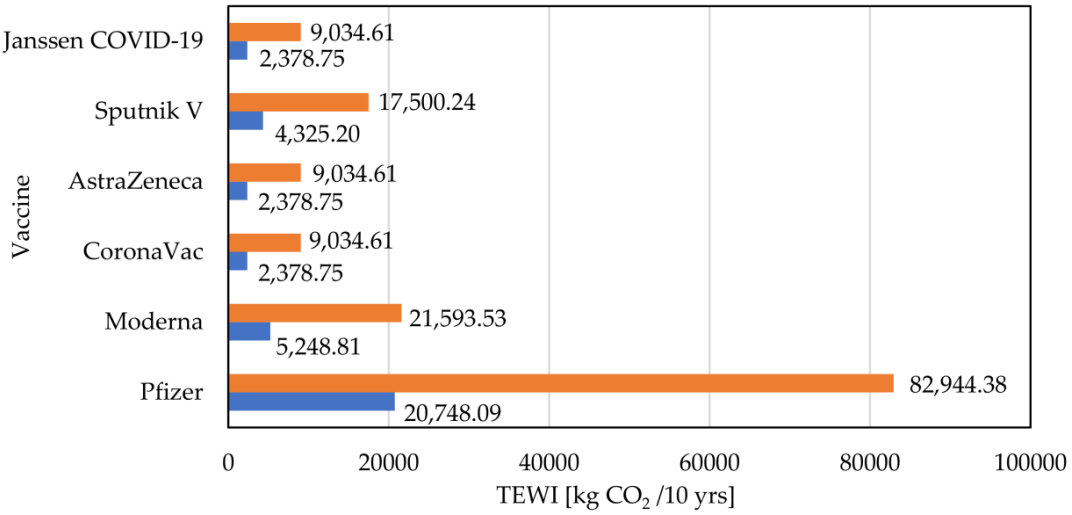

Figure 5-1 TEWI values of 100,000 doses vaccine refrigeration in Brazil and the USA for 10 years – Brazil in blue bars and USA in orange bars.[39]

5.1 Ultra-low and low (-70 to -20 °C) temperature cascade systems

5.1.1 Equipment using the vapor compression cycle

Auto cascade systems are widely available on the market. They are preferred due to their low initial cost. Unfortunately, these systems are relatively inefficient compared with cascade ULT freezers as shown in Table 5.1. Adequate cost-price estimates for the various ULT freezers could not be obtained due to the current prevailing competitive market conditions. Sales prices largely depend on the quantities ordered and special requests submitted by clients.

According to California Electronic Technical Reference Manual[40] HFC EnergyStar ULT freezers can save up to 40% compared with baseline systems. Furthermore, it was demonstrated that HC EnergyStar ULT freezers can reduce energy consumption further by 15 to 50% compared with HFC EnergyStar ULT freezers. Field tests showed that HC units can reduce energy consumption by 22 to 34% compared with high efficiency HFC ULT freezers[41].

5.1.2 Equipment using other cycles

Air cycle machines have demonstrated high COPs for ULT applications for small size capacities (around 5 kW). Third party testing[42] has demonstrated that open air cycle equipment with a humidity extraction system has a higher full-load maximum COP than a big (over 100kW) optimized cascade system or a liquid nitrogen system, at temperatures below -70°C when operated at heat sink of 30°C ambient temperature. The study also showed that at -80°C, the air open-cycle system's full-

load maximum COP is 0.44, the cascade's is 0.40, and the liquid nitrogen's (directly from production) is 0.20.

Table 5.1. Energy Efficiency for ULT freezers

ULT Freezer type	Refrigerant	Volume (litre)	Daily energy consumption (kWh/day)	Normalized energy consumption (Wh/day-litre)	Relative Performance
Cascade 1	HC	729	7.06	9.7	100%
Cascade 2	HC	729	7.87	10.8	111%
Cascade 3	HFC	815	17	20.9	215%
Cascade 4	HFC	793	17.8	22.4	231%
Stirling	H_2/C_2H_5	780	6.67	8.6	89%
Auto cascade 1	HC blend	556	16.3	29.3	302%
Auto cascade 2	HC blend	300	5.2	17.3	178%
Auto cascade 3	HC blend	74	5	67.6	697%

5.2 Temperatures between -20 to 10 °C

5.2.1 Equipment using the vapor compression cycle

For these low temperature applications, HC-290 has been found to be more efficient than R-404A due to the lower compression ratio at the same working conditions. Furthermore, compressor manufacturers have focused their attention on the improvement of HC-290 compressors while the R-404A compressor efficiencies trailed.

