Ren, T, Ren, J, Matellini, DB and Tammas-Williams, S

Characteristics, Challenges, and Opportunities of Vaccine Cold Chain

http://researchonline.ljmu.ac.uk/id/eprint/16405/

Article

Citation (please note it is advisable to refer to the publisher's version if you intend to cite from this work)

Ren, T, Ren, J, Matellini, DB and Tammas-Williams, S (2021) Characteristics, Challenges, and Opportunities of Vaccine Cold Chain. Global Business and Management Research: An International Journal, 13 (3). pp. 33-43. ISSN 1947-5667

Global Business and Management Research: An International Journal
Vol. 13, No. 3 (2021)

Characteristics, Challenges, and Opportunities of Vaccine Cold Chain

Tianran Ren*
*Department of Mechanical and Maritime Engineering, Liverpool John Moores University, Liverpool, United Kingdom
E-mail: T.Ren@2020.ljmu.ac.uk

Jun Ren
Department of Mechanical and Maritime Engineering, Liverpool John Moores University, Liverpool, United Kingdom

Ben Matellini
Department of Mechanical and Maritime Engineering, Liverpool John Moores University, Liverpool, United Kingdom

Sam Tammas-Williams
Department of Mechanical and Maritime Engineering, Liverpool John Moores University, Liverpool, United Kingdom

*Corresponding Author

Abstract:
Purpose: Main attention regarding vaccine supply chain has been drawn on strategic decision level with a limited concentration on tactical and operational levels. Temperature maintenance along the vaccine supply chain remains to be one of the challenging logistical problems. The purpose of this paper is to understand the characteristics, challenges and opportunities of the vaccine cold chain today and how emerging technologies (e.g. vaccine vial monitoring, thermostable vaccines and new packaging systems) affect its development and implementations that can be done before the availability of new technologies.
Design/methodology/approach: Literature review is done on the topic of vaccine cold chain, with the key search word of vaccine cold chain. Supporting resources include the official websites of the World Health Organisation (WHO) and Covid-19 vaccine manufacturers.
Findings: The gap between the existing literature and the potential requirements; Trend to future research on vaccine cold chain.
Research limitations/implications: Contents about strategic decision level of vaccine supply chain are excluded.
Practical implications: Pending for empirical studies; Does not consider cost-effectiveness and environmental impacts on the vaccine supply chain.
Originality/value: The number of vaccines has expanded in the past years due to improved immunization programs across the world, and the vaccines for the Covid-19 pandemic have the nature of high demand and pressuring time requirement, posing a need for improvement on the existing cold chain. Many existing pieces of literature on this topic are case-specific or scenario-based, and more general operation management insights are important as well, which can be beneficial to the decision-makers in the vaccine supply chain.

Keywords: Vaccine, transportation, storage, cold chain, packaging
Category: Conceptual Paper

1. Introduction

The vaccine supply chain contains vaccine development, storage, transportation, and administration. The vaccine cold chain mainly focuses on the storage and transportation of vaccines. Two major components of a cold chain are cold chain infrastructures, including active and passive cooling devices to control the cold chain temperature and cold chain management systems, including temperature monitoring/indicating of the cold chain (Cavallaro et al., 2018).

The major task of a cold chain is to control and monitor the temperature during transportation and storage (Cavallaro et al., 2018). Two modes of cooling for cold chains are active and passive cooling/refrigeration. Active refrigeration refers to refrigeration equipment that controls the temperature, such as freezers and refrigerated cars. Passive refrigeration uses cold storage to maintain the temperature, such as cold storage boxes, cold storage bags, incubators and iceboxes, etc. Cold storage boxes/bags sometimes contain phase change materials (PCM), often combined with the use of insulation materials, such as polystyrene. PCM is a new trending passive cooling material, receiving great research attention in the field of cold chain transportation (Zhao et al., 2020). The cold storage boxes or incubators are often used in air transport during emergencies or in remote outreach due to their flexible attributes compared to conventional active refrigerators (Li et al., 2020).

