Available online at: https://proceeding.researchsynergypress.com/index.php/rsfconferenceseries1
RSF Conference Series: Business, Management, and Social Sciences
e-ISSN 2807-5803/p-ISSN 2807-6699
Volume 2 Number 1 (2022): 78-87

A short note for vaccine cold chain network models

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Abstract

Vaccine shortages in current COVID-19 pandemics have highlighted that vaccine production and distribution are resource-intensive processes. In addition to manufacturing new vaccines for emerging epidemics, existing stockpiles must be maintained as well. With limited resources available during this crisis, it is critical to identify efficient ways to utilize the scarce materials. To do so requires a better understanding of how vaccine supply chains are currently operating under normal and scarce circumstances, where supplies can be procured from multiple sources and stored at various locations before distribution to hospitals and clinics. This study seeks to determine what influences these network structures by assessing historical vaccine supply chain networks, including temperature levels, storage temperatures, transport methods, time delays, etc. By summarizing a bibliometric study of the Dimensions and Web of Science databases, the review is intended to enable researchers to identify optimal strategies for developing relevant vaccine production and distribution models.

Keywords: *COVID-19, vaccine supply chain, logistics, network models.*

INTRODUCTION

The current COVID-19 pandemics have given rise to a diverse array of questions. Specifically, this study seeks to answer two questions: (1) How are vaccines produced and distributed in a world with vaccine shortages? (2) How can this information be used to improve COVID-19 vaccine production and distribution? The current vaccine shortage has highlighted that vaccine production and distribution are resource-intensive processes that bottleneck population coverage. In particular, vaccine production requires a large amount of capital, labour, materials, and time. Most major vaccine research spanning from 2020 to 2022 are COVID-19 related, of which a majority rely on cold chain and ultra-cold chain distribution networks. Since the vaccine supply chain is notoriously slow, and its cold chain systems prone to error and subsequent wastage, effective strategies for such networks must be used to avoid shortages and oversupply.

METHODOLOGY

To address these research questions, bibliometric coupling and co-citation analysis were used in a prior study to distinguish some of the most commonly cited references inside the extant literature. A brief diagram of these two techniques are shown in Figure 1; two publications are bibliographically coupled if they cite the same source, while two references are co-cited if they are cited by the same publication. These two techniques allow researchers to pinpoint the relevant total citations made only by sources within the initial search, and not of external, less relevant sources. To obtain the metadata for this bibliographic study, searches were performed on the Dimensions and Web of Science databases using the names of WHO-approved vaccines, vaccine cold chain search terms, and COVID-19 terms. The articles with the highest bibliographic coupling and co-citation scores were then investigated.

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DOI: https://doi.org/10.31098/bmss.v2i1.519