For medium and high temperature applications, HC-600a has been concluded to be more efficient than HFC-134a, mainly due to the lower compression ratio at working conditions. Furthermore, compressor manufacturers have continued to develop HC-600a compressors while the development of HFC-134a compressors has received less attention since the 2000s.

6. Technology availability (need for capacity building)

Availability can be considered from a refrigerant, equipment, and trained personnel point of view. Particular obstacles to availability exist for the vaccine distribution chain that are not experienced in the rest of RACHP sectors. Overall, there is a need to expand capacity in a way that promotes equitable access and leaves no one behind.

6.1 Refrigerants

Some of the refrigerants used for ULT equipment are usually not used in many countries. Fortunately, the servicing requirements are relatively limited for newer equipment; consequently, the refrigerant consumption is not projected to be high. The responsibility for the availability of refrigerant amounts for service, while convincing importers to import these refrigerants (which might not be in big demand), could be part of the Extended Producer Responsibility (EPR) or treated as an essential import. The procurement of thousands of systems for the cold chain also can be considered as a unique chance for technology upgrading and environmental and climate resilience by including certification of technicians into the contracts.

6.2 Equipment

Pharmaceutical refrigeration has specific attributes: delivering temperature accuracy, uniformity of interior temperature throughout the refrigerated space, temperature-time history, data logging, maintenance & temperature recovery after door opening, ambient tolerance, and microprocessor monitoring.

Equipment sizes depend on the number of vaccine doses to be stored. Different types of countries need various sizes of freezers which might create a problem in the uniformity of supply. Equipment for storage facilities will encounter the same challenges as other elements of the cold chain: age, leakage, power stability, and availability.

The age of any equipment can also be measured in terms of the refrigerant used in the equipment. According to data (2009-2017) from 81 countries across all 6 WHO regions, between 12-16 percent of all cold chain equipment still contains CFC refrigerants[43] even though a global ban on the use of CFCs has been in place since 2010.

Different applications need different approaches, for example, for vaccines shipped in dry ice containers, there is a need for a facility to make dry ice close to the storage facility. Manufacturers are normally reluctant to export their newer technologies to developing countries to avoid potential warranty and reputation problems; the need for ULT vaccine refrigeration might make the process faster. Equipment for essential use is normally exempted from complying to standards for energy efficiency. However, because the larger part the equipment used for vaccine transportation and storage is covered by cold chain Minimum Energy Performance (MEPS) and Energy Efficiency (EE) standards, it should not pose a problem to availability.

Case Study – Australia

ULT storage are essential for central hubs that are located based on population distribution. It important to locate central ULT storage hubs close to the airport where imports arrive.

Australia's vaccine cold chain has 3 central ULT hubs; each constituting of appropriate number of ULT fridges based on nearby population. Each ULT fridge holds 140,000 doses and is about twice the size of a large domestic refrigerator-freezer.

The doses are later transported to over 200 cold storage facilities in dry ice boxes at -70°C. At the point of vaccination, vaccines are thawed to 2 – 8°C and should be administered within 5 days.

6.3 Trained personnel

Unlike the cold chain, the users of vaccine storage equipment are paramedical and medical. They will most likely have to work with this type of equipment for the first time and may not have basic technical knowledge how to operate the equipment. Maintenance and reliability of vaccine storage equipment relies upon the competence of the technicians who are servicing that equipment. This equipment often uses technology that differs from the conventional air conditioning and refrigeration systems. Therefore, technicians that are expected to work on vaccine storage equipment should receive dedicated training for the specific technologies involved. While training is always needed, circumstances might not allow for the proper training of all users, nevertheless, efforts should be made to ensure it will be put in place. Mistakes made when servicing that type of equipment have potentially far-reaching consequences, far beyond the loss of cooling capacity.

6.4 Article-5 specific challenges

The efficiency of the whole vaccine cold chain depends on its ability to deliver vaccines in the last mile towards remote locations where service points might not be available. For example, most chest freezers are designed as per the standard IEC 62552 with Class T requirements to operate in ambient temperatures up to 43°C. Few manufacturers design freezers for outdoor applications up to 46°C. This can pose a challenge when those freezers will be delivered to remote areas with high ambient temperatures where they must operate in a non-conditioned space.