Besides active and passive cooling of the vaccines, cold chain regulatory systems are also needed to keep track of the temperature during cold chains. It is important to monitor the temperature continually during vaccine transportation and storage since the refrigerator or the cold storage box may not always succeed due to adverse events like power outages and improper handling of humans, etc. Some common ways of cold chain temperature monitor are the uses of electronic temperature sensors inside containers, passive labels or tags indicating the shelf-life of the products(Zhou and Chakrabartty, 2017).

For vaccine cold chain, exposure to temperatures outside the recommended temperature range can cause great damage to the vaccines. Exposure to heating can damage vaccines by changing the tertiary protein structure, dissociating polysaccharides from protein carriers in polysaccharide conjugate vaccines and reducing live-attenuated vaccines' infectiveness. Usually, the impact of heat damage is cumulative, and one coping method is the use of Vaccine Vial Monitoring (VVM), in which a sticker or label is affixed to a vaccine vial and aims to estimate the remaining shelf life of vaccines when exposed to continuous heat (Chen and Kristensen, 2009). The mechanism of VVM is the color changes based on the Mean Kinetic Temperature (MKT), which indicates the total thermal stress vaccine experiences in a period (Ross et al., 2020).

Freezing of vaccines could also affect the vaccines adversely, e.g. causing clustering of the adjuvanted particles, antigen degradation and molecular changes of vaccines, which poses additional stress to the cold chain (Kurzątkowski et al., 2013). The WHO Shake Test is designed to detect if freezing happens in a vaccine vial. During a Shake Test, first, one vial from a batch is selected as the control vial. Then it is frozen overnight and thawed after. Second, another vial is selected for testing, and then a visual comparison of the sedimentation rates of the two vials (control and testing vials) is made. When the sedimentation rate of the test vial is the same or greater than the controlled one, it is an indication that freeze/thaw occurs in this test vaccine vial. In this case, the whole batch of vaccines should be abandoned (*World Health Organization. Module 2: The Vaccine Cold Chain.*, 2015).

Global immunization programs have expanded in the past few years, increasing the need to expand or upgrade related infrastructure and the vaccine supply chain management systems. Administration and distribution costs of vaccines are usually greater than the cost of vaccine production. Many vaccines require cold chains, but some still struggle to maintain and monitor the required cold chain (Bajrovic et al., 2020). The impact of the sudden occurrence of a pandemic, such as the Covid-19 pandemic, can pose an additional threat to the already fragile cold chain (Li et al., 2020).

The structure of this paper includes the introduction, literature review, method, results and findings and conclusions.

This paper aims to investigate the characteristics, challenges and opportunities of the current vaccine cold chain. The literature review is done to investigate innovations regarding the vaccine cold chain in the last five years (2016 to 2021).

2. Literature Review

Characteristics and key issues of the vaccine supply chain were discussed by Duijzer et al. (2018) and Chandra et al. (2019). Duijzer et al. (2018) identify three characteristics of the vaccine supply chain: both demand and supply sides have high uncertainty; suppliers, public health organizations and end-user have misalignments of objectives and decentralized decision making; it is a complex and time-pressuring decision-making process (Duijzer et al., 2018). Chandra et al. (2019) identified 25 key issues in the vaccine supply chain of developing countries. Key operational issues include geographical distance, inventory management, vaccine stock-outs and monitoring of vaccine cold chain, etc. It shows that more innovated and digitalised cold chain equipment and technologies can improve vaccine coverage (Chandra and Kumar, 2019). The vaccine cold chain concentrates on the transportation and storage segments of the vaccine supply chain, involving cold chain cooling infrastructures/devices and temperature monitor systems.

Different vaccines have different heat and freeze sensitivity when exposed to the temperature outside the recommended range. Kartoglu and Milstien (2014) plot graphs of heat sensitivity versus freeze sensitivity of vaccines and categorized the vaccines into two main types: live vaccines, made of weakened virus or bacteria, and inactivated vaccines, made of the inactivated virus typically with adjuvants. Heat sensitivity depends on the structure of antigen for live vaccines, whereas freeze sensitivity links to additives and adjuvants for inactivated vaccines. Live vaccines are both heat and freezing-sensitive, whereas inactivated vaccines are relatively heat-stable but freeze-sensitive (Kartoglu and Milstien, 2014). However, emerging vaccine manufacture innovations have made it hard to categorize vaccines into simple heat/freeze sensitive groups.

