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Optimal design and planning of supply chains for viral vectors and RNA vaccines

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Abstract

This work develops a multi-product MILP vaccine supply chain model that supports planning, distribution, and administration of viral vectors and RNA-based vaccines. The capability of the proposed vaccine supply chain model is illustrated using a real-world case study on vaccination against SARS-CoV-2 in the UK that concerns both viral vectors (e.g., AZD1222 developed by Oxford-AstraZeneca) and RNA-based vaccine (e.g., BNT162b2 developed by Pfizer-BioNTech). A comparison is made between the resources required and logistics costs when viral vectors and RNA vaccines are used during the SARS-CoV-2 vaccination campaign. Analysis of results shows that the logistics cost of RNA vaccines is 85% greater than that of viral vectors, and that transportation cost dominates logistics cost of RNA vaccines compared to viral vectors.

Keywords: SARS-CoV-2 vaccines, vaccination campaign, mathematical programming, economic analysis, vaccine availability.

1. Introduction

The COVID-19 pandemic has accelerated the research and development of new platform technologies for the production of vaccines against infectious diseases, including the novel corona virus, also known as Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2). Platform technologies such as viral vectors (Voysey et al., 2021) and RNA (Walsh et al., 2020) have been used to develop vaccine candidates to combat COVID-19. However, these new vaccines pose both logistics and distribution challenges. For example, unlike conventional vaccines, certain RNA-based vaccines require ultra-low temperature throughout the distribution network to avoid loss of potency.

Vaccine supply chain is a complex network that facilitates the transport of vaccines from manufacturing plants to administration points, such as GP surgeries, hospitals, pharmacies, clinics, and mass vaccination centers. The storage and transport conditions required by vaccines determine the type of cooling technology (e.g., fridge, freezer, or ultra-low freezer) to be installed at storage locations. During transportation, ultra-low temperature is maintained using thermal shippers loaded with dry ice (liqulified CO₂).

The structure of a typical vaccine supply chain comprises manufacturing plants or import locations, fill-finish plants, warehouses/central stores, regional stores, and administration points. A manufacturing plant, aka primary manufacturing, consists of several unit operations used in the production of drug substance, which is the main ingredient in vaccines, while a fill-finish plant, also known as secondary manufacturing, inserts
vaccines (drug substances and excipients) into sterile glass vials or bags that are further packaged into cartons.

The design and planning of vaccine supply chains addresses the following: optimal selection of storage locations, production planning at manufacturing and fill-finish plants, inventory management/storage capacity planning, distribution planning, selection of routes and transport types, etc. In the recent past, Lee and co-workers (2014; 2015, 2016) have applied a simulation-based analytical tool, known as HERMES—Highly Extensible Resource for Modeling Supply Chains, to assess and re-design vaccine supply chains in low- and middle-income countries. However, HERMES does not support optimisation of supply chains, leading to solutions that could be suboptimal. Cavalho et al. (2019) developed a mixed-integer linear programming (MILP) model for optimal design and planning of a sustainable vaccine supply chain. The key performance indicators used to assess candidate supply chains are related to economic, environmental, and social performance. Kis et al. (2019) developed a supply chain model for the distribution of vaccine candidates such as RNA vaccines, outer membrane vesicle vaccines with genetically customizable membrane antigens virus-like particle vaccines with genetically configurable epitopes, and humanized yeast-produced vaccines. The model optimizes both supply-chain configuration and delivery type. Recently, Georgiadis & Georgiadis (2021) developed a MILP model for the distribution of COVID-19 vaccine and proposed an efficient method to solve the complex model. Nevertheless, the model does not account for quality control checks, fill-finish plants, production planning, selection of transport mode, and more importantly, management of vaccine thermal shippers.

This work develops a multiple-product MILP supply-chain model that supports the planning and distribution of viral vectors and RNA-based COVID-19 vaccines, from manufacturing plants to vaccination centers where vaccines are administered to targeted individuals. Unlike previous work, the proposed optimisation-based supply chain model comprises of five echelons, including manufacturing plants, fill-finish plants, imports, warehouses, regional stores, and administration points. A recycle loop for vaccine thermal shippers from warehouses to administration points and back to warehouses is implemented to ensure efficient management of vaccine thermal shippers. Including these entities within the supply-chain model allows efficient distribution of viral vectors and RNA-based vaccines, in addition to setting production targets at manufacturing and fill-finish plants. The performance of candidate supply chains is assessed using relevant key performance indicators such as vaccine availability, logistics cost, logistics cost per fully immunized patients, etc.

