



Optimization methods for large-scale vaccine supply chains: a rapid review

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Abstract

Global vaccine revenues are projected at \$59.2 billion, yet large-scale vaccine distribution remains challenging for many diseases in countries around the world. Poor management of the vaccine supply chain can lead to a disease outbreak, or at worst, a pandemic. Fortunately, a large number of those challenges, such as decision-making for optimal allocation of resources, vaccination strategy, inventory management, among others, can be improved through optimization approaches. This work aims to understand how optimization has been applied to vaccine supply chain and logistics. To achieve this, we conducted a rapid review and searched for peer-reviewed journal articles, published between 2009 and March 2020, in four scientific databases. The search resulted in 345 articles, of which 25 unique studies

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met our inclusion criteria. Our analysis focused on the identification of article characteristics such as research objectives, vaccine supply chain stage addressed, the optimization method used, whether outbreak scenarios were considered, among others. Approximately 64% of the studies dealt with vaccination strategy, and the remainder dealt with logistics and inventory management. Only one addressed market competition (4%). There were 14 different types of optimization methods used, but control theory, linear programming, mathematical model and mixed integer programming were the most common (12% each). Uncertainties were considered in the models of 44% of the studies. One resulting observation was the lack of studies using optimization for vaccine inventory management and logistics. The results provide an understanding of how optimization models have been used to address challenges in large-scale vaccine supply chains.

Keywords Rapid review · Vaccine · Supply chain · Optimization · Logistics · Vaccine allocation · Vaccination strategy

1 Introduction

Efficiently operating large-scale vaccine supply chains is a global challenge. Optimization is one decision tool that can help mitigate challenges in this \$59.2 billion industry (Guzman, 2019) of large-scale vaccine supply chains. Those challenges include budget limitations, transportation, temperature control, inventory management, and high and uncertain demand. Poor management of the vaccine supply chain can lead to a disease outbreak (Sharomi and Malik, 2017), or at worst, a pandemic. The purpose of this work is to understand how optimization has been applied to large-scale vaccine supply chain and logistics in the past. This paper utilizes a rapid review method to systematically analyze optimization models in four areas of the vaccine supply chain. The rapid review methodology was selected because it provides a structured search, organization, and analysis technique for investigating a topic of interest (Ganann et al., 2010; Khangura et al., 2012; Tricco et al., 2015). Specifically, this rapid review investigates vaccine inventory management, vaccination strategies, vaccine logistics, and vaccine market competition.

- *Vaccine supply chain management* is the general set of processes and activities involved in the planning of a vaccination campaign, including production and procurement of vaccines, vaccine inventory management, vaccine distribution, vaccine logistics, vaccine administration, vaccination strategies, among other activities. The main difference when comparing a normal supply chain with that of vaccines is that it has great uncertainty of demand and supply. When it comes to the prevention of vaccine-preventable diseases, it is crucial that combat actions are taken quickly, otherwise, the demand for immunobiological can increase exponentially. Another important point when we consider the vaccine supply chain is that we have vaccine allocation decisions being taken by the government, often politically influenced.

We identify unique characteristics of the vaccine supply chain: high uncertainty in both supply and demand; misalignment of objectives and decentralized decision making between supplier, public health organization and end customer; complex political decisions concerning allocation and the crucial importance of deciding and acting in time.

Vaccine supply chain management exists in every country where it adapts to local characteristics and obstacles regarding prevalent diseases, population, geographic distribution,

infrastructure, and economic power. Even though the fight against immuno-preventable diseases and vaccine development is not new, management of the vaccine supply chain still faces a number of obstacles; this paper will investigate how operations research has been used to overcome these obstacles (Lemmens et al., 2016; Ashok et al., 2017; Kasonde and Steele, 2017; Lee and Haidari, 2017).

Four sub-components were investigated at a deeper level: inventory management, strategies, logistics, and market competition.

- *Vaccine inventory management* involves the stock management, storage, rationing, and demand-side management of the vaccine supply chain (Lim et al., 2017; Gagnon et al., 2016). Due to the manufacturing lead time of the producers, vaccine production and planning is carried out over a long period (e.g., sometimes over a year). Thus, population growth, vaccination schedules, regional characteristics, etc., can drastically change inventory levels. Misaligned planning with the current scenario can reflect negatively on the vaccination campaign, especially when demand is underestimated and left unmet. In contrast, overestimating demand can also have negative impacts on the vaccine supply chain since the vaccines are perishable and incur large refrigeration holding costs. As could be observed during the COVID-19 pandemic health crisis, vaccine manufacturing is an extremely important issue and one that directly affects the vaccine supply chain (Duijzer et al., 2018; Lemmens et al., 2016). However, this issue requires that the approach consider the availability of raw material, government purchase planning, as well as demand estimation itself. Thus, this Rapid Review does not address manufacturing problems, focusing on managing these products as soon as they are available on the market.
- *Vaccination strategies* refer to the decision-making behind who should be given vaccines, when they should be given, and how often they should be given (Kress, 2006). Some vaccines are a very limited and costly resource, so some research has focused on the optimization of the distribution among the population (considering, for example, age, gender, location, etc.) (Harvey et al., 2016; Shoukat et al., 2016; Giersing et al., 2017; Kurosky et al., 2016; Hardt et al., 2016).
- *Vaccine logistics* refers to the manufacturing and distribution of vaccines to the population. This stage of the vaccine supply chain management can be disrupted when it is difficult to access a region [mainly in developing countries (Anparasan and Lejeune, 2018)], or due to unexpected vaccines loss when the physical integrity of the vaccines is compromised due to breakage, improper handling, or temperature deviation (Lee et al., 2017; Mvundura et al., 2017; Lloyd et al., 2015; Uddin et al., 2016). This type of uncertainty in the vaccine supply chain causes challenges with the optimal allocation of vaccines across a region. It is common that in the same country two regions face completely different scenarios such as lack of vaccines and loss due to expiration (Huang et al., 2017; Moore and Lessler, 2015; Yuan et al., 2015).
- *Market competition* refers to the laboratory competition on the price of vaccines. This stage refers to the use of pricing models with respect to supply, demand, peer competition, contracts, and insurance (Lauton et al., 2019).