Because freeze sensitivity depends on the additives and adjuvants in vaccines and many vaccines contain adjuvants, the research attention has shifted from heat to freeze damage on vaccines (Dipika M. Matthias et al., 2007). The first literature review on vaccine freezing was reported in 2007, and a following updated literature review regarding the freezing issue in the vaccine cold chain was conducted by Hanson et al. (2017) in 2017. In both reviews, temperature monitoring studies are collected, which unit of analyses (refrigerators, cold boxes, etc.), cold chain segments (storage, transport, outreach), sample sizes and occurrence of temperatures below freeze threshold are reported and analyzed. The number of articles concerning vaccine freezing has increased, from 33 studies in 2007 to 45 studies in 2017, which shows rising awareness of the freezing issue in the cold chain, mainly due to improved monitoring technologies and more rigorous monitoring techniques implemented.

There are still challenges with the vaccine cold chain. First, cold chains do not always function perfectly, and inadequate temperature maintenance can damage vaccine potency. Second, the cold chain infrastructure and facilities are limited or dated in some regions due to lack of power or fuel, etc. Third, the cold chain equipment is usually expensive and the effort of cold chain monitoring is great (Bui-Le et al., 2021; Chen and Kristensen, 2009). To tackle these obstacles, many methods have been proposed, such as freeze-drying, immobilization of viral particles onto carbohydrate glass, the addition of sugars to vaccine formulations and encapsulation in silica, etc. but still require temperature control of 2 to 8°C or following complex reconstitution processes. Therefore, cold chain infrastructure upgrades and temperature monitor regulations are still important for vaccine cold chain development. Understanding how new technologies and innovations affect the vaccine cold chain development is also important.

Another characteristic of the vaccine cold chain is that different packaging configurations, such as the stacking of packages, show different cooling maintaining behaviors (Ng et al., 2020). This is an issue applied to almost all of the cold chain products, not only to vaccines but also to other perishable cold chain products, such as fruits, vegetables, meat, etc. Also, the increase of detection of adverse events in the cold chain does not always relate to a poor cold chain system but sometimes it is due to rigorous monitoring. Moreover, temperature excursions do not always lead to vaccine damages. It suggests that a single temperature excursion or repeated heat exposure cannot guarantee serious damage to vaccines (Goldwood and Diesburg, 2018). Ross et al. (2020) uses the mathematical principles backing VVMs on real, continuous temperature monitoring data in Africa, and shows that heat exposure or power outages in a time duration may not affect the vaccine shelf life remaining, unlike what is normally assumed. One problem about VVMs is their inability to accurately detect freezing since freezing is a complex process. Repeated cycles of freeze-thaw are sometimes needed for vaccines to lose their potency (Chen and Kristensen, 2009). Therefore, decision-making in vaccine cold should be data-driven instead of simple temperature indicating.

3. Methodology

The method used in this research is literature review, and the main database used is the web of science database. The search keyword used is a combination of ‘vaccine’ and ‘cold chain’. Other resources used are websites of the World Health Organisation (WHO). Snowballing technique is used to include any additional useful resources.

For the collection of papers regarding innovations of vaccine cold chain in the past five years (2016 to 2021), an initial result of 340 papers was collected searching ‘vaccine’ and ‘cold chain’ in the web of science. The next step was to select any studies related to vaccine cooling systems and temperature monitor in the vaccine cold chain after reading titles and abstracts. The studies about vaccine formulations, such as vaccine drying or solvent-free vaccines and about temperature/heat simulations, were excluded in this paper. Then studies containing innovative methods were further collected, which an innovation refers to come up with a new method for the first time with promising testing results and potential applications in the cold chain. Eventually, 13 papers were collected.