2. Methodology
2.1. Vaccination scheduling
Vaccination campaigns against infectious diseases are mostly preceded by scheduling of targeted individuals as well as healthcare personnel needed to administer vaccines. For the COVID-19 vaccination campaign, targeted individuals are selected according to risk of mortality and hospitalization when exposed to the highly contagious disease. Next, the targeted individuals are stratified, giving rise to cohorts to be schedule for the vaccine administration. The cohorts are prioritized according to risk-factors and vulnerability to COVID-19. Based on the COVID-19 vaccine regimen, the total number of doses required is estimated, and hence the vaccine demand profiles. By dividing the daily/weekly number of vaccinations by workload, it is possible to estimate the number of healthcare
workers that should be schedule on daily/weekly basis in order to ensure a successful vaccination campaign. This calculation may be carried out separately or embedded within the supply-chain model described in Section 2.2.

2.2. Design and planning of vaccine supply chains

The proposed vaccine supply-chain model supports the distribution and administration of vaccine candidates developed using various platform technologies, including viral vectors and RNA-based vaccines. The proposed supply chain comprises five echelons: manufacturing plants/imports, fill-finish plants, central stores, regional stores, and administration points (see Figure 1). Vaccines flow from manufacturing plants to vaccination centers via transportation modes, which can be a refrigerated van, a refrigerated truck, or an airplane. For vaccine candidates requiring ultra-low cooling temperatures, vaccine “thermal shippers” are used to ensure that the recommended temperature is not compromised during transportation. A recycle loop from warehouses to clinics and back to warehouses is implemented to enable efficient management of thermal shippers. The model inputs and outputs are summarised in Table 1.

Table 1. Vaccine supply chain inputs and outputs

| Inputs | Outputs |
|--------|---------|
| i. vaccine demand profile | i. optimal supply chain configuration |
| ii. proposed supply chain structure (optional) | ii. transport mode per route |
| iii. minimum and maximum inventories (manufacturing and fill-finish, warehouses, regional stores, and administration points) | iii. backlog in each time period |
| iv. minimum and maximum capacities of manufacturing plants, fill-finish plants, and import rate | iv. vaccine availability and vaccine wastage at administration points |
| v. minimum and maximum capacities of transportation modes | v. vaccine supplied to administration points per time period |
| vi. operating cost and capital cost factors (manufacturing and fill-finish, warehouses, regional stores, and administration points) | vi. vaccine import rate and production rates in manufacturing and fill-finish plants |
| vii. travel distances and times | vii. capacity of quality control facilities |
| | viii. capital cost, operating cost, and total annualised cost of supply chain facilities |
| | ix. total transportation cost and transport cost per route |
| | x. inventories of vaccines in manufacturing, fill-finish, warehouses, regional stores, and administration points |
| | xi. inventories of vaccine thermal shippers (full and empty) in warehouses, regional stores, and administration points |

Note that thermal shippers are needed only for vaccines stored and transported at ultra-low temperature. Also, constraints are included in the supply chain model to ensure that vaccines stored at clinics do not stay longer than their shelf-life. The objective function used to assess the performance of candidate supply chains include logistics cost, logistics
cost per fully immunized patient, and total cost of supply chain components. The model is built in GAMS, where the solver CPLEX is used to optimise the MILP model.

Figure 1. Schematic of the proposed vaccine supply chain comprising internal and external manufacturing and fill-finish plants, in-country warehouses, regional vaccine stores and administration.

3. Application

This section illustrates the capabilities of the proposed multi-product vaccine supply-chain model against COVID-19 in the UK, considering both viral vectors (AZD1222) and RNA vaccines (BNT162b2). The targeted individuals, as recommended by the UK Joint Committee on Vaccination and Immunization (JCVI), includes: care home residents, residential care workers, age 80 plus, health care workers, social care workers, age group 75-79, age group 70-74, clinically extremely vulnerable (under 70), age group 65-69, at risk (under 65), age groups 60-64, 55-59, and 50-54. For both vaccines, individuals are required to take two doses to be fully immunized. Vaccine doses are administered at least three weeks apart, leading to a vaccination timeframe of 38 weeks. The optimal supply chain distribution network is determined by the supply-chain model together with production targets at manufacturing and fill-finish plants, as well as vaccine inventory at storage locations, distribution planning, selected transportation mode, number of shippers and quantity of dry ice needed, etc. The total logistics cost and cost of supply chain components for viral vectors and RNA vaccines are shown in Figure 2 and Table 2, respectively.

