A MULTI-CRITERION APPROACH TO OPTIMAL VACCINATION PLANNING: METHOD AND SOLUTION*

Abstract

Seasonal influenza is a serious public health concern, against which vaccination is one of the most effective ways to protect people. However, the effect of vaccination on containing influenza spread critically depends on the immunization programme adopted. Therefore, the problem of finding the optimal combination of vaccination strategies, with a view to decreasing the programme cost, enhancing vaccination efficiency, and improving societal benefits, is of great theoretical and practical importance. We develop a multiple criteria mathematical programming model to address the problem, analyze the model, and derive the structural properties of the optimal solution. Conducting extensive numerical studies to assess the merit of the model, we find that an integrated strategy embracing early-stage indiscriminate mass vaccination with late-stage targeted vaccination outperforms other strategies in cost and efficacy.

Keywords: influenza vaccination; vaccine supply chain; targeted vaccination; optimal vaccination strategy

---

*This paper is a corrected, extended, and enriched version of the paper presented at the International Conference on Industrial Logistics ICIL-2018, Beer Sheva, Israel, 15-17 May, 2018.

1. Introduction

An acute respiratory illness that spreads as a seasonal epidemic and necessitates the development of a new vaccine every year, influenza annually causes great losses in both human lives and financial expenses. Seasonal influenza has become a serious public health concern, against which vaccination is one of the most effective ways to protect people. Specifically, usage of vaccination can significantly reduce the transmission rate of infection from the infected to susceptible individuals, curtailing the disease spread. This results in lower morbidity and mortality in the population, see, e.g., World Health Organization (WHO) (2011), Turner et al., (2003), Andre et al. (2008), Clements et al. (2011), Özaltin et al. (2011), Center for Disease Control and Prevention (CDC) (2013), Hovav and Herbon (2017) etc.

Different vaccination strategies can be adopted, depending on the timing of the epidemic outbreak and medical resources availability. In this study we distinguish among three main types of vaccination strategy, namely *mass*, *random*, and *targeted vaccination*. *Mass vaccination* involves administration of vaccine doses to a large population over a short period of time, *random vaccination* means to vaccinate randomly chosen members of the community, while *targeted vaccination* seeks to vaccinate a comparatively small group of people that either have the highest impact on the disease spread (e.g., medical staff) or are most likely affected by the disease (e.g., children, seniors).

The effectiveness of a vaccination strategy over a planning horizon is typically evaluated with respect to the following performance measures: (i) the cost of the immunization programme comprising a specific vaccination strategy or a combination of vaccination strategies, (ii) the vaccination efficacy, and (iii) the societal benefits. The planning horizon is the time period that spans the three main stages of an influenza season, comprising the (i) beginning (during October), (ii) peak (from November to January), and (iii) ending (from February to March) stages.

The *cost* of a vaccination strategy is estimated as the sum of direct and indirect costs incurred in the entire vaccination supply chain, to be described in detail below. *Vaccination efficacy* (VE) is defined as the fraction of people no longer susceptible and immune due to vaccination, which, in turn, leads to decrease mortality and morbidity. A convenient and popular way to estimate VE is to measure the integrated characteristic known as post-vaccine reproduction number PVRN (see, e.g., Halloran et al., 1997; Becker and Starczak, 1997; Tanner et al., 2008), whereby the smaller the PVRN is, the lesser is the morbidity of the epidemic and the faster the epidemic dies out. Finally, *societal benefits* (SB) include the number of prevented visits to doctors and the mean number of saved working days in terms of cost (see, e.g., Özaltin et al., 2011, and Hovav and Tsadikovich, 2015).

It is important to note that the above three performance measures (criteria) are in conflict, i.e., there is no single optimal strategy that simultaneously optimizes all three criteria. Optimal vaccination planning over a planning horizon subject to a limited budget and medical resources is a challenging task. Thus, finding a solution for such a multi-criterion optimization problem amounts to a search for a so-called *Pareto-optimal* solution, which constitutes the main purpose of our work. Recall that a Pareto-optimal solution is a feasible solution that cannot be improved with respect to one criterion without worsening at least one of the other criteria. After all the Pareto-optimal solutions (or their sufficiently complete subset) are found, a decision-maker may select among them the most preferred alternative.

Complementary to Becker and Starczak (1997), Tanner et al. (2008), and Glasser et al. (2010), we focus on determining the optimal amounts of vaccine doses to be assigned to different population *groups at risk.* Yet the main difference between our work and theirs is that we take into account the three vaccination strategies (mass, random, and targeted) discussed above and solve the problem in the context of multi-criterion optimization. It is worth noting that the mathematical model that we develop recommends, as an optimal solution, an integrated approach to vaccination planning whereby the mass or random strategy is to be used in the first stage, whereas the targeted strategy is to be deployed in later stages of the influenza season. Despite more than five decades of research on classical vaccination planning, which is primarily based on the susceptible-infectious-recovered (SIR) model (to be described below), to the best of our knowledge, this is the first time that application of multi-criterion analysis for optimal vaccination planning is considered with regard to epidemiology and operations research.