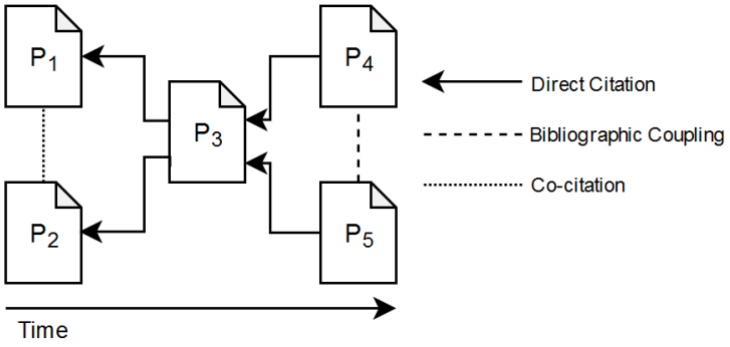

Fig. 1. Bibliographic coupling and co-citation analyses

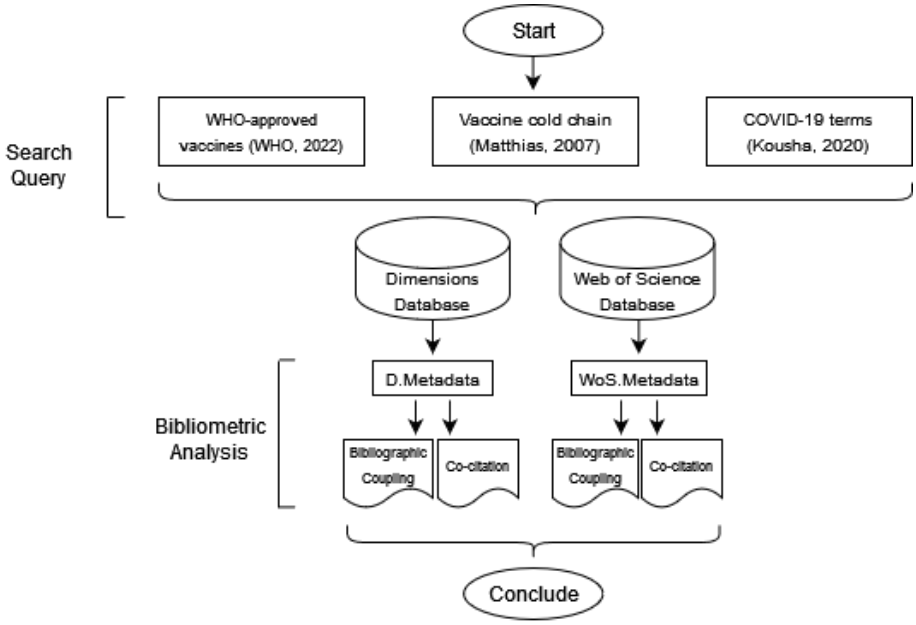

Fig. 1. Query and analysis methodology for the background study

Subsequently, these metadata obtained from these results were analysed with VOSViewer software (Van Eck, 2014) and by the Bibliometrix R package (Aria, 2017). Some of the key sources discovered in this search and their findings are discussed below.

FINDINGS

Historical Development of VSC

The development of the modern vaccine industry began after World War II and the formulation of the live oral polio vaccine (OPV). After mass immunization campaigns, OPVs became a key part of the Global Polio Eradication Initiative (GPEI), resulting in the elimination of wild poliovirus transmission worldwide by 1988. The vaccine used for this initiative was the Sabin-Chumakov vaccine, which could be frozen at -20℃ for one week and safely refrigerated at 2-8℃ (Cai, 2020). The vaccine's efficacy, however, declined over time due to lack of maintenance and limited

cold chain capacity, and countries with limited storage and transportation infrastructure were slower to eradicate polio than those with adequate resources.

As a result, new technologies and standards were introduced in a series of developments in order to increase vaccine safety and availability. First, a standardized formulation of the polio vaccine was established. Second, cold chain distribution vehicles and containers were used to transport vaccines from manufacturing sites to regional and national storage centers, then to the endpoint facilities, reducing lead times and eliminating waste. Third, the development of lyophilized formulations by researchers such as Kraan (2014) allowed long-term storage at room temperature, reducing the need for cold chain systems. COVID-19 vaccines are currently in the second stage of this development: while further research into lyophilization technologies is currently underway, it has yet to be approved by the WHO (Mabrouk, 2021).

The adaptation of other vaccine supply chains to cold chain constraints has also propagated. To this end, Dujizer (2018) highlighted the priority areas of the WHO's 2020 immunization vision as (1) products and packaging, (2) supply system efficiency, and (3) environmental impact. The first two priorities include the advancement of cold chain technology and the implementation of high-quality vaccine supply chain management. The third priority includes the use of renewable energy, recycling, and carbon emission reduction. In addition to the above-mentioned initiatives, the introduction of the Internet of Things has also contributed to vaccine distribution, allowing real-time tracking of vaccines in the supply chain.

The requirements for a specific vaccine define its network design constraints. Lemmens (2016) defined 3 model categories for VSC network design: mathematical programming, heuristics, and analytical methods. Under each approach, modeling techniques were grouped as single-criterion or multi-criteria, many of which contained solution methods that were exclusive to each group. Mathematical programming uses a set of objective and constraint functions to solve the optimal solution, while heuristic methods involve finding the most optimal solution under time constraints through trial and error. Meanwhile, the analytical heuristic methods sought to represent the decision problem as a hierarchy of sub-problems that could be solved iteratively, reducing computational time.