Figure 2. Total logistics cost required to deliver vaccines from manufacturing plants to administration points in England, Scotland, Wales, and Northern Ireland. The costs of precuring AZD1222 and BNT162b2 are not included, since logistics cost is the sum of total annualized capital cost, transportation cost, and total operating cost.
Figure 2 compares the logistics cost and logistics cost per fully immunized patient (FIP) for viral vectors and RNA-based vaccines. Note that there is no inventory of vaccines at warehouses and regional stores throughout the vaccination campaign, leading to zero operating cost, as shown in Figure 2. In this case study, vaccine inventory accumulates at administration points only. Note that this work considers a fixed supply chain structure in order to mimic the existing vaccine distribution network in the UK. Therefore at the design level, the supply chain model selects the transport type between echelons and their corresponding delivery frequency, which are discussed below.

From the results, the logistics cost of RNA vaccines is 6-fold larger than that of viral vectors. Similar trend is observed for logistics cost per FIP. Logistics cost is the sum of total annualized capital cost, transportation cost, and total operating cost. The high logistics cost observed for RNA vaccines is due to the large delivery frequency required to deliver sufficient vaccines to administration points during the vaccination campaign. RNA vaccine candidate, BNT162b2, has a shelf life of five days when stored at 2-8°C or kept in thermal shippers (without re-icing) and two hours at room temperature. Hence vaccine inventory can be kept to satisfy demand for five days only in order to avoid loss of potency and vaccine wastage. On the contrary, viral vector candidate, AZD1222, have a shelf life of six months at 2-8°C, thus warehouses, regional stores, and administration points can hold vaccine inventory for a longer period, consequently reducing the delivery frequency, but increasing the total annualized capital cost (see Figure 2). The increase in total annualized capital cost is due to the larger cold chain storage facility required to hold vaccine inventory. Another factor that leads to high transport cost for RNA vaccines is that BNT162b2 is produced in Pfizer-BioNTech manufacturing plant in Puur, Belgium, and have to be transported using an expensive transport mode (airplane) to warehouses in London, Edinburgh, Cardiff, and Belfast. On the other hand, viral vector candidate, AZD1222 is produced in the UK transported using refrigerated truck.

In addition to logistics cost and logistics cost per (FIP), the supply-chain model estimates the cost of other vaccine supply- chain components (see Table 2), including thermal shipper, dry ice, vaccinator wages, vaccine procurement, and quality control checks.

Table 2. Total cost of vaccine supply chain components such as vaccine thermal shippers, dry ice, vaccinator wages, vaccine procurement, and quality control checks.

| Item (in million $)                      | AZD1222 | BNT162b2 |
|-----------------------------------------|---------|----------|
| Cost of vaccine shipper                 | -       | 7.72     |
| Cost of dry ice                         | -       | 20.30    |
| Cost of vaccinating individuals         | 1880.0  | 1880.0   |
| Cost of vaccinating individuals at care home | 24.10   | 24.10    |
| Cost of vaccine procured                | 450.0   | 2000.0   |
| Cost of quality control checks          | 59.90   | 59.90    |
| Total cost                              | 2420.0  | 3990.0   |

In Table 2, the total supply chain components cost for AZD1222 and BNT162b2 are $2.42 and $3.99 billion respectively. The selling price of BNT12b2, $18 per dose, is higher than that of AZD1222, $3 per dose, leading to 78% increase in the procurement cost of vaccine needed to vaccinate the entire UK target population of approximately 53 million individuals with two doses. AZD1222 does not require ultra-low cooling during
transportation, hence no thermal shipper and dry ice are required. Apart from the recycle loop for vaccine thermal shippers, the supply chain structure for ADZ1222 and BNT162b2 is similar. Also worth mentioning is that the storage technology for the two supply chains differs, i.e., refrigerators (2-8°C) for AZD1222 and deep freezers (-80°C) for BNT162b2. Deep freezers lead to high operating cost as a result of energy consumption needed for ultra-low temperature cooling.

4. Conclusions

A multi-product MILP vaccine supply chain model has been developed considering the essential features of a typical vaccine supply chain. The model can be used to design, plan, and optimize the distribution and administration of vaccine candidates developed using the most advance platform technologies, i.e., viral vectors and RNA. A case study compared the logistics costs when either viral vectors or RNA-based vaccines are used during a vaccination campaign against COVID-19 in the UK. The results show that the logistics cost of RNA-based vaccines (BNT162b2) is far greater than that of viral vector (AZD1222). Transportation cost dominates logistics cost of RNA-based vaccines as a result of high delivery frequency needed to supply sufficient vaccines to administration points. The long shelf life of viral vectors allows this vaccine type to be stored at administration points for a period of up to 6 months, consequently increasing capital cost related to storage facility.

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