4. Findings and Discussion

4.1. Cold chain cooling systems

Most research attention has been drawn to the field of passive cold storage systems (6 out of 13). Innovative passive cooling packages increase the number of possible alternatives for the packaging/containers used in the vaccine cold chain. These innovative passive cold storage systems have pros of low cost and low energy usage compared to traditionally powered refrigerators. Also, it is easy to be carried, suitable for vaccine distribution in rural areas where the power lacks and the choices of transportation are limited. (Yin et al., 2020; Zhao et al., 2020). The PCM-based packaging system is one popular topic. Zhao et al. (2020) and Yin et al. (2020) both develop vaccine transporting cold storage systems by using PCM coupled with other insulation materials, which are usually polymer materials or card boards. The combined use of PCM and other insulation materials can increase the temperature maintenance property than the use of simple insulation material (Yin et al., 2020; Zhao et al., 2020a). Dao et al. (2018) use N-Tetradecane as the PCM material for vaccine cold chain PCM packaging boxes, which shows better temperature maintaining behavior than the use of water. Besides the applications of PCM, other materials are considered to be used as passive packaging boxes for vaccines during the cold chain as well. Lugelo et al. (2020) design several locally made passive cooling devices, and one of them, called ‘Zeepot Clay’, has a cost of $11 per unit showing great temperature maintenance behaviour. A field test (12-month phases) indicates this ‘Zeepot Clay’ device can maintain below 26°C when the ambient temperature is 42°C. The low-cost and easy manufacture make it a promising alternative passive cooling packaging choice for the vaccine cold chain. More suitable materials are to be explored, and their performances in all dimensions (technically, economically, environmentally, etc) should be further assessed.

Some vaccines require an Infection and Treatment method, in which the live parasites are injected together with the vaccine, and the live parasites need cold chain preservations as well. Liquid nitrogen is used for the low-temperature maintain of the live parasites concurrently injected with the East Coast fever vaccines. An alternative cold chain for storing and transporting East Coast fever vaccines uses a dry ice cold chain system replacing the liquid nitrogen. In vitro assessment experiments on East Coast fever vaccine stabilate (T.parva) found that the dry ice system can maintain a temperature of -80°C for 30 days (Atuhaire et al., 2020). The use of dry ice is a good substitute in logistic applications but its environmental impact need further evaluations.

Apart from passive cold storage systems, innovations in active cooling systems, e.g. refrigerations, are also found. To reduce temperature excursion risks, water bottles are used in domestic refrigerators as a thermal ballast. But how variable thermal ballast loading affects refrigeration behavior has not been studied before. Chojnacky and Rodriguez (2020) find that 15% of the total refrigerator volume can maintain vaccine temperature at 2°C to 8°C for 4 to 6h during power outage events. Innovative designs of refrigerators can lower temperature excursions, but they may not perform well in other risk events, which further studies are needed. Absorption cooling is another cooling technique that uses zeolite as the adsorbent and heat energy to maintain a temperature of 2°C to 8°C. Solar energy can be used as the source to heat zeolite. Nasruddin et al. (2018) study the behaviors of solar heaters that can be used as portable vaccine coolers. This portable vaccine cooler can be folded and carried easily, suitable to be used in rural areas or during emergencies. Another portable cooling device designed by Hassaan-Younis and Haroon-Ur-Rashid (2018) uses the Peltier module, a solid-state device based on semiconductor conjunctions, to design an automatic temperature-controlled portable cooling cabinet. This cabinet is cost-efficient and environmentally friendly compared to conventional vapor compression cooling refrigeration systems. One of the important things for active refrigeration is the power usage. Since the risk of the poor performance of active cooling systems during power outages, the use of combining active refrigeration and suitable passive cooling systems, such as the PCM packaging, is one good solution, which more detailed empirical studies are needed.