Access to electricity, apart from reliable power, may require equipment that is battery operated. The technology elements exist; however, it needs to be developed and applied. Article 5 countries might experience some or all the challenges mentioned in the previous sections. Careful preparation and frequent checks are therefore needed at every step of the process.

7. Linkage to the Cold Chain

7.1 Overall situation in Article 5 countries and challenges for the COVID and other vaccines cold chain

Many low- and middle-income countries do not have a robust 2°C to 8°C cold chain for existing medical needs, neither do they have -70 to -80°C cold chains. At minimum, a Covid-19 vaccine requiring cold storage will require the most significant build-out of cold chains in the developing world ever, as long as ULT temperatures are considered.[44]

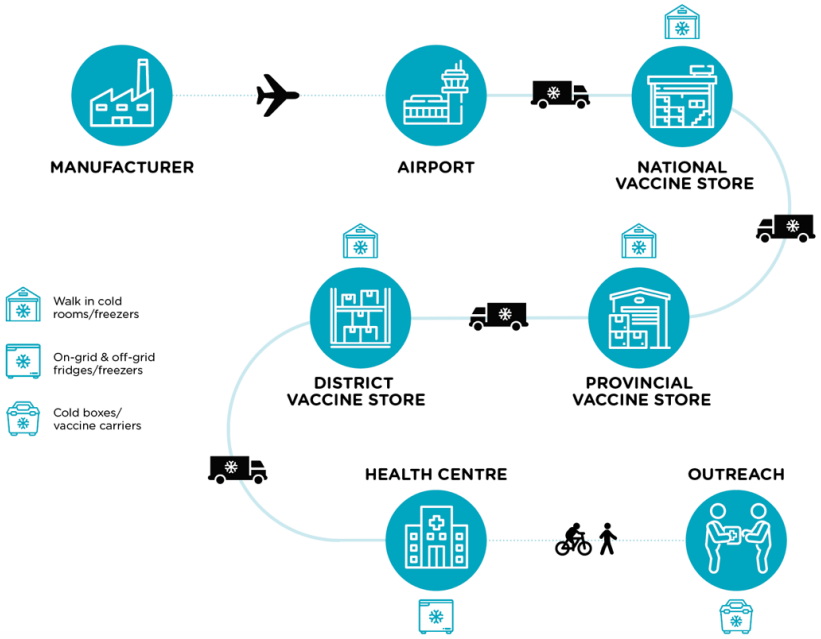

Figure 7.1 General structure of vaccine cold chain in routine immunization programmes. Error! Bookmark not defined.

The challenges to Article 5 countries are mainly in the availability of storage facilities for the right temperature level and the availability of a reliable power source to operate the refrigeration system. There is also the challenge of equitable access to remote locations. Vaccines are normally temperature sensitive, and their viability decreases as the ambient temperature increases. Figure 7-2 shows the relationship for the Oral Polio Vaccine (OPV) which has been well-managed and distributed globally.[45]. The vaccine vial monitor (VVM) temperature is the temperature at which the vaccine should discarded.

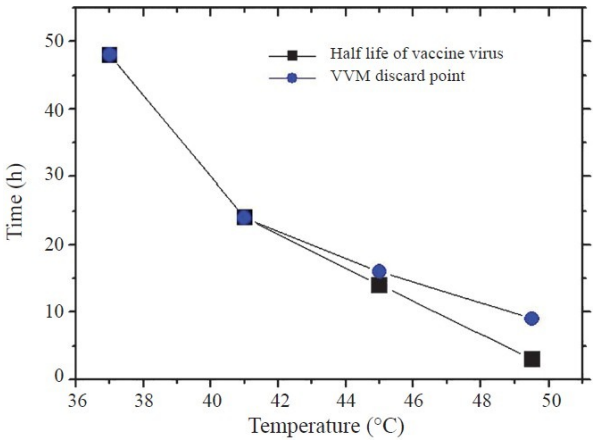

Figure 7-2 Half-life of vaccine virus compared to the discard point of vaccine vial monitors. Each point represents the time at which all bottles reach discard point. Error! Bookmark not defined.