In addition to those challenges just described, another critical challenge in large-scale vaccine supply chains is that most operate at a budget limit which is often far from ideal (Loze et al., 2017; Onishchenko et al., 2019), making financial decisions a challenge. Likewise, supply chain management operations are also complex and challenging due to the batch sizes, expiration date, temperature control, vaccination strategies, disease outbreaks, among others (Raeven et al., 2019; Chen et al., 2018).

These problems have a common feature: solutions can be developed through optimization methods. In view of this, a rapid review was conducted to investigate how optimization has been used to improve the supply chain of vaccines worldwide. To the best of our knowledge, there exists three literature reviews related to the topic of this paper. First, Lemmens et al. (2016) reviewed models on general supply chain network design (SCND) and discussed whether these models could be applied to the key issues of the vaccine supply chain, specifically the case of the rotavirus vaccine. They focused on the distribution and production phases of the supply chain and concluded that existing general SCND models cannot address the complexities of the vaccine supply chain.

Meanwhile, Duijzer et al. (2018) reviewed operations research and operations management (OR/OM) literature already applied to vaccine supply chains and categorized it into four supply chain components: product, production, allocation, and distribution. They identified the main challenges of vaccine logistics and shed light on ways that the OR/OM community can contribute to improving the vaccine supply chain components and integrations among them. In contrast, the search method for this rapid review only overlaps that of Duijzer, van Jaarsveld and Dekker in four articles, meaning that we review 21 new manuscripts.

Lastly, Boeck et al. (2019) dove into the specifics of vaccine distribution chains (VDC) within low- and middle-income countries and included both quantitative and qualitative studies (i.e., case studies, interviews, etc.) in their analysis. They classified studies into four VDC parts (sourcing, storage, transportation, and administration of vaccines) and discussed the gaps between the qualitative and quantitative works within these countries to make results relevant to both practitioners and the OR/OM community.

Our work contributes a different perspective on the OR/OM literature on vaccine supply chains. First, our rapid review process is more systematic and reproducible than the literature reviews in those papers. Second, we perform an analysis of the type of optimization methodology used in each study. Finally, we categorize the vaccine supply chain into four stages: vaccination strategy, inventory management, logistics, and market competition. Therefore, our results show how different studies applied different optimization methods to the identified stages and what their objectives were. In addition, the rapid review notes what optimization methods have been used and whether the manuscripts addressed data uncertainties and outbreak scenarios. Thus, we identify additional interesting optimization research opportunities within the vaccine supply chain.

Next, Sect. 2 presents the rapid review method used to identify relevant papers and Sect. 3 gives the analysis of the selected papers. Finally, concluding remarks are given in Sect. 4.

2 Method

In this section, we define the method used to conduct our review. In general, a review can be defined as the analysis of evidence that seeks to answer a clear question. It consists of selecting, evaluating and criticizing relevant primary research. The basic premise of a review is that your methods are clearly presented and reproducible (Ganann et al., 2010; Harker and Kleijnen, 2012).

There exists several types of reviews like Systematic Review, Rapid Review, Mapping Review, Meta-Syntheses, Mixed Methods Review, Overview of Reviews, Accuracy Review, Network Meta-Analysis and Living Systematic Review, to mention a few. Each type of review has a characteristic regarding their final objective, scope definition, time availability, available resources, etc. (Ganann et al., 2010; Khangura et al., 2012; Tricco et al., 2015; Banomyong et al., 2019).

Table 1 Search strategy and bibliographic databases used to retrieve the articles falling into the scope of this rapid review

Bibliographic databases (primary sources)	Search strategy (descriptors and Boolean operators)
SciVerse Scopus—Elsevier	(Optimization OR optimisation) AND (distribution OR logistics) AND vaccine
Compendex—Engineering Village	
Web of Science	
Google Scholar	Manual searches according to the reference lists of the articles

The type of review adopted in this work was that of Rapid Systematic Review, also known as a Rapid Review. This method follows similar procedures of a full-systematic review; however, it aims to answer a more restricted question and has its execution in less time (from 4 to 8 weeks, depending on the scope of the research, whereas other methods can take many months). The databases searched are also limited due to the execution time. However, the studies included in the review are selected in a careful, transparent, and replicable manner. And yet, the evaluation of the studies is critical and rigorous, and findings can be both qualitative and quantitative. Rapid reviews can be opportune to bring synthesis of evidence to decision-makers. They are designed to address new or emerging issues, to update previous analysis, or to assess what is already known (Khangura et al., 2012; Tricco et al., 2015; Lei et al., 2015).

Each step of our Rapid Review is described below and is organized as follows. Section 2.1 presents the question we aim to answer with this review, Sect. 2.2 presents the search strategy used to find the manuscripts, Sect. 2.3 presents the eligibility criteria, and Sect. 2.4 presents how data were organized and analyzed.

2.1 Focused question

Faced with the challenge of managing the supply chain of vaccines, this review intends to shed light on how optimization has been used to aid decision-making in these problems. Given that, the question to be answered was the following:

How has optimization been applied to the fields of vaccine strategy, logistics, inventory and market competition?

2.2 Search strategy

This rapid review of scientific studies followed the guidelines of the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) (Liberati et al., 2009). Four databases were systematically searched for applications of optimization in the vaccine supply chain as presented in Table 1.

2.3 Eligibility criteria

Papers written in English, Spanish, and Portuguese, and published between 2009 and March 2020 were accepted. Only original studies presenting new OR models (that excludes reviews)

Table 2 Division of the manuscripts into four vaccine supply chain components and their corresponding descriptions

Vaccine supply chain components	Description
Vaccination strategy	Decision-making to reduce the proliferation of vaccine-preventable diseases by determining which populations (e.g., identified by age, location, gender, risk of disease contagion, etc.) should receive vaccines
Logistics	Transportation and distribution of vaccines to the population in order to meet the pre-defined vaccination schedules and demand
Inventory management	Stock management, storage, rationing, and demand-side planning of vaccines
Market competition	Impact of laboratory competition on the price of vaccines

were included in this rapid review. Although the search already contemplated the language, dates and peer-reviewed journal papers criteria, that information was verified again during a full-text screening. The inclusion criteria for the supply chain aspect of papers was that studies should apply optimization in one of the following activities of vaccine supply chain: (1) Vaccination strategy; (2) Logistics; (3) Inventory management; or (4) Supply Chain Management (Competition). The definition of each of these four areas is presented in Table 2.