Table 1: Vaccine cold chain cooling system innovations from 2016 to 2021 Jan

Innovation description	Active/Passive cooling system	Temperature maintained	Reference
Use of dry ice replacing liquid nitrogen in cold chain	Passive	80°C for 30 days	(Atuhaire et al., 2020)
Development of PCM based on Tetradecane (TD) and lauryl alcohol (LA), coupled with expanded graphite (EG)	Passive	2 - 8°C for 50.02h	(Zhao et al., 2020b)
Development of PCM based on paraffin/SiO2 aerogel, coupled with polystyrene board	Passive	Maintain time increased by 99 times compared to with only insulation board.	(Yin et al., 2020)
Development of a passive cooling device (PCD), 'Zeepot Clay'	Passive	Maintain below 26°C at an ambient temperature of 42°C.	(Lugelo et al., 2020)
Design of a thermal ballast using watering bottles in domestic refrigeration	Active	2 - 8°C for 4 to 6h during power outages	(Chojnacky and Rodriguez, 2020)
Design of solar heater for the regeneration of adsorbent (zeolite) chamber	Passive	-	(Nasruddin et al., 2018)
Design of automatic temperature controlled portable cooling cabinet	Active	Achieves 2°C within 30 mins	(Hassaan-Younis and Ur-Rashid, 2018)
The use of a separate refrigerator for cooling packs	Active	-	(Goldwood and Diesburg, 2018)
Development of n-tetradecane as insulation materials for vaccine packaging box	Passive	-	(Dao and Suk, 2017)

4.2. Cold chain temperature monitoring

Besides cold chain cooling systems, temperature monitoring is also essential for keeping a cold chain work efficiently. Temperature indicating materials, which change colours at temperature excursions, are important for temperature maintain because it is the way of telling whether the cooling system has worked during cold chains. A new temperature excursion indicator material is developed based on the solution of photochromic spirogyra compounds dissolved in a mixed solvent with a critical phase change temperature at 8°C, suitable for vaccine transportation since 2°C to 8°C is the WHO-recommended vaccine cold chain temperature range for many vaccines (Gao et al., 2020). Since each the time requirements of different vaccines are different, materials with different phase change temperatures can be tested and used for suitable vaccines as indicators during cold chains.

New temperature monitor techniques, such as self-powered sensors and remote monitoring, show promising potentials to be used in vaccine cold chains. Temperature monitor devices usually require continuous power supply during cold chains and can be designed integrally on the transportation packages. Self- powered sensors can alleviate the power supply burden greatly. Zhou et al. (2017) and Cavallaro et al. (2018) both design temperature monitoring devices for vaccine cold chains. Most of the monitor devices are attached to the packaging containers, but Zhou et al. (2017) propose a self-powered sensor that can be embedded with passive RFID tags and can be integrated with packages. The temperature sensitivity of this sensor is tested to be 1.5mV/◦C over a monitoring duration of 100 hours, suitable to be used in cold chain transportation. A study by Cavallaro et al. (2018) proves the feasibility to implement remote temperature monitoring devices (RTMDs) in Haiti, and suggests RTMDs could be a good refrigeration option during high volumes of vaccines or lack of conventional refrigerators.

Finding temperature excursion events is important; however, not all temperature excursions lead to vaccine damages. Therefore, the detection of real harm caused is important. Both excessive heating and freezing of the vaccines can cause great harm to the vaccines, and the focus was on heat damages before 2007. But the number of freeze-sensitive vaccines, e.g. DTP-hepatitis B, liquid Hib, and influenza, has grown these years, needing more attention in this field (Hanson et al., 2016). WHO Shake Test is often used for vaccine freeze detections but it has several limitations, e.g. poor accuracy. An alternative Shake Test is designed by Briggs et al. (2020), using water proton Nuclear Magnetic Resonance (wNMR) relaxometry for aluminum adjuvanted vaccines. Conventional WHO Shake Test depends closely on visual observations which can be hard to make when the liquid volume inside the vial is small or when there is a label on the vial. Since variations exist among all the vials in a whole batch, the WHO Shake test may not be always accurate, and more refined methods are needed (Kartoglu et al., 2010). The working principle of this wNMR method is that freeze/thaws inducing aluminum particle cluster in vaccine vials, which is different from vials that experienced no freeze/thaw events, can be detected by wNMR signals. This wNMR measurement is quantitative, fast(10-30s per vial), not based on human judgments and noninvasive to the vaccines, serving as a good alternative method to the WHO Shake test for vaccine freeze detection (Briggs et al., 2020).