The rest of the paper is organized as follows: In the next section we describe a typical vaccine supply chain (VSC) and discuss the main vaccination strategies. In Section 3 we provide a brief survey of the closely related literature. In Section 4 we introduce the problem under study and formulate a multi-criterion mathematical programming model. We present the solution algorithm and computational experiments in Section 5. In Section 6 we summarize the research findings and discuss the managerial insights, whereas in Section 7 we conclude the paper and suggest future research topics. For the sake of completeness, we give the basic definitions from immunization theory in the Appendix.

2. The Vaccine Supply Chain

The influenza vaccination process begins at the moment the WHO determines and announces the expected influenza epidemic risk, strain type, vaccine type, and production rate (this usually takes place in January in the northern hemisphere). After that, vaccine manufacturers initiate the vaccine

production process. After being produced, the vaccine undergoes testing, which usually takes 45 to 60 days. Assume that the vaccine testing is performed in June and July, and that the vaccine is packed and ready to be shipped from the manufacturers in August. The vaccination planning horizon starts in August and terminates in March of the following year, with a total duration of 33 weeks.

Figure 1, which is borrowed from Hovav and Tsadikovich (2015), illustrates a typical VSC. The chain consists of two major "players", namely a manufacturer and a healthcare organization (HCO). The cooperation between them starts when the HCO sends a request for the vaccine to the manufacturer. The production of the influenza vaccine starts before a vaccination season. The produced vaccine goes through control checking and then is packed and transported from the manufacturer to the distribution centres (DCs) of the HCO, and then from the DC to clinics, hospitals, and other customers in accordance with their demands. Finally, at the clinics the vaccine is distributed among the population groups (see Figure 1). The interested reader can find detailed explanations for the operations of the VSC with an emphasis on product type, production process, and vaccine distribution in Duijzer et al. (2018).

The main role of the VSC is three-fold: (a) to ensure effective vaccine storage, handling, and stock management; (b) to guarantee effective logistics management, and (c) to provide rigorous temperature control in the cold chain. The ultimate goal is to ensure the uninterrupted availability of quality vaccines from manufacturers at acceptable service/delivery levels so that opportunities for vaccination will not be missed because vaccines are unavailable.

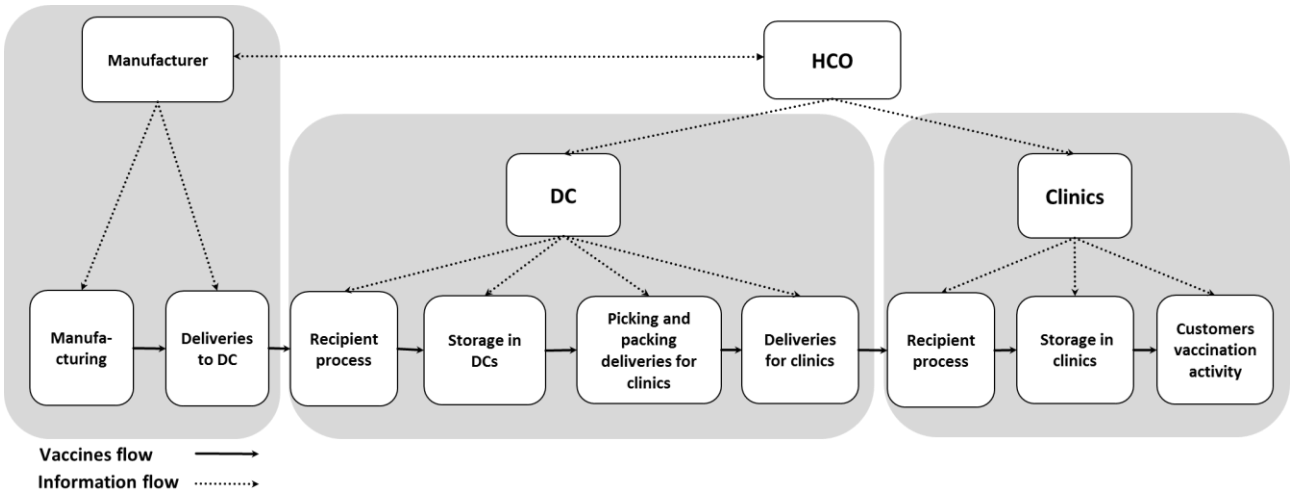


Figure 1. Main VSC components and process flows (source: Hovav and Tsadikovich, 2015)