2.4 Data pooling and analysis

The search for manuscripts was performed by one reviewer in the four databases following the definition of descriptors presented in Sect. 2.2. The search process resulted in 345 articles. Of this total, 172 were from Scopus, 90 from the Web of Science, 79 from Compendex, and 4 were included after manual search in Google Scholar. Figure 1 presents the screening and selection processes. The records retrieved from the search were analyzed by one examiner in RefWorks (ProQuest), a web-based bibliography and database manager, and 193 duplicate manuscripts were removed. The remaining 152 articles were initially screened by title and abstract, at which point 110 were excluded. The remaining 42 papers then went through a full-text screening, resulting in 26 included manuscripts. In questionable cases during screening, the final verdict was reached by having two reviewers discuss the classifications and reach a common agreement. The reasons for exclusion of articles in both screenings (that is, manuscripts excluded during the title and abstract screening and the full-text screening) were: (1) out of the original scope of the research, (2) focused on health care instead of vaccines, (3) optimization approaches were not used, and (4) optimization was not applied to the supply chain aspect of vaccines (i.e., optimization of vaccine efficacy in the human body).

Two publications were related to the same project, so their information was combined. After all the steps, a total of 25 unique studies met the search criteria (“Appendix A”). The manuscripts that met the inclusion criteria were extracted from the RefWorks platform and their information was organized into an Excel table. With the information compiled and organized, it was possible to proceed with the exploratory analysis according to the study design explained below.

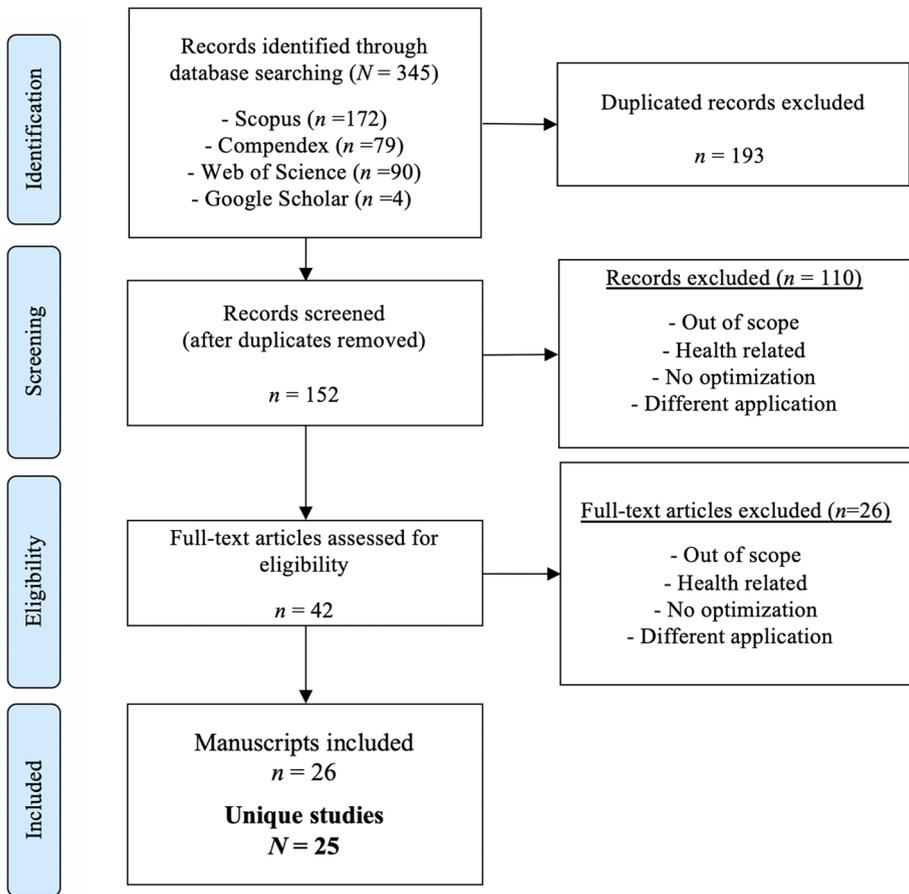


Fig. 1 PRISMA flow diagram of the search strategy comprising the identification of potentially relevant material, preliminary screening, and final selection of the studies included in this review (based on PRISMA guidelines) (Liberati et al., 2009)

For each of the manuscripts included, we identify the main objective, type of vaccine, the supply chain stage being studied, country of study, and the optimization method used. The main objectives were identified with free text. The types of vaccines under consideration in the studies are classified by the name of the specific vaccines or the disease being studied (in cases of studies of developing vaccines). The supply chain stage is classified within four key areas of the chain as defined in Sect. 2.3. Under this characteristic, we also analyze whether or not the study considers outbreak (or pandemic) scenarios. The country of study refers to where the application of the solution occurred or where the data was retrieved from, not the country of affiliation of the authors. The optimization method characteristic is also binary. Information on whether the studies considered uncertainty and whether they dealt with the problem as a network problem were also collected under the optimization method characteristic.

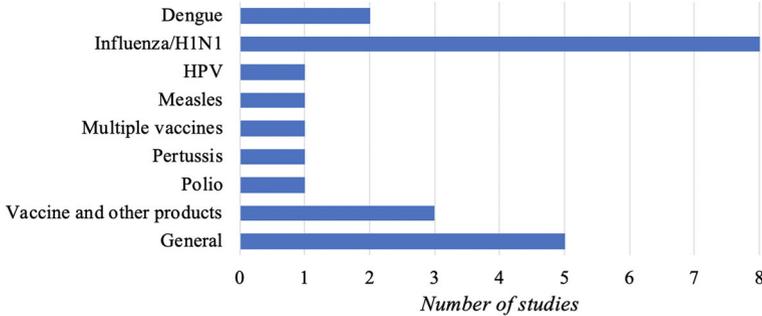


Fig. 2 List of vaccines addressed by the studies included in the rapid review

3 Results and discussion

In this section, we present and discuss the characteristics of the papers that met all of the eligibility criteria of this rapid review. The characteristics discussed below are: country of study, type of vaccine, study objectives, supply chain stage, and optimization method. The following subsections address each one individually.