A vaccine cold chain normally contains both cooling devices (active and passive) and temperature monitor systems (Zhao et al., 2020). It is important to assess the overall cold chain performance instead of the single components of it. The emerging new techniques should be further tested within integrated cold chain systems, and how each component affects each other requires further research. Nine studies regarding cold chain cooling systems and four studies regarding cold chain monitor and detection are analysed. The number of studies collected is lower than expected, highlighting the lack of attention in this field of research. It is also noticed that some research has been done in the area of vaccine formulations, e.g. nano-vaccines or solvent-free vaccines (Bui-Le et al., 2021; Chen et al., 2009). As the nature and properties of vaccines change, the way how cold chains work will be influenced. Therefore, the design of cold chains needs to improve and meet the requirements of the emerging new types of vaccines as well.

Table 2: Vaccine cold chain monitor and detection innovations from 2016 to 2021 Jan

Innovation description	Cold chain Monitor/ Detection	Characteristic	Reference
Water proton transverse relaxation rate by Nuclear Magnetic Resonance relaxometry (wNMR relaxometry)	Freezing variability test	Experiments on free/thaw on three freeze sensitive adjuvants	(Briggs et al., 2020)
Design of an accurate and low-cost thermochromism temperature indicator.	Temperature indicating material	The designed indicator has critical phase change temperature at 8°C.	(Gao et al., 2020)
Feasibility of remote temperature monitoring devices (RTMDs) in Haiti	Temperature Monitor	Remote temperature monitoring devices (RTMDs)	(Cavallaro et al., 2018)
Development of a self-powered sensor monitoring time-temperature without external powering	Temperature Monitor	Self-powered time-temperature monitor	(Zhou and Chakrabartty, 2017)

5. Conclusion

This research studies the innovations on vaccine cold chain that have been designed and developed in the past few years, both on the cooling devices and temperature monitors/indicators from 2016 to 2021 Jan. New technologies and innovations in vaccine cold chain have emerged in the past few years. For example, PCM combined with other insulation materials show good temperature control behaviors and is a promising passive cold storage system candidate for vaccine cold chain. Characteristics and challenges of the vaccine cold chain are discussed in this study. It is found that improved temperature monitor techniques have helped reveal more issues because adverse events can remain hidden due to the lack of monitoring/indicating knowledge before. Therefore, increasing adverse events found does not always indicate poor cold chain setup but shows improved monitor techniques. It also shows that temperature excursions during transportation do not always lead to actual damage to the vaccines. Therefore, shelf life predictions can be a better indication than a simple temperature monitor. Another often overlooked finding is that the stacking of containers affects the cooling performance of the vaccine cold chain, which should be considered in cold chain simulation. But there are still challenges faced. For adjuvanted vaccines, freezing is still an ongoing issue causing damages to vaccines. A substitute freeze detection method to the WHO Shake test has been designed, called the wNMR relaxometry, which is less dependent on human visual observation and is faster.

This paper is beneficial for all the stakeholders in the vaccine cold chain to keep updated with the emerging innovative methods. How innovations affect the development of the vaccine cold chain is worth thinking about and researching further. One limitation of this research is that the papers collected regarding innovative vaccine cold chain techniques may not be enough (13 papers) to draw firm conclusions. The time frame should be extended (e.g. 20 years) to better identify the key trends and applications in this field. Also, innovations in vaccine formulations, such as solvent-free and microneedle vaccines can impact greatly on the existing vaccine cold chain because they require less or even no cold chain, which is excluded in this research. But their impacts on the cold chain should not be ignored. The cost of the innovations and public attitudes are not discussed in this paper, and further empirical studies are needed to better evaluate the current status and further trend of the vaccine cold chain.

Abbreviations

phase change materials (PCM)
Vaccine Vial Monitoring (VVM)
Mean Kinetic Temperature (MKT)
World Health Organisation (WHO)
water proton Nuclear Magnetic Resonance (wNMR)
Tetradecane (TD)
lauryl alcohol (LA)
expanded graphite (EG)
remote temperature monitoring devices (RTMDs)

6. References

Atuhaire, D. K., Lieberman, D., Marcotty, T., Musoke, A. J., Madan, D. (2020). An alternative cold chain for storing and transporting East Coast fever vaccine. *Veterinary Parasitology*, *288*, 109304. https://doi.org/10.1016/j.vetpar.2020.109304

Bajrovic, I., Schafer, S. C., Romanovicz, D. K., Croyle, M. A. (2020). Novel technology for storage and distribution of live vaccines and other biological medicines at ambient temperature. *Science Advances*, *6*(10), eaau4819. https://doi.org/10.1126/sciadv.aau4819

Briggs, K. T., Taraban, M. B., Yu, Y. B. (2020). Quality assurance at the point-of-care: Noninvasively detecting vaccine freezing variability using water proton NMR. *Vaccine*, *38*(31), 4853–4860. https://doi.org/10.1016/j.vaccine.2020.05.049

Bui-Le, L., Brogan, A. P. S., Hallett, J. P. (2021). Solvent-free liquid avidin as a step toward cold chain elimination. *Biotechnology and Bioengineering*, *118*(2), 592–600. https://doi.org/10.1002/bit.27587

Cavallaro, K. F., Francois, J., Jacques, R., Mentor, D., Yalcouye, I., Wilkins, K., Mueller, N., Turner, R., Wallace, A., Tohme, R. A. (2018). Demonstration of the Use of Remote Temperature Monitoring Devices in Vaccine Refrigerators in Haiti. *Public Health Reports*, *133*(1), 39–44. https://doi.org/10.1177/0033354917742119

Chandra, D., Kumar, D. (2019). Prioritizing the vaccine supply chain issues of developing countries using an integrated ISM-fuzzy ANP framework. *Journal of Modelling in Management*, *15*(1), 112–165. https://doi.org/10.1108/JM2-08-2018-0111

Chen, D., Kristensen, D. (2009). Opportunities and challenges of developing thermostable vaccines. *Expert Review of Vaccines*, *8*(5), 547–557. https://doi.org/10.1586/erv.09.20

Chojnacky, M., Rodriguez, A. L. (2020). Effect of thermal ballast loading on temperature stability of domestic refrigerators used for vaccine storage. *Plos One*, *15*(7), e0235777. https://doi.org/10.1371/journal.pone.0235777

Dao, V.-D., Suk, C. H. (2017). N-tetradecane/Water Emulsion as a Low-cost Phase Change Material for Efficient Packaging and Shipping of Vaccines. *Clean Technology, 23*(3), 325–330.

Dipika M. Matthias, Robertson, J., Garrison, M. M., Newland, S., Nelson, C. (2007). Freezing temperatures in the vaccine cold chain: A systematic literature review. *Vaccine*, *25*(20), 3980–3986. https://doi.org/10.1016/j.vaccine.2007.02.052

Duijzer, L. E., van Jaarsveld, W., Dekker, R. (2018). Literature review: The vaccine supply chain. *European Journal of Operational Research*, *268*(1), 174–192. https://doi.org/10.1016/j.ejor.2018.01.015

Gao, M., Lian, C., Xing, R., Wang, J., Wang, X., Tian, Z. (2020). The photo-/thermo-chromism of spiropyran in alkanes as a temperature abuse indicator in the cold chain of vaccines. *New Journal of Chemistry, 44*(36), 15350–15353. https://doi.org/10.1039/d0nj02975k

Goldwood, G., Diesburg, S. (2018). The effect of cool water pack preparation on vaccine vial temperatures in refrigerators. *Vaccine*, *36*(1), 128–133. https://doi.org/10.1016/j.vaccine.2017.11.024

Hanson, C. M., George, A. M., Sawadogo, A., Schreiber, B. (2017). Is freezing in the vaccine cold chain an ongoing issue? A literature review. *Vaccine*, *35*(17), 2127–2133. https://doi.org/10.1016/j.vaccine.2016.09.070