A secondary problem is vaccine selection. While some vaccines can be stored and transported at refrigeration temperatures between 2 and 8 degrees Celsius, such as the oral polio vaccine, other vaccines must be stored at "ultra-cold" temperatures to prevent deterioration. Some historical examples of vaccines that can be stored at temperatures of -20°C to 5°C without significant degradation include the yellow fever, hepatitis A, and influenza vaccines. Meanwhile, vaccines that require storage at extreme subzero temperatures include Merck's Ebola vaccine, while other vaccines, such as the measles, mumps, rubella, and cholera vaccines, are stored at lower freezing temperatures. Multiple dosages are another key factor, generating additional scheduling and delivery constraints.

Thus, the delivery requirements of the vaccine also influence the structure of the supply network. For instance, the development of the cold chain infrastructure and its accompanying standards have resulted in the emergence of three different types of vaccine distribution network stages. These include (1) linear, (2) tree, and (3) hierarchical hub-and-spoke. The linear and tree distribution modes use a central warehouse to store and distribute vaccines to regional distribution centers, differing in that linear structures branch out towards the end of the supply network. These two former models are common in countries with limited cold chain capacity. However, the hierarchical hub-and-spoke distribution model focuses on production, linking multiple nodes to efficient central

facilities. Models proposed by researchers such as Xu (2021) suggest that the hub-and-spoke model is preferred for countries with extensive cold chain infrastructure, such as the United States.

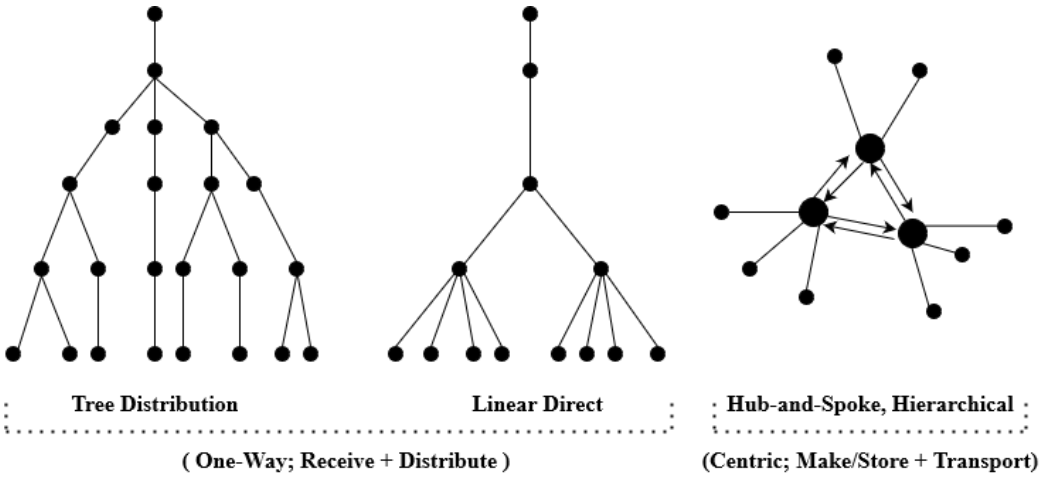

Fig. 1. General vaccine distribution networks

Yadav (World Bank, 2021) noted that most countries are currently shifting their COVID-19 networks from tree distribution structures to linear direct structures. The stated reasons for this involved data transparency, data load reduction, and cold chain equipment centralization. With fewer branches in the network and a single unified main branch, a centralized warehouse could perform logistical support for multiple districts at one time. Additionally, a larger volume of data can be transported along fewer pathways.

The linear model, however, is not without shortcomings. For example, the linear structure is less resilient to disruptions, as the primary nodes in the network are more susceptible. The linear structure also has the potential to lose effectiveness in terms of lead time and capacity planning due to node congestion. James (2021) instead highlighted the success of hub-and-spoke models in systems such as the Tanzania vaccine supply chain, and more recently, the US government's Moderna vaccine distribution network.