3.1 Country

We have identified the countries of origin of the data used by the studies. Data from the United States was used in 28% of the studies, data from Pakistan was used in 8% of the studies (Agusto and Khan, 2018; Thakkar et al., 2019), and data from Brazil (Ferreira et al., 2018) and Israel (Hovav and Tsadikovich, 2015) were used in 4% each. Data from more than one country was used in 20% of the studies—these included the UK, Wales, France, USA, Niger, Thailand, Vietnam, Brazil, and the Netherlands. The other 36% of the studied were general applications, not directed to a specific country.

3.2 Type of vaccine

The manuscripts included in this review dealt with different types of vaccines as shown in Fig. 2. The vaccine with the highest number of studies was Influenza/H1N1 with 32%, followed by Dengue with 8% (Agusto and Khan, 2018; Rodrigues et al., 2014), and HPV (Demarteau et al., 2012), Measles (Thakkar et al., 2019), Pertussis (Girard, 2010), and Polio (Tebbens et al., 2010) were each considered in 4% of studies. Addressing vaccines and other products (including antidotes, vital vaccines, medicines to treat HIV/AIDS, malaria, tuberculosis, among others) occurred in 12% of papers, and 4% of studies addressed multiple vaccines (Engineer et al., 2009). A total of 20% of the studies were included in the general category (which includes articles that exclusively deal with vaccines but do not specify which).

3.3 Study objectives

We divide the studies into six categories according to their objectives. Many of the studies, 40%, aimed at reducing impacts of an outbreak or pandemic by helping in the decision-making

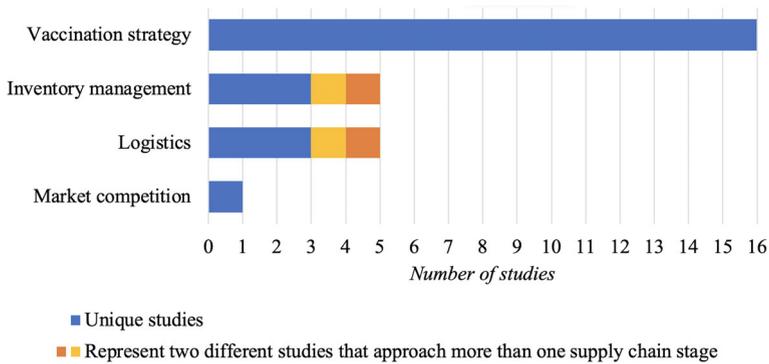


Fig. 3 Stage of the supply chain addressed by each study included in the rapid review

process under such situations. The cost reduction with vaccination or vaccine allocation limited by budget was the goal of 20% of the studies. Meanwhile, allocation or availability of vaccines was sought to be optimized in 20% of the studies (Chen et al., 2014; Preciado et al., 2014; Samii et al., 2012), and another 20% of studies dealt with the general reduction of disease impacts (Engineer et al., 2009; Ferreira et al., 2018; Medlock and Galvani, 2009; Meyers et al., 2009). Two other objectives that were identified, each of them addressed in 4% of the studies, were: to understand the impacts of new manufacturers on vaccine prices (Lauton et al., 2019) and to improve stockpile management of vaccines for eradicated diseases (Tebbens et al., 2010), which are common operations research applications.

3.4 Supply chain stage

The studies were separated into four unique categories, as shown in Fig. 3, according to the vaccine supply chain stage addressed. More than half, 64%, addressed vaccination strategy. Of these, a portion of the studies focused on the allocation of vaccines in cases of disease outbreak while others focused on the best use of resources in a situation of a limited budget. Studies addressing the inventory management and logistics stages accounted for 12% each, and 8% dealt with both of these stages (shown by the yellow and orange bars in Fig. 3) (Chen et al., 2014; Venkatramanan et al., 2019). Finally, only 4% of studies addressed competition (specifically, the impact of new manufacturers on vaccine prices) (Lauton et al., 2019).

If we consider the definition of a vaccination strategy, it could be thought of as part of strategic planning. However, in this review, we can see the difference in studies that focused on general management activities from those that focused specifically on vaccination distribution. This is shown by 64% of the studies which exclusively aimed at improving vaccination strategies. Their strategies were defined in order to meet the momentary needs of a country or region such as increase vaccine coverage of all or a portion of the population, prevent an outbreak, control it or reduce its impact, improve resource allocation, etc.

3.5 Optimization

We identified 14 different types of optimization used in the manuscripts included in the review. Figure 4 presents the identified models. You may notice that there are 29 studies shown in the figure. This is because three studies make use of 2 optimization types and

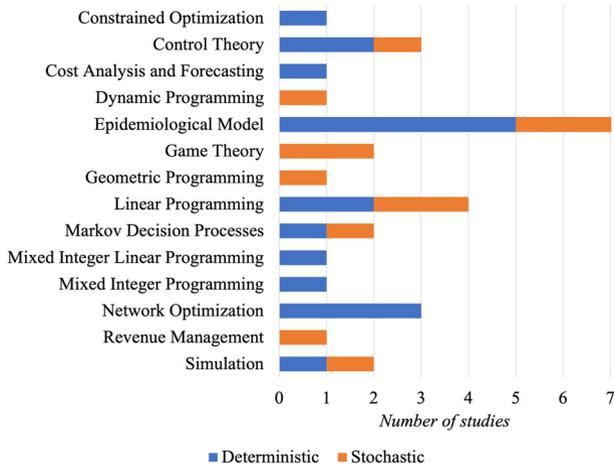


Fig. 4 Number of studies included in the rapid review on each optimization approach

are therefore represented twice in the figure. Many of the studies approached their models from an epidemiological perspective, however, not all specified the optimization type they used. Therefore, the epidemiological model category in Fig. 4 is a general category for the studies that do not dive into the specifics of their optimization models. The most common optimization type was Linear Programming (Chen et al., 2014; Demartean et al., 2012; Tebbens et al., 2010; Hovav and Tsadikovich, 2015), followed by Control Theory (Agusto and Khan, 2018; Ren et al., 2013; Rodrigues et al., 2014) and Network Optimization (Dimitrov et al., 2009; Hovav and Tsadikovich, 2015; Donghyun et al., 2016). We also looked into the nature of the studies and identified them as theoretical or applied (applied work referring to articles that applied their model in a real life scenario). Results show that 56% were theoretical papers while 36% had applied content, and 8% conducted simulation using real data (Lauton et al., 2019; Peng et al., 2019).