In order to provide an overall high-quality vaccination service, the HCO needs to make a set of strategic decisions before the start of the influenza vaccination season. Particularly, the HCO has to decide how many vaccine doses should be ordered to minimize the total VSC cost. In particular, the

VSC costs (including the direct/indirect medical/non-medical costs) contain the following main components:

- the costs associated with the selection of vaccine manufacturers and assignment of DCs to manufacturers in case of multiple manufacturers and multiple DCs,
- the expenses of the DCs, i.e., the cost of transporting vaccines from the manufacturers to the DCs, the cost of the logistics service from the DCs to clinics, and inventory costs at the DCs,
- the expenses of the clinics, i.e., the cost of transporting and delivering vaccines from the DCs to the clinics, the inventory/storage costs at the clinics, the service costs of administering vaccine injections made by nurses and physicians to diverse groups of population, and the costs associated with possible vaccine shortage.

Therefore, the decisions regarding the number of doses to be ordered and distributed in each stage of the vaccination season has a major impact on disease propagation and it is heavily dependent on the chosen immunization programme comprising various vaccination strategies. In the next sub-section we discuss the different types of vaccination strategies in detail.

2.1. Vaccination Strategies

There is a vast body of medical literature on diverse vaccination strategies and their combinations. However, their mathematical modelling is limited to the study of the simplest cases (we refer to Tanner et al. (2008) for a review of the current situation). In the present paper we concentrate on studying three main types of vaccination strategy, namely the *mass*, *random*, and *targeted strategies*, while exploration of a wider variety of vaccination strategies is the subject of our future research.

Aiming to vaccinate large population groups over a short period of time, *mass vaccination* seems to be the most effective strategy when the budget is unlimited. This vaccination strategy ensures that the entire population is prepared for future attacks, so decreasing the need for surveillance of contacts. However, in real life, resources are often limited, so such a strategy becomes impractical. On the other hand, *random immunization* means to randomly select a fraction of individuals to be vaccinated without accounting for their heterogeneity (age, gender, occupation, and so on). Such a strategy can lead to vaccination of sustainable-to-disease individuals or persons who are in general isolated from the main mass of the population. Consequently, the impact of *random immunization* on preventing the disease spread may be relatively small.

On the other hand, *targeted vaccination* is mainly directed towards the high-risk groups, which can be heavily affected by the disease (e.g., elderly people, children, people with chronic illnesses,

medical workers), as well as groups that are responsible for the disease spread (e.g., medical staff). Such a strategy allows better utilization of the scarce resources, such as vaccines, logistics resources, and finances.

The existence of various vaccination strategies raises a crucial question of finding an optimal immunization programme. The following literature review section addresses this issue.

3. Literature Review

Vaccination is known to be a primary strategy used by modern health organizations in the battle against influenza. Mathematical modelling plays a major role in analyzing and evaluating different strategies to allocate limited resources for guaranteeing the best quality of the vaccination service during influenza outbreaks. To date, two major modelling approaches have been developed; deterministic and stochastic. In this paper, the focus is on the analysis and development of the deterministic approach, which consists of the following three major groups.

The first group, constituting the majority of all the models, seeks to evaluate predetermined vaccine composition strategies in order to see which composition of the proposed vaccine strains may be the most effective. The main objective of such models is to reduce the susceptible population below the epidemic threshold at the minimum cost, see, e.g., Muller (1997), Patel et al. (2005), Pourbohloul et al. (2005), Wu et al. (2005) etc. For instance, Wu et al. (2005) investigated whether the forecasted epidemic strain policy suggested by the WHO can be further improved by including the antigenic history of the vaccine. They developed a dynamic program to determine the optimal strain composition. Özaltin et al. (2011) showed that choosing several most prevalent strains for the vaccine composition might be beneficial.

Determining the optimal strain composition for the vaccine is not sufficient to guarantee that the disease spread will be successfully contained. In particular, the optimal but lately produced vaccine composition may have a very small positive effect on disease prevention. This means that synchronization between the release date of the vaccine and its efficiency should be taken into account. The tradeoff between the timing of vaccination and the effectiveness of the response has been extensively studied by Duijzer et al. (2018b) and Özaltın et al. (2018). Complementarily to the above works, our study focuses on finding the optimal vaccination strategy rather than the composition of the vaccine.

Due to their computational complexity, exact solution methods for determining the optimal strain composition, e.g., linear and mixed-integer programming, become ineffective for solving medium- and large-scale problems. This is why the development of heuristic algorithms has received substantial attention from researchers. In this context, we would like to highlight the comparatively

new techniques of artificial immune learning (El-Sherbiny and Alhamali, 2013), social engineering optimization (Fathollahi-Fard et al., 2018), virus colony search (Fathollahi-Fard and Hajiaghaei-Keshteli, 2018), three-level metaheuristics (Hajiaghaei-Keshteli and Fathollahi-Fard, 2018), and hybrid metaheuristics (Sahebjamnia et al., 2018) which are being used in practice along with the classical heuristics like genetic algorithms and tabu search.