Finally, the characteristics of the end-users are considered. In a normal situation, a vaccine is used by a fairly small fraction of the population. However, in a pandemic, the vaccine may be required by an entire country. This results in triage problems, where supplies cannot meet the needs of all patients, and at-risk groups must be prioritized. Thus, depending on national policy, the population allocation problem can further confound a distribution network.

Survey of COVID-19 VSCs

To answer the questions posed in the previous section, the literature review identified current research in the field of COVID-19 vaccine distribution networks. As of March 2022, the WHO has approved 10 COVID-19 vaccines for emergency use listing. Information on the vaccine storage temperatures was obtained from the COVID-19 vaccine development tracking website by Shrotori et al. (2021) and from each vaccine provider's WHO recommendation page and corresponding manuals.

Table 1. List of WHO-approved COVID-19 vaccines, March 2022.

Name	Institution	Type	Storage Temperatures
Spikevax (mRNA-1273)	Moderna	mRNA	-40- -20°C (6mo), 2-8°C (30d), 25°C (12h)
Comirnaty (BNT162b2)	Pfizer/BioNTech	mRNA	-80- -60°C (6mo), 2-8°C (5d), 25°C (2h)
Vaxzevria (AZD1222)	Oxford/Astrazeneca	Viral Vector	2-8C°C (6mo), 25°C (6h)
Covishield (ChAdOx1-S recombinant)	Serum Institute of India/Astrazeneca	Viral Vector	[identical to Vaxzevria]
Janssen (Ad26.COV 2.5)	Johnson & Johnson	Viral Vector	-85- -65°C (4y), -25- -15°C (24mo), 2-8°C (4.5mo), 25°C (12h)
Covilo (BBIBP-CorV)	Sinopharm (Beijing)	Inactivated	2-8°C (24mo)
CoronaVac	Sinovac	Inactivated	2-8°C (12mo), 25°C (42d)
Covaxin	Bharat Biotech	Inactivated	2-8°C (9mo)
Nuvaxovid (NVX-CoV2373)	Novavax	Protein subunit	2-8°C (9mo)
Covovax	Serum Institute of India/Novavax	Protein subunit	[identical to Nuvaxovid]

The three major classes of vaccines currently approved by the WHO are RNA, Viral Vector, and the Inactivated and Protein Subunit vaccines. Although the efficacy of RNA vaccines is high, their production and distribution present significant challenges. Of particular note is Pfizer/BioNTech's Comirnaty vaccine, which requires "ultra-cold" subzero freezing storage temperatures at -70°C. Meanwhile, the viral vector vaccines vary. Unlike Johnson & Johnson's Janssen vaccine, Oxford/Astrazeneca's Vaxzevria and its Indian-produced counterpart Covishield cannot be stored at freezing temperatures, but require storage in a refrigerator. Lastly, the inactivated vaccines and protein subunit vaccines, such as Sinovac and Novavax, can also be stored with conventional refrigeration.

Manufacturing

The process of mRNA vaccine production requires numerous supply chain partners, which are by necessity international. First, the raw materials for the vaccine are produced by a pharmaceutical company, followed by the isolation of the RNA from the cell culture. The RNA is then purified and extracted, and finally, the vaccine is assembled and packaged. While Pfizer/BioNTech produce their mRNA actives at their own plants in the US and in Belgium, Moderna has elected to contract with Lonza in the US and in Switzerland. This step involves the cloning of bacterial DNA and requires roughly 9 days. The DNA is then transported to production facilities that use the DNA as mRNA templates, which takes about 4 days. Afterward, the mRNA is shipped to a manufacturing facility, where it is combined with lipid nanoparticles, the bottleneck step, and then packaged. In terms of lead time, Pfizer has reported a total production lead time of 110 days, of which half is dedicated to quality assurance, though the company has set its sights on 60 days.