We also analyzed the studies in order to understand if the authors considered uncertainty in their models. Approximately, 52% of the studies did not consider uncertainties in their models (i.e. models were deterministic, shown by blue bars in Fig. 4), while 48% did so, meaning that they included stochastic data in their models. In order to deepen our understanding of how this characteristic was included in the model, we also identified the variables that were considered to be uncertain. The articles were split into two uncertainty type categories: (1) need for vaccines and (2) transmission of disease.

(1) Within the vaccine need category, one half considered the demand for vaccines to be uncertain, of which one also considered the uncertainty of the arrival of new donations of supplies (in this case, the work dealt with items that were perishable in humanitarian operations, including other products in addition to vaccines) (Ferreira et al., 2018). The other half of the articles in this category considered the lead time of the arrival of new vaccines to be uncertain. One of these included warehouse stock uncertainty, vaccine efficacy and disease severity (Lauton et al., 2019).

(2) The second category considered disease transmission to be uncertain. One of the papers addressed the probability of a traveler initiating an epidemic at the destination (Dimitrov et al., 2009). And a very specific case considered the rate of mosquito bites as stochastic, as well as the mosquito's lifetime, in the transmission of dengue (Agusto and Khan, 2018). One

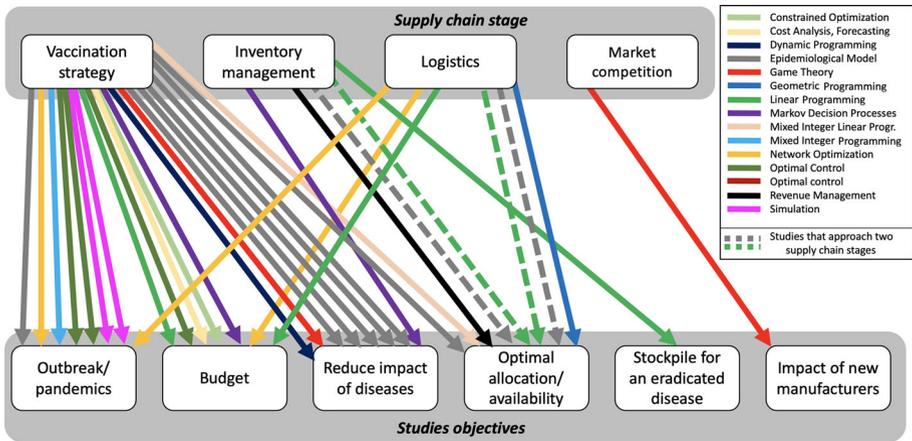


Fig. 5 Relation of the supply chain stage, studies objectives and optimization methods addressed by the manuscripts included in the rapid review

study dealt with the chances of disease transmission in the face of different perceptions of the transmission scenario and different decision making (Hota and Sundaram, 2019).

3.6 Insights

Given the results above, Fig. 5 now illustrates how the studies scaled different optimization methods to the different supply chain stages and what their main goals were. All 25 papers are shown by the arrows (dotted arrows of the same color represent the same paper). We can make the following observations and draw some conclusions from this figure. Even though control theory was one of the most common methods, it was only applied within the vaccination strategy stage and addressed decision-making challenges related to budget and outbreaks/pandemics. Similarly, mathematical modeling is also applied to vaccination strategy with the objective of reducing the impact of diseases and managing budget. Linear programming, on the other hand, is seen to be applied to three different stages (vaccination strategy, inventory management and logistics) and with multiple objectives. Likewise, mixed integer programming was applied to vaccination strategy and logistics towards optimal allocation/availability, reducing impact of diseases and outbreaks/pandemics.

In a similar manner, we can continue to trace the arrows and notice that there's opportunity for future research apply these optimization methods to less common supply chain stages (like supply chain management) and focusing on issues like the impact of new manufacturers or the stockpile for an eradicated disease. There is no doubt that vaccination strategy is one of the most important activities within supply chain management. However, the defined strategies have a direct impact on the other areas of the chain (such as distribution, stocks, etc.). Thus, there is a lack of more comprehensive studies that investigate the effects of such strategies on the rest of the supply chain and a lack of optimization and operations research applications to the integrations of multiple stages. Finally, this rapid review analyzes 25 articles, of which 21 were not included in the most recent work on this topic (Duijzer et al., 2018). We shed light on the applications of optimization methods on the vaccine supply chain and highlight interesting research directions for future works.

3.7 Impact of the studies

In 2011, UNICEF, the World Health Organization and various partners and stakeholders from industry and non-governmental organizations released a document entitled “Developing a Vision for Immunization Supply Systems in 2020”. The document heralded the vision for the future of the supply chain of immunizations at the end of the decade. The expected scenario for 2020 was that supply systems would adapt to global change to be able to take vaccines to the right place, in the right quantity, in the right conditions, and at a good cost (PATH, 2011; Zaffran et al., 2013). The study also mentioned 5 priority areas for achieving this goal: (1) Vaccine products and packaging, (2) Immunization supply system efficiency, (3) Environmental impact of immunization supply systems, (4) Immunization information systems, and (5) Human resources.