The second group considers strategic planning in the context of broad socio-economic analysis of the VSC. Such a broad view permits coordination of the global interests in the entire supply chain, on the one hand, and the corporate (local) interests of all the individual stakeholders, such as DCs and geographically distributed clinics, on the other hand. Dasaklis et al. (2012) defined the role of logistics operations and examined their management that may assist the control of epidemic outbreaks.

Through an analysis of selected papers on epidemics control and logistics operations, they posed open questions on supply chain management in the context of epidemics control. In this stream of research, Gerdil (2003), Chick et al. (2008), Herlin and Pazirandeh (2012), Hovav and Herbon (2017), Hovav et al. (2017), and Duijzer et al. (2018a) considered different aspects of strategic vaccination supply chain management. Although the main driver behind this study is to reduce the total cost associated with the operation of the VSC, our suggested solution approach is quite different. Specifically, instead of focusing on better coordination among the different actors within the VSC, hence improving management decisions, we reduce the operational costs by determining the optimal vaccination strategy.

The third group focuses on identifying the optimal vaccination strategy. In particular, exploiting a graph representation of the disease spread, Cohen et al. (2003) proposed a novel efficient strategy for immunization, requiring no knowledge of the nodes' degrees or any other global graph information. The proposed strategy, referred to as acquaintance immunization, calls for the immunization of random acquaintances of random nodes (individuals). In turn, Holme (2004) showed that the targeted immunization strategy, wherein a neighbour with the highest number of the neighbours is vaccinated, outperforms the random strategy. Pastor-Satorras and Vespignani (2002) revealed that the random uniform immunization of individuals does not lead to the eradication of infections in all complex networks. Successful immunization strategies can be developed only by taking into account the inhomogeneous connectivity properties of scale-free networks. In particular, targeted immunization schemes, based on the nodes' connectivity hierarchy, sharply lower the network's vulnerability to epidemic attacks. Ferguson et al. (2006) showed that since school-age children have the highest transmission rates, they should be vaccinated first. On the other hand, vaccinating the elderly first gives the lowest impact on transmission. Bansal et al.

(2006) presented a comparative analysis of two vaccination strategies: (a) mortality-based - targeted at high-risk population groups and (b) morbidity-based - targeted at high-prevalence groups. Their findings show that the choice of the optimal strategy is heavily dependent on the reproductive rate of the virus. Specifically, for a moderate transmissible disease, the morbidity-based strategy prevails over the mortality-based strategy. On the other hand, for a highly transmissible disease, the mortality-based strategy is better. Aballéa et al. (2007) compared two traditional strategies, namely universal mass vaccination (UMS) and a targeted vaccine programme (TVP), based on a cost-effectiveness analysis. They found that UMS is better than TVP. Similar to Aballéa et al. (2007), Clements et al. (2011) found that UMS outperforms TVP in terms of probability of influenza-related illness and costs associated with the necessary medical interventions. Duncan et al. (2012) observed that UMS may have a substantial advantage, from individual and societal perspectives, in comparison with TVP. However, it is important to realize that even when effective vaccines are created, acute shortages are possible, especially in areas with limited production capacities, making it difficult or impossible to obtain a sufficient number of vaccines in time to protect the at-risk populations. The prospect of a shortage motivates health authorities to devise strategies for ensuring that people who are most likely to suffer the complications of influenza are vaccinated first. Hence, CDC (CDC, 2013) recommended that the populations that should be targeted first are pregnant women, infants, seniors, and healthcare workers. For instance, Meltzer et al. (2005), Glasser et al. (2010), Nichol (2008, 2011), and Duijzer et al. (2018a) focused on identifying the optimal vaccine allocation strategies to reduce influenza morbidity and mortality within age-structured populations. Using simulation, they found that vaccinating either younger children or older adults averts the most deaths. Based on mathematical models, as well as epidemiological data, Longini and Halloran (2005), and Medlock and Galvani (2009) showed that targeting vaccination towards school-age children is a preferred strategy to prevent mortality and morbidity in the population group. Chen et al. (2008) sought to find the best strategy to immunize a population with a minimum number of immunization doses. They proposed a new graph-partitioning strategy that requires 5% to 50% fewer immunization doses compared with the targeted strategy, while achieving the same degree of immunization.

Recently, Nguyen and Carlson (2016) provided a comparative analysis of different vaccination strategies depending on when and how many vaccine doses become available. Yamin et al. (2016) found that prioritizing individuals on the basis of age and co-morbidities along with considering individual infection history may have a greater impact on disease reduction in targeting and promoting influenza vaccinations. Recently, