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Review article

"THE NEED FOR SPEED'' DEFIANCE'S ABOUT DELIVERIES OF COVID-19 VACCINES

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Abstract

While many new vaccines have been distributed around the developing world, cold chain systems are struggling to effectively support national immunisation programmes in ensuring the availability of safe and powerful vaccines. Good Distribution Practice (GDP) is a quality system related to organization, supervision and distribution of medicines and medical devices under certain rules and regulations.
This work aims to collect the data regarding the conservation conditions of the vaccines against the SARS-CoV-2 virus that are applied to the population of the Republic of North Macedonia.
This narrative literature review included many published papers during the last two years, different reports and guidelines regarding the Good Distribution Practice of vaccines and the cold chain logistic.
The pharmaceutical industry already possesses belong to other stages of distribution through hospitals or vaccination centers. This problem is more pronounced in developing countries and in economically weaker countries.

Keywords: Covid -19 vaccines, good distribution practice, cold chain challenges

1. Introduction

Every year, millions of lives are saved through vaccination, which is widely recognized as the world's most successful and cost-effective health intervention. (WHO 2019; Lloyd *et al*, 2016).
New vaccines typically take more than 10 years to be developed and approved. COVID-19 vaccines already had been approved for emergency use and registered domestically some eight months after this new disease was notified to the WHO. The development of COVID-19 vaccines is following a "pandemic paradigm", i.e., a compressed timeframe and with many steps executed in parallel rather than sequentially, according to the Coalition for Epidemic Preparedness Innovation (CEPI). The first vaccine candidate was in clinical testing just two months after the publication of the genetic sequence of SARS-CoV-2, the virus that causes COVID-19.
Therefore, this program is one of the main priorities to stop the ongoing COVID-19 pandemic (Ashvin et al, 2016). In June 2021, WHO noted the establishment of 287 registered COVID-19 vaccines, with 102 at the clinical stage (WHO, 2021b).
However, national immunization programs face major challenges in terms of how vaccines are distributed. Vaccine cold chain and logistics systems are central to addressing some of these challenges (Kaufmann JR et al, 2011; Humphreys G et al. 2011; The Vaccine Alliance, Bill & Melinda Gates foundation 2015; Zaffran M et al. 2013). The success of a vaccination program is based not only on the percentage of vaccine effectiveness but also on cold supply chain management. This is because when this fails, the high effectiveness becomes wasted (Lee, B.Y et al, 2017; Omole, T.M et al, 2019). According to the Global Express Association (GEA), guidance may be needed for vaccine shippers and manufacturers so that operators are not forced to reject shipments for non-compliance with dangerous goods shipping requirements (e.g. dry ice for vaccine refrigeration or other dangerous goods). If specialized reusable cold

storage containers and equipment are required, it will then be essential to ensure that their rapid reutilization for distribution in other countries is not unnecessarily delayed. Poor transportation and storage, including breaks in cold chain integrity, can lead to patients receiving substandard, unsafe, or impotent vaccines (GEA). One poorly understood infrastructure challenge that is fundamental to the success of any COVID-19 vaccination program, is the fact that vaccines need to be stored and transported in a seamless and unbroken temperature-controlled environment throughout the distribution journey, from point of manufacture to point of immunization. This key requirement demands all countries, regardless of climate or level of economic development, to procure additional cold-chain3 equipment as well as re-engineer the existing capacity to improve cold chains' ability to meet the increases in volume and distribution speed necessary to ensure uninterrupted availability of quality COVID-19 vaccines on the ground in every city, town, village and remote settlement or homestead across the globe. Apart from the existing government-controlled vaccine cold-chains, countries should also consider and identify the cold-chain space that the private cold-chain operators can offer (Leyla S. *et al,* 2020).

2. Materials and methods

This narrative literature review included a large number of published papers during the last two years, different reports and guidelines regarding the Good Distribution Practice of vaccines, and the cold chain logistic.

3. Results and discussion

Cold chain logistics

When arriving at healthcare facilities, COVID-19 vaccine immunogenicity and effectiveness are highly dependent on the following factors: vaccines must have been stored in the required cold chain, the cold chain must be adequately monitored, and vaccines must be used up within critical timeframes after being removed from the cold chain or after a puncture in the multidose vial (Holm MR *et al*, 2021; Grau S *et al*, 2021). By having appropriately trained managers on cold chain equipment who are tasked to manage and monitor cold chain, accidental interruption of the storage temperature conditions and hence vaccine instability can be avoided. Consequently, fewer vaccines are rendered ineffective and wasted (Grau S *et al*, 2021; World Health Organization; 2008, republished 2020 under the license).
The cold chain can be standard (2 °C to 8 °C) or Deepfreeze (as cold as −70 °C). The cold chain requires building extensive infrastructure and is very expensive to maintain. The complexity of the cold chain is illustrated in documents, such as the CDC Vaccine Storage and Handling Toolkit (Yu YB *et al*, 2021)

Types of Cold Chains

Traditional cold chain. This is also called the refrigerated chain. Temperatures range between 2°and 8°C, which is the usual temperature range of a refrigerator. Several vaccine candidates in the pipeline can be distributed using traditional cold chains.
Frozen chain. Frozen chains must maintain a temperature of –20°C, which is typical of freezers and may already be in use to transport other frozen products or medical materials such as organs and tissues. Among the currently approved COVID-19 vaccines, Sputnik V requires a temperature of –18 °C.
Ultra-cold chain. Ultra-cold chains also called deep freeze, are those whose temperatures are –70°C or lower. Some vaccines, such as Pfizer/BioNTech’s COVID-19 vaccine and Merck’s Ebola vaccine, require such low temperatures to remain effective. Ultra-cold chains pose significant challenges for developing countries as they often have very limited capacity to handle such low cold chain temperatures. (ADB

Briefs.)
According to the Vaccine Storage and Handling Toolkit (U.S. Department of Health and Human Services, 2021), COVID-19 vaccine products may impact the types of vaccine storage units and temperature monitoring devices used to maintain the cold chain, including the use of ultra-cold storage. Temperature ranges for COVID-19 vaccines may also differ from those for other vaccines. Carefully review the COVID-19 vaccine storage and handling addendum for information about which storage units and monitoring devices are appropriate, including specifications for monitoring devices that can monitor ultra-cold temperatures, how best to monitor temperatures, and how a specific vaccine product's cold chain requirements may affect other vaccines in a storage unit.
Different types of COVID-19 vaccines will need different handling and storage requirements and must answer to different quality and regulatory requirements.

Storage of Covid-19 vaccines

Primary packaging materials include glass vials and syringes, along with stoppers and seals. Packaging for distribution, includes secondary and tertiary packaging for vaccines. Secondary packaging assist in reducing volume, cost-saving, minimizing logistical burden, and reducing carbon footprint. Vaccine storage units at the healthcare facilities site usually consist of purpose-built or pharmaceutical-grade (large or compact) or household-grade refrigerators or freezer (Wolicki J et al, 2020.)

Pfizer's mRNA vaccine

Pfizer's mRNA vaccine demands the most stringent storage needs. It is required to be stored in a−70°C ultra-cold freezer. Packed as a 2 mL, glass preservative-free vial containing 5 doses, the Pfizer mRNA vaccine is packed for delivery in trays of 195 vials each. Five trays of 4,875 doses will be included in each shipment of dimensions 15.7″ L×15.7″ W×22″ H and will require to be packed with dry ice and weigh approximately 34 kg. The vials are subjected to quality measures, so no broken vials are present. Without opening the outer packaging (except inspecting the vial once to see if any is broken), each shipper can be stored for up to 10 days. Dry ice is replenished if the shipper is stored in a warmer climate and/or is opened more frequently than once for inspection of vials. GPS-enabled temperature-monitoring devices are placed inside to ensure end-to-end distribution occurs within the required temperature range. Upon the arrival of the shipper, the vaccine must be transported into an ultra-cold freezer within 5 min. Simultaneously, the GPS-enabled logger is disabled, and the shipper is sent back to the supplier within 10–20 days of arrival. The vaccines can be thawed in the refrigerator (2–8 °C) for up to 5 days (120 h), after which it should be discarded. Each dose needs to be diluted with normal saline before use and is stable for up to 6 h at room temperature, after which time it should be discarded. Pfizer has incorporated a QR code linked to the Emergency Use Authorisation (EUA) website, a lot number, and expiration date on the label for each vial for documentation purposes (Holm M, *et al*, 2021; Ramakanth D *et el*, 2021). Pfizer BioNTech recently submitted data to the Food and Drug Administration (FDA) to update the storage requirements to a more reasonable temperature ranging anywhere between−25 and−15 °C (Pfizer. Pfizer and Biontech Submit Covid-19 Vaccine Stability Data At Standard Freezer Temperature To The U.S. Fda: Pfizer; 2021 updated February 19, 2021. February 19, 202).

AstraZeneca (AZ)'s the adenovirus-vectored vaccine

AstraZeneca (AZ)'s adenovirus-vectored vaccine will be shipped in pallets. Each pallet will contain 85 cases packed with 20,400 vials. 10 vials per carton will contain 100 doses. Case dimensions are 11.6″ L×9.3″ W×7.4″

H. AZ's vaccine is required to be stored in the refrigerator at 2–8 °C upon arrival. It should be light-protected and can be stored for up to 6 months in the refrigerator (2–8 °C). To prevent prolonged light exposure, the vaccine must be kept in the original packaging until use and is not to be frozen. No reconstitution or special preparation is required. After the vial is punctured, it can be stored in the refrigerator for up to 6 h, after which the vaccine must be discarded. One advantage is that no reconstitution or special preparation is required for this formulation (Holm MR et al, 2021).

Sinopharm/ BIBP COVID-19 vaccine

The product can be stored at 2-8oC for 24 months. The presentation is 1ml pre-filled syringe (PFS) with 0.5 ml/ syringe. A 2 ml vial presentation containing 0.5 ml of vaccine is also available. Both presentations are mono dose. The vaccine does not require reconstitution with a diluent.

Cold Chain requirement: Secondary packaging includes- 1. Syringe in the paper holder (94.9 cm3) 2. Syringe with blister package (124.9 cm3) 3. 1 vial/carton packaging (61.8 cm3) 4. 3 vials/carton packaging (21.2 cm3)

Tertiary packaging includes- 1) an Outer box with 300 cartons with a total of 300 syringes (300 doses) 2) an Outer box with 240 cartons with a total of 240 syringes (240 doses). 3) Outer box with 400 cartons with a total of 400 vials (400 doses), Outer box with 200 cartons with a total of 600 vials (600 doses) (WHO).

Recommendations for best practice

One aspect of this massive challenge that is mostly overlooked is the opportunity it presents for building a more sustainable and resilient cooling economy. With the urgent need for building new cold- chains and re-engineering the existing ones, there is an opportunity to address gaps not only in medical cold chains but also in other sectors, with zero/low carbon technologies with natural/low-GWP refrigerants. According to Leyla et.al, overall, any deployment decision should be made considering targets related to the reduction of GHG emissions and other pollutants as well as SDGs, providing a legacy.

4. Conclusion

Many vaccines require adequate cold chain, including proper temperature control during the manufacturing, transport, and distribution. This is a major challenge in many parts of the world that has been especially highlighted by the current Covid-19 pandemic.

The spread of SARS-CoV-2 can be considered a very important issue in creating reliable and prolonged cooling chains of vaccines, including ultra-low temperatures.

The pharmaceutical industry has a very well-established refrigeration chain staffed that knows how to handle ongoing shipments and avoid potential problems that may arise from temperature changes. 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.

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