When compared to the priority areas of the 2011 document, it is possible to observe that the studies included in this review are in line with the first four areas. Within the first principle are the studies relating to supply chain management (pricing and funding). Within the second principle are studies that address a better regional distribution of warehouses (optimal design of the supply chain infrastructure), storage management, as well as logistics and transport management. Within the third principle are studies that address route optimization for the delivery of vaccines. The fourth principle, which deals with immunization information systems (planning, immunization records, logistics management, etc.), is contemplated by all the optimization models that have the capacity to be integrated into a supply chain management system.

Additionally, the authors of this review participated in a researched project that aimed to improve the vaccine distribution managed by the Brazilian Ministry of Health. Brazil has a unique public health system (SUS) that includes the National Immunization Program (PNI) which is responsible for combating immuno-preventable diseases in the country. The PNI distributes 45 immunobiological types of vaccine and immunoglobulins to a population of approximately 220 million inhabitants, served by more than 34,000 vaccination rooms. Its size reflects in the complexity of the management of this chain, which is increased by the limitation of resources and by the agency’s objective of offering free health services to all citizens at any time. Worldwide, it is estimated that vaccine losses in the chain reach 55% (Parmar et al., 2010). These losses occur due to a variety of reasons such as poor handling during storage and transportation, expiration, lack of demand for the number of units inside the bottle and poor temperature control. Moreover, it is well known that the latter is responsible for a large share of the losses, and it is one of the great problems still faced by the Brazilian government. However, no study in the review has addressed the issue, which is a lack of optimization application in this subject. Therefore, it represents a new research direction for future work in this field of particular interest to the authors.

3.8 Limitations

There were a few biases present in the execution and analysis of this rapid review. First, the short timeline of the rapid review and the authors’ subjective evaluation of inclusions/exclusions criteria undoubtedly introduced bias to the review outcomes. The limitation of years of the study may have left out studies relevant to the discussion. However, we chose to focus on the most recent advancements in the field. In addition, studies published in languages other than those included in this review may have relevant results that have been disregarded. Reviewers may also have missed some relevant articles during the design of the

search process due to double-meanings of certain terms. For example, the term “distribution” has several meanings in the context of vaccines where it sometimes refers specifically to the logistics phase of vaccines and other times to the way in which the vaccines were divided for the population. In these cases, to avoid misinterpretation of the terms, the context of the paper was taken into consideration, and the studies were classified according to the definition of the terms presented in this paper. In some stages, the authors had difficulty classifying the studies. For example, the supply chain stage characteristics were not explicit and their categorization was subjective. In these cases, to reduce bias, more than one reviewer participated in the analysis of the studies, and the categorization was performed by consensus.

4 Conclusions

This rapid review summarized how 14 optimization methods are scalable to the challenges of the vaccine supply chain, specifically to the four identified components. The 25 studies that met the inclusion criteria were classified according to their objectives, type of vaccine, supply chain stage and type of optimization used. The manuscripts were also analyzed to see if uncertainties were considered and if the problem was addressed as a network problem.

Results showed that most studies (56%) applied optimization methods to improving vaccination strategies. Under different scenarios, those studies sought to help decision-makers better distribute vaccines to specific portions of the population. To a lesser extent, (20%) of studies dealt with inventory management and logistics. Given that these are two areas where optimization is commonly used in general supply chains, we expected a greater proportion of the studies to address these two stages within large-scale vaccine supply chain. Therefore, we encourage future research in these areas. We also comment on the lack of studies that integrate two or more components of the supply chain. Changes and improvements in one stage will impact other stages, therefore, the OR community should consider this as future research directions.

Author Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by JML, CCM and MA. The first draft of the manuscript was written by JML and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability All information discussed in this work about the studies included in the review is available in “Appendix A”.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Appendix A

Summary of the 20 manuscripts included in the rapid review.

Table 3 Manuscripts included in the rapid review

References	Main goal	Supply chain part	Vaccine/Disease	Optimization approach	Solution applied	Outbreak	Uncertainty	Network
Agusto and Khan (2018)	Outbreak/pandemics	Vaccination strategy	Dengue	Optimal control	No	Yes	Yes	No
Briat and Verriest (2009)	Outbreak/pandemics	Vaccination strategy	General	Epidemiological model	No	Yes	No	No
Chen et al. (2014)	Optimal allocation/availability	Logistics and inventory management	General	Linear programming	Yes	No	No	Yes
Demarteau et al. (2012)	Budget	Vaccination strategy	HPV	Markov model and linear programming	No	No	No	No
Dimitrov et al. (2009)	Outbreak/pandemics	Logistics	H1N1	Network optimization	No	Yes	Yes	Yes
Tebbens et al. (2010)	Stockpile for eradicated disease	Inventory management	Polio	Linear programming	No	Yes	Yes	Yes
Engineer et al. (2009)	Reduce impact of diseases	Vaccination strategy	Multiple vaccines	Dynamic programming	Yes	No	No	No
Ferreira et al. (2018)	Reduce impact of diseases	Inventory management	General	Markov decision processes	No	No	Yes	No
Girard (2010)	Budget	Vaccination strategy	Pertussis	Cost analysis, forecasting	Yes	No	No	No
Goldstein et al. (2010)	Outbreak/pandemics	Vaccination strategy	Influenza	Simulation	Yes	Yes	Yes	Yes
Hovav and Tsadikovitch (2015)	Budget	Logistics	Influeza	Linear programming + Network	Yes	No	No	Yes
Donghyun et al. (2016)	Outbreak/pandemics	Vaccination strategy	General	Network optimization	No	Yes	No	Yes
Lauton et al. (2019)	Impact of new manufacturers	Supply chain management	Vaccine and other products	Game theory	Yes	No	Yes	No
Medlock and Galvani (2009)	Reduce impact of diseases	Vaccination strategy	H1N1	Epidemiological model	Yes	Yes	No	No