Most countries do already have an existing vaccine cold chain for the temperature range of up to -20°C. However, these types of equipment are not so widely available than the ones for the temperate ranges of +2°C to +8°C. WHO Effective Vaccine Management (EVM) data from 81 countries collected between 2009 and 2017 indicates that cold chain storage equipment for -20°C is not available at the service point and district level. Even at the sub-national level, only 85 percent do have vaccine storage capacities for temperature levels around -20°C.[38]

In low and middle-income countries, a large proportion of the population live in rural, remote areas with geographical barriers, poor infrastructure — such as lack of transportation and bad road conditions — and where access to health and immunization services is generally limited. An estimated 25% of the 8 billion vaccines used globally every year – that is before the Covid-19 epidemic occurred- are lost due to transportation and storage problems[iv]. Covid-19 will accentuate the problem as the number of needed vaccines are tripling to around 25 billion. The cost of vaccine wastage due to exposure to temperatures outside the recommended range is estimated at USD 34.1 billion annually, a figure that does not include the physical and financial cost of avoidable illnesses with on-time delivery of effective vaccines.[46]

Regarding temperature reliability, estimations from 2013 suggest that 46 percent of health facilities in India and more than 30 percent of healthcare facilities in Sub-Saharan Africa do not have access to electricity.**Error! Bookmark not defined.** Data available from a WHO assessment reveal that many facilities across the vaccine cold chains, especially the service points, suffer from an unreliable energy supply, as shown in Figure 7-3.[47]

Furthermore,

1. only 2% of the vaccine cold chain is reported to be operating in optimal conditions,
2. 23% are outdated but functional,
3. 41% are poorly performing,
4. 14% are non-functional, and
5. the remaining 20% of the facilities are not (well) equipped.[38]

A recent study by DHL highlights the issues around equitable access. According to its estimations, the current vaccine cold chain can only deliver the vaccine at freezing temperatures to 2.5 billion people in around 25 developed countries. The number doubles to 5 billion if the vaccine would require the conventional temperature storage in the range of 2–8°C. Due to a lack of cold chain capacity, Africa, Asia, and South America cannot be readily supplied at scale to date. Furthermore, the current Covid vaccines are unlikely to reach the majority of Africa due to high ambient temperatures and the lack of a cold chain infrastructure.[48]

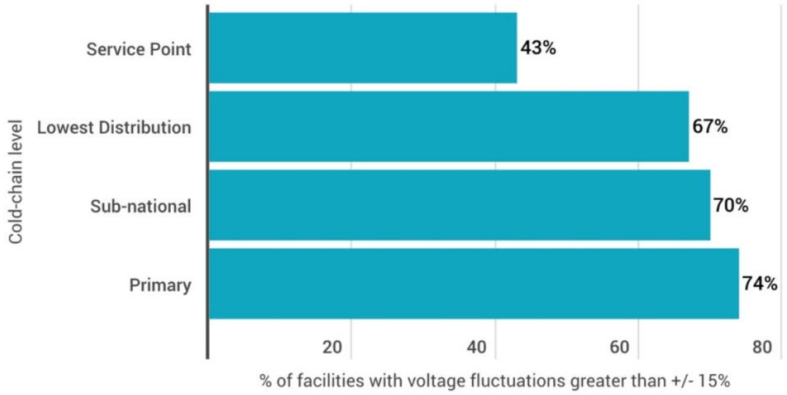

Figure 7-3 Facilities with voltage fluctuations greater than +/- 15% (%).[44]

[iv] The World Bank webinar on vaccine distribution February 2021

[49] Case study India

Serum Institute of India (Serum) and Bharat Biotech (BB) began dispatches of their vaccine consignments that require to be kept at 2-8 °C. Serum's initial vaccine consignment of about 1,088 kg left its Pune facility in special trucks for the city airport to be dispatched by air to 14 cities. BB dispatched its first batches of vaccines (each vial containing 20 doses) via air to 11 cities.

As they arrive to the airport, vaccines are transported to the National Vaccine Stores or the Government Medical Store Depots (GMSD) in Karnal, Mumbai, Chennai, and Kolkata. From these four nodal locations, the vaccines are then transported in refrigerated or insulated vans to state/provincial vaccine stores. India has 37 state vaccine stores, which are meant for bulk storage. All states have at least one state-level regional vaccine store. Uttar Pradesh has nine, Madhya Pradesh and Gujarat have four, Kerala has three while Jammu and Kashmir, Karnataka and Rajasthan have two each, as per Union Health Ministry data.

After that, state governments are responsible to ensure that the vaccine vials reach the eventual vaccination centre safely and with minimal or zero waste. Vaccines are then typically transported from state vaccine stores to district and sub-district stores and primary health centres. District stores are temperature controlled. As on December 6, there were 28,932 cold chain points, 240 walk-in coolers, 70 walk-in freezers, 44,226 ice lined refrigerators, 40,792 deep freezers and 294 solar units, according to the National Cold Chain Management Information System (NCCMIS).

During the entire movement of the vaccine, information is fed on the Co-WIN (Covid-19 Vaccine Intelligence Network) digital platform and mobile application. Co-WIN is an extension of eVIN (electronic Vaccine Intelligence Network) software that has been in use for India's universal immunisation programme, covering children and pregnant women. During transportation, real-time information is fed into the digital platform on quantity of the vaccines and storage temperature. This helps programme managers flag relevant authorities in the event a particular storage point has less than ideal temperature.

The last mile delivery of the vaccines happens in 'passive' equipment such as iceboxes and vaccine carriers that do not require electricity. All other previous storage points either run on electricity or are solar powered. There is a provision to check temperatures in iceboxes and carriers as well.

India's administrative coverage data show that the total number of doses administered under the Universal Immunisation Programme (UIP) in 2019 was around 400 million. Assuming a packed vaccine volume per dose of 5.2 ml, the storage volume required for 400 million doses equates to around 2 million litres. If India were to achieve herd immunity, assuming a herd immunity threshold of 65 per cent, then the required vaccine volume is around 9.5 million litres. ***Error! Bookmark not defined.*** *This is almost four times what is normally needed.*

7.2 Capacity Building

An increased focus on the whole vaccine cold chain to cover the widespread global demands as initiated by Covid-19 is an absolute must. For the coronavirus vaccination, it is anticipated that up to 70 percent of the global population will need to be vaccinated, in most cases two times within a few weeks and maybe even a third time after a longer time frame. Although many countries have an existing cold chain for conventional vaccines, it is unlikely that the infrastructure of many Article 5 countries is prepared to handle such a widespread and vast number of doses. Consequently, most countries are requiring rapid improvements of their vaccine cold chains and will therefore need to imminently acquire large numbers of new facilities and equipment. Since both the cold chain and the vaccine distribution chain are still based on some HFC refrigerants covered by the Kigali Amendment, Parties to the Montreal Protocol are expected to have an interest in extending HFC phase-down programmes in relation to the vaccine distribution chain.

It needs to be mentioned here again that, while a lot of equipment still uses high GWP refrigerants, equipment using low GWP refrigerants is widely available.[38]

8. Concluding remarks

Many vaccines require a proper cold chain, including adequate temperature control during manufacturing, transport, and distribution (via national distribution centres). This is a major challenge in many parts of the world that has been particularly highlighted by the current Covid-19 pandemic. The SARS-CoV-2 virus outbreak can be considered as a turning point in establishing reliable and extended vaccine cold chains, including for ultra-low temperatures. The pharmaceutical industry already has a very well-established cold chain in place with staff that knows how to tackle ongoing shipments and possible temperature problems. There might currently still be a challenge in how rapidly one can get new, well-trained people employed for handling the various (types of) vaccines at different places in the cold chain. In general, the estimated HFC-23 emissions associated with the Vaccine Cold Chain are expected to be 3 orders of magnitudes lower than the current annual emissions.

While most current vaccine cold chains rely on technologies available on the market, the use of ultra-low temperature equipment using high GWP HFC refrigerants and/or their availability and accessibility in Article 5 countries present a clear challenge to the community. The challenges to developing countries are mainly in the availability of storage facilities for the right temperature level and availability of a reliable power source to run the refrigeration system. A relatively new challenge lies in the establishment of procedures to get vaccines requiring certain temperatures during transport and local storage from the producer to the point of inoculation without damaging the vaccines during transport and storage.

The Covid-19 pandemic has stimulated a lot of research and development where it concerns the application of mRNA and other protein- based vaccines for a number of diseases. One recent example is the use of proteins from the salvatory glands of mosquitoes for the vaccinating against malaria; these proteins need to be stored at ultra-low temperatures again. It is also possible that, in future, Covid-19 vaccines will have to be taken regularly, particularly when new, highly transmittable Covid-19 variants will go around. This might require continuous use of ultra-low temperature storage means. In case this would become the trend for the (near) future, it will be essential to build a permanent infrastructure, which does currently not exist.

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