The production of viral vector vaccines by Oxford/Astrazeneca and Johnson & Johnson involves, by definition, the modification of a different, weakened adenovirus vector that contains the antigen DNA. These viruses are propagated on human cell cultures, and then purified to remove the culture. Similarly, the Sinopharm and Sinovac vaccines involve the cultivation of attenuated live virus strains on animal cells, but also require a secondary stage of inactivation. Similarly, the protein

subunit vaccines are also grown in culture, but do not require inactivation. While these vaccines contain fewer production stages than their mRNA counterparts, they must also undergo rigorous quality assurance testing. As such, although the production time for viral vector and attenuated vaccines is significantly shorter than mRNA vaccine production's, their estimates range from 40 to 50 days.

Delivery Factors

Cold Chain Equipment

James (2021) noted that there are four categories of temperature-defined cold chains: 2-8℃, -20℃, -80℃ and < -150℃. Of these categories, only two vaccines have historically been developed for storage at the -80℃ range: Pfizer-BioNTech's Comirnaty (COVID-19) and Merck's Ervebo (Ebola). The WHO supply and logistics guidance handbook (2021) recommends the use of active storage freezers and passive coolers to keep vaccines at ultra-low temperatures (-80 to -60℃) while unpowered. These containers have a capacity of 7.9L and last 5 days, and two containers are estimated to be needed per district. However, it was noted that very few low to middle-income countries (LMICs) have these facilities, except for the countries that were previously invested in Ebola vaccination initiatives.

Data Management

De Boeck (2020) highlighted data flow handling in vaccine supply chains. In many developing countries, information is often unavailable or unused, or even limited to paper-based data collection. Furthermore, many LMICs lack sufficient IT infrastructure, which means that even if the data is available, it is difficult to extract meaningful information. Lastly, the lack of standardization in the vaccine industry itself makes data analysis difficult. To address these challenges, Vander Stichele (2020) proposed three measures to enable data tracking: QR code technology to facilitate verification, GS1 Datamatrices to mark individual data, and Pharmaceutical Product Identifier numbers. At the strategic level, the WHO's COVID-19 vaccination supply and logistics guidance manual proposes the following data requirements for the vaccine cold chain:

Table 2. List of WHO-advised COVID-19 vaccine supply chain data requirements

Name	Key data
Cold chain storage capacity	• Current available storage capacity per site. • Forecasted storage requirements.
Cold chain performance	• Temperature monitoring logs. • Cold chain equipment functionality / time since reported failure • Cold chain equipment generator performance / functionality.
Supply chain	• Delivery timeliness performance. • Proportion of successful planned deliveries. • Inventory levels and COVID-19 vaccine usage rate. • Inventory location.
Reverse logistics	• Vial tracking. • Collection and data reporting must occur after each vaccination round.

Uncertainty

Researchers such as de Treville (2014) have noted that vaccine supply chains are particularly slow, meaning that they is particularly sensitive to stochastic conditions. Vaccine delivery uncertainty is due to a number of factors, including demand, the unpredictable distribution of patients, and the risk of delays during the transport period. While it is difficult to estimate the precise demand, it is clear that the vaccines will be used by a certain population of people. In addition, the arrangement of large-scale vaccine deployments may result in significant delays during transportation.

Table 2. Researched vaccine supply chain uncertainties

	Strategic	Operational
Supply	Unreliable facilities Unreliable transportation	Delivery lead time Processing lead time Transportation time
Demand	Demand scenarios (Winning a tender)	Fuzzy, Normal, Poisson, Triangular

Lemmens (2016) classified vaccine supply research on uncertainty under two intersecting categories: strategic and operational, against supply and demand. Research supply uncertainty deals with unreliable facilities and transportation, which generally involve disruptions. Operational supply uncertainty shows a gap in variable lead, processing, and transportation times. Operational demand uncertainty usually defaults to normal distribution models, with some research dealing with fuzzy, Poisson, and triangular demand. As such, reducing uncertainty by minimizing unnecessary members in the distribution network, while maintaining intended capacities, will improve vaccine supply chain performance.