Table 3 continued

References	Main goal	Supply chain part	Vaccine/Disease	Optimization approach	Solution applied	Outbreak	Uncertainty	Network
Meyers et al. (2009)	Reduce impact of diseases	Vaccination strategy	H1N1	Epidemiological model	Yes	Yes	No	No
Preciado et al. (2014)	Optimal allocation/availability	Logistics	Vaccine and other products	Geometric programming	Yes	Yes	Yes	Yes
Ren et al. (2013)	Outbreak/pandemics	Vaccination strategy	H1N1	Optima control + Mixed integer programming (MIP)	No	Yes	No	No
Rodrigues et al. (2014)	Budget	Vaccination strategy	Dengue	Optimal Control	No	Yes	No	No
Samii et al. (2012)	Optimal allocation/availability	Inventory management	Influeza	Revenue management	No	No	Yes	Yes
Savachkin and Uribe (2012)	Outbreak/pandemics	Vaccination strategy	Influeza	Simulation	Yes	Yes	No	Yes
Peng et al. (2019)	Reduce impact of diseases	Vaccination strategy	General	Epidemiological model	No	Yes	Yes	Yes
Standaert et al. (2019)	Budget	Vaccination strategy	Influenza	Constrained optimization	Yes	No	No	No
Thakkar et al. (2019)	Reduce impact of diseases	Vaccination strategy	Measles	Epidemiological model	No	No	Yes	No
Hota and Sundaram (2019)	Reduce impact of diseases	Vaccination strategy	General	Game theory applied to epidemiological model	No	Yes	Yes	Yes
Enayati and Özaltn (2020)	Optimal allocation	Vaccination strategy	Influenza	Epidemiological model, mixed-integer programming (MIP)	No	Yes	No	No
Venkatramanan et al. (2019)	Optimal allocation	Inventory and logistics	Influenza	Epidemiological Model	No	No	No	Yes

Appendix B

Appendix B presents a summary of each of the manuscripts included in the study, presenting the problems addressed, their objectives, the application of optimization in the supply chain, and the results achieved.

Table 4 Manuscripts included in the rapid review

References	Overview of the problem description
Agusto and Khan (2018)	This paper investigates the transmission dynamic of dengue and studies the impact of imperfect vaccine in the bid to control the dengue. Their approach is to write and solve the optimal control theory model and then using sensitivity analysis to test and develop control strategies that reduce transmission. Specifically, they focus on the use of insecticide and the use of vaccination. Results showed that the use of both significantly reduce transmission; also, as the cost of one increases, the use of the other increases as well
Briat and Verriest (2009)	This work presents a modified SIR model that includes a distribute delay when modeling the rate at which infected people recover. The model is validated with data from an influenza epidemic in a school and was used to develop an optimal vaccination strategy (control theory application) by measuring the cost of campaign and the time spent by the population being sick. The model is run through a numerical example
Chen et al. (2014)	This paper develops a linear programming model for the distribution networks of generic WHOEPI vaccines in developing countries. They run 4 different scenarios in addition to the baseline model. The model was applied to the supply chains of 3 countries, making it easy to adapt it to different environments and use it as a planning and evaluation tool
Demarteau et al. (2012)	This paper presents two model: a markov decision model and a linear program. The markov model estimates the cost and the number of cervical cancer cases for a population of 100 000 women at prevention steady state level, for each prevention strategy analysed separately. Then, using this as input, the Linear Program finds the optimal mix of cervical cancer prevention strategies to minimize the expected cervical cancer incidence rate within a fixed budget, with additional constraints on screening and vaccination coverage. It was applied in UK and Brazil data and resulted in a reduction of cancer cases
Dimitrov et al. (2009)	This paper presents an optimization model for distributing a stockpile for treatment of infected cases during the early stages of a pandemic, prior to the wide availability of vaccines. The optimization method efficiently searches large sets of intervention strategies applied to a stochastic network model of pandemic influenza transmission within U.S. cities. Two main results arise: (1) for mildly transmissible strains, an aggressive community-based antiviral treatment strategy involving early, widespread, pro-rata distribution of antivirals to States can contribute to slowing the transmission, and (2) For more highly transmissible strains, outcomes of antiviral use are more heavily impacted by choice of distribution intervals, quantities per shipment, and timing of shipments in relation to pandemic spread. The results provide support for the management of future influenza pandemics

Table 4 continued

References	Overview of the problem description
Tebbens et al. (2010)	This paper develops a framework for determining the optimal management of a vaccine stockpile over time. It is applied to the polio vaccine stockpile for the post-eradication era. The framework includes a Linear Program and is used to discuss issues on the development and use of the polio vaccine stockpile. This serves as context in discussions among decision makers by demonstrating how optimization may lead to useful results in terms of the ordering strategy that minimizes the present value of public health and vaccine costs
Engineer et al. (2009)	The authors examine the complicating characteristics of the catch-up scheduling problem and design a Dynamic Programming algorithm that constructs a schedule for a child based on their vaccination history and current age that are optimal with respect to the potential coverage provided to the child. The paper presents four solutions obtained for two different real-life scenarios for children requiring catch-up schedules
Ferreira et al. (2018)	This paper aims to build a Markov decision-making model to find the optimal ordering (collecting) policy and inventory management of perishable items for humanitarian organizations in continuous aid operations, considering uncertain (stochastic) demands and donations and deterministic deterioration rate. Different experiments are presented to show the different optimal ordering policies for different shelf lives of critical perishable goods. The outputs of the model are the actions that must be executed at each decision period, as a function of the inventory level at the onset of the current decision period
Girard (2010)	This paper performs a cost analysis that compares the total costs and benefits among different immunization programs with varying percentages of vaccination coverage. Data from England and Wales is used. When minimizing the total social costs, they find that the program with 90% coverage maintained over time is best since the social benefits outweigh the costs
Goldstein et al. (2010)	This paper develops a stratified mass-action model and tests different influenza vaccination strategies on a population in Utah using simulation and representing the dynamics as a network. Considering age as the stratification, they found that the top priority in an allocation of a sizeable quantity of seasonal influenza vaccinations goes to young children (0–6), followed by teens (14–18), then children (7–13), with the adult share being quite low. They compare the results with influenza vaccination coverage in the US
Hovav and Tsadikovich (2015)	In this work, the authors aimed to reduce the costs of vaccine distribution without reducing the effectiveness of the existing vaccination campaign. They consider the number of manufacturers, distributing to distribution centres and clinics. The developed Mixed Integer Programming Model is applied to simulate several different scenarios of demand and supplier numbers. They achieved a 12% reduction in costs in a simulated scenario