Hassaan-Younis, M., Ur-Rashid, H. (2018). Energy efficient, peltier based portable cabinet c. *2018 International Conference on Power Generation Systems and Renewable Energy Technologies (PGSRET)*, 1–4. https://doi.org/10.1109/PGSRET.2018.8685969

Kartoglu, U., Milstien, J. (2014). Tools and approaches to ensure quality of vaccines throughout the cold chain. *Expert Review of Vaccines*, *13*(7), 843–854. https://doi.org/10.1586/14760584.2014.923761

Kartoglu, U., Ozgüler, N. K., Wolfson, L. J., Kurzatkowski, W. (2010). Validation of the shake test for detecting freeze damage to adsorbed vaccines. *Bulletin of the World Health Organization*, *88*(8), 624–631. https://doi.org/10.2471/BLT.08.056879

Kurzątkowski, W., Kartoğlu, Ü., Staniszewska, M., Górska, P., Krause, A., Wysocki, M. J. (2013). Structural damages in adsorbed vaccines affected by freezing. *Biologicals: Journal of the International Association of Biological Standardization*, *41*(2), 71–76. https://doi.org/10.1016/j.biologicals.2011.10.011

Li, G., Wang, G., Ma, Y., Yue, L., Zhao, W. (2020). Research on Cold Chain Transport of Vaccines in Major Outbreaks. *IOP Conference Series: Earth and Environmental Science*, *526*, 012189. https://doi.org/10.1088/1755-1315/526/1/012189

Lugelo, A., Hampson, K., Bigambo, M., Kazwala, R., Lankester, F. (2020). Controlling Human Rabies: The Development of an Effective, Inexpensive and Locally Made Passive Cooling Device for Storing Thermotolerant Animal Rabies Vaccines. *Tropical Medicine and Infectious Disease*, *5*(3), 130. https://doi.org/10.3390/tropicalmed5030130

Nasruddin, Djubaedah, Gurky, R. G., Alius, Q. H., Arsyad, A. P. (2018). Design, development and performance prediction of solar heater for regeneration of adsorbent chamber. In F. H. Juwono, E. Kusrini, C. R. Priadi, E. A. Setiawan (Eds.), *2nd International Tropical Renewable Energy Conference (i-Trec) 2017* (Vol. 105, p. 012004). Iop Publishing Ltd. https://doi.org/10.1088/1755-1315/105/1/012004

Ng, C. Z., Lean, Y. L., Yeoh, S. F., Lean, Q. Y., Lee, K. S., Suleiman, A. K., Liew, K. B., Kassab, Y. W., Al-Worafi, Y. M., Ming, L. C. (2020). Cold chain time- and temperature-controlled transport of vaccines: A simulated experimental study. *Clinical and Experimental Vaccine Research*, *9*(1), 8–14. https://doi.org/10.7774/cevr.2020.9.1.8

Ross, J. C., Saidu, Y., Nzuobontane, D., Voukings, M. Z., Embrey, S. R. (2020). Application of the remaining vaccine vial monitor life calculation to field temperature monitoring data to improve visibility into cold chain equipment performance. *Vaccine, 38*(48), 7683–7687. https://doi.org/10.1016/j.vaccine.2020.09.078

World Health Organization. Module 2: The Vaccine Cold Chain. (2015). https://www.who.int/immunization/documents/IIP2015_Module2.pdf

Yin, H., Gao, S., Cai, Z., Wang, H., Dai, L., Xu, Y., Liu, J., Li, H. (2020). Experimental and numerical study on thermal protection by silica aerogel based phase change composite. *Energy Reports*, *6*, 1788–1797. https://doi.org/10.1016/j.egyr.2020.06.026

Zhao, Y., Zhang, X., Xu, X., Zhang, S. (2020). Development of composite phase change cold storage material and its application in vaccine cold storage equipment. *Journal of Energy Storage*, *30*, 101455. https://doi.org/10.1016/j.est.2020.101455

Zhou, L., Chakrabartty, S. (2017). Self-powered continuous time-temperature monitoring for cold-chain management. *2017 IEEE 60th International Midwest Symposium on Circuits and Systems (MWSCAS)*, 879–882. https://doi.org/10.1109/MWSCAS.2017.8053064