Delivery Networks

Much of the consensus on vaccine distribution network analysis is that it can be viewed in two stages: the first from the manufacturer to the recipient distribution centers, and then from the distribution centers to the last mile delivery. Once the manufacturing chain has made its delivery to the vaccine distribution, its responsibility for the product ends, and the domestic vaccine distribution chain is managed at the national level. A simplified version is shown in Figure 2:

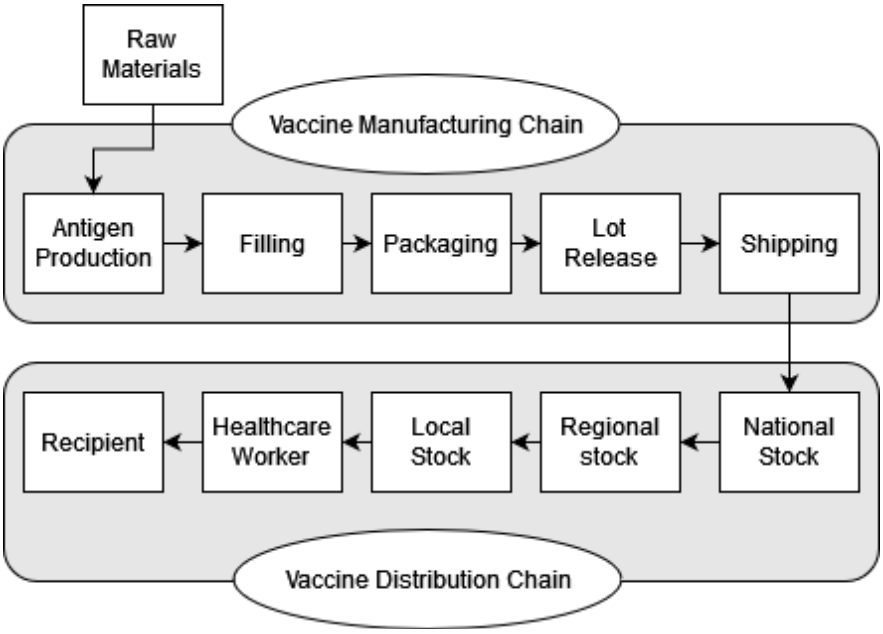

Fig. 2. General vaccine distribution chain structure, adapted from Decouttere (2015)

Under this distinction from Decouttere (2015), it is also noted that vaccine manufacturing and distribution most often occur in separate nations. From this perspective, one of the most relevant research problems involves distribution. A vaccine supply chain inventory routing problem is constrained by known but stochastic supply and demand, and the need for optimal distribution of vaccines across multiple sites. The unstable nature of vaccines often requires cold preservation facilities that double as central hubs in a distribution network, adding complexity to the problem in terms of various costs, locations, and delivery time windows. One additional major concern is network expansion, which requires time and careful planning

CONCLUSION AND FURTHER RESEARCH

As noted by Dujizer (2018), the distribution network is a critical component of any pandemic response. If the system is not well designed before implementation, significant problems such as delays in vaccine distribution will arise, which impact the ability of healthcare workers to treat patients. The growing trend in many countries is to adapt viral vector, attenuated, and protein subunit virus vaccines suggests that these may provide an alternative to RNA vaccines. Furthermore, the development of new delivery networks for vaccine distribution and reverse logistics will require further feasibility studies regarding their sustainability.

In this review, manufacturing and distribution networks for COVID-19 vaccines approved by the WHO were studied. It was found that many vaccine supply networks were being optimized for speed of transport, information flow, and equipment centralization/cost, but not necessarily for all of these factors at the same time. Furthermore, it was also reported that many distribution chains were shifting their designs to favor the latter 2 factors. This study suggests that a more comprehensive optimization process is needed in order to design effective vaccine cold chain networks. While the ideal network would have no delays or shortages, several years are required before such networks can become fully operational. Furthermore, capital investment requirements

will likely deter most governments from investing in them without the guarantee of returns. Thus, the most beneficial models must demonstrate suitability for their locales.

Future research trends suggest improving the scalability of vaccine production facilities, and the design of more robust vaccine distribution networks that consider operational demand uncertainty. These networks should be flexible enough to accommodate various vaccine types, as well as changes in demand over time, and should ideally be able to scale up quickly if necessary. In addition, improved methods for monitoring and managing cold chain equipment are needed in order to ensure optimal performance and prevent breakdowns. These challenges must be addressed to facilitate the transition from delivery network development to implementation.

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