Table 4 continued

References	Overview of the problem description
Donghyun et al. (2016)	This work aims to improve the distribution of vaccines based on the concept of minimal flow, and thus reduce the number of infected people until a cure emerges. They introduce the problem as the social-relation-based vaccine distribution planning problem (SVDP). Based on simulations, their model presents a better distribution strategy than a random distribution
Lauton et al. (2019)	The work aims to understand the impacts faced by a non-for-profit buyer related to the inclusion of a new manufacturer. It is understood that the entry of a new generic supplier can help to reduce the cost of the product but contributes to an increase in supply chain risk. The work divides a buyer's performance into two stages: negotiation and coordination. For the bilateral negotiation model, the Nash Bargaining Model is used, and in the coordination model, a Mathematical Model is used
Medlock and Galvani (2009)	This paper focused on determining optimal vaccine allocation for influenza considering five outcome measures: deaths, infections, years of life lost, contingent valuation, and economic costs. The model tracks 17 age groups and tests all possible age-based vaccination policies. They found that optimal vaccination is achieved by prioritizing schoolchildren and adults aged 30 to 39 years. An explanation for this is that children are most responsible for transmission, and their parents serve as bridges to the rest of the population. Therefore, age-specific transmission dynamics is paramount to the optimal allocation of influenza vaccines
Meyers et al. (2009)	On this occasion, the authors focused on determining optimal vaccine allocation for influenza considering three outcome measures: deaths, infections and hospitalizations. It was found that optimal allocations of vaccine among people in different age groups and people with high-risk conditions depends on the schedule of vaccine availability relative to the progress of the epidemic. For the projected schedule of H1N1 vaccine availability, the optimal strategy to reduce influenza-related deaths is to initial target high-risk people, followed by school-aged children (5–17) and then young adults (18–44). The optimal strategy to minimize hospitalizations, however, is to target ages 5–44 throughout the vaccination campaign, with only a tiny amount of vaccine used on high-risk people. Optimizing at each vaccine release time independently does not give the overall strategy
Preciado et al. (2014)	This work, in addition to considering the existence of vaccines, takes into account the existence of drugs that can prevent the continuation of a disease, such as an antidote. The objective then was to find the optimal distribution of both limited-budget and unlimited-budget products. The problem is solved in polynomial time using geometric programming (GP). They illustrate the solution applied to a real aerial network

Table 4 continued

References	Overview of the problem description
Ren et al. (2013)	This work presents a multi-city resource allocation model to distribute a limited amount of vaccine in order to minimize the total number of fatalities due to a smallpox outbreak. The model decides the amount of limited supplies to deliver and which infection control measure (isolation, ring, or mass vaccination) to use in each location in order to decrease the number of fatalities. The proposed model approximates the disease propagation dynamics in order to represent the problem as a mixed integer programming problem. The model is applied to a case study in planning an emergency response to a hypothetical national smallpox outbreak, which shows the possibility of saving a significant number of lives compared with a prorated allocation policy
Rodrigues et al. (2014)	This work considers a scenario where a vaccine for dengue is existent. Thus, the objective is to simulate the optimization of disease control according to vaccine efficacy and vaccine coverage. Also, the scenario where the pediatric population would be vaccinated, and the scenario where the entire population would be randomly vaccinated are simulated. They perform an analysis with an optimal control approach to understand the impact of introducing a vaccine
Samii et al. (2012)	This work addresses the optimization of vaccine distribution and management of reserved stocks when there are two classes of the population. It is common for a vaccination to be carried out with priority for a portion of the population, such as health professionals. They perform numerical simulations to sense the impact of the model on the actions of different decision-makers. They conclude that in some scenarios the allocation of vaccines outweighs or impacts the reserve of vaccines for a specific population
Savachkin and Uribe (2012)	This work uses simulation-optimization to create a dynamic vaccine allocation model. The study presents a simulation using data from 4 counties in Florida. The presented model has the capacity to redistribute resources in face of the changes that occurred during the outbreak situation. The main contribution of the study is that it gives the decision maker a model that allows him to modify the parameters as the situation of an epidemic changes
Peng et al. (2019)	This work presents a susceptible-infected-susceptible model. The model considers the probability of individuals becoming infected with heterogeneous spatial conditions. The study takes into account the impact of infections by individuals who move and with heterogeneous conditions of proximity. The study confirmed that the distance radius in individuals directly impacts the agility with which an epidemic is fought. The results obtained were observed through simulations
Standaert et al. (2019)	This study proposes a constrained optimization model to test influenza vaccination strategies in the American scenario. The study considers the existence of multiple vaccines and tests multiple vaccination strategies with US data. The objective was to confirm that the model can determine an optimal vaccination strategy based on different age groups when the scenario is of a limited budget

Table 4 continued

References	Overview of the problem description
Thakkar et al. (2019)	This study considers the scenario of vaccination campaigns against measles in Pakistan, and its results were used in the 2018 vaccination campaign. One of the main contributions of this study is that it considers scenarios where the supply chain infrastructure is not perfectly adequate, which matches the reality of many developing countries
Hota and Sundaram (2019)	This study considers the scenario of decisions regarding vaccination in the face of different possibilities of human behaviour (perspection). They investigated "decentralized vaccination decisions by human decision-makers against networked SIS epidemics in a population game framework"
Enayati and Özaltın (2020)	This study focuses on optimizing the vaccination strategy to halt the advance of an early-stage epidemic. The study proposes separating vaccine distribution for different age groups and regions to find the best distribution strategy. The study is composed of epidemic model models with a nonlinear mathematical program and a global optimization algorithm
Venkatramanan et al. (2019)	This study considers the US scenario regarding seasonal Influenza. Through simulation, the study seeks to find the best way to distribute vaccines to American states, in order to reduce the risk of an epidemic. The study found that sending vaccines in advance to regions that start epidemics can reduce vaccination campaign size by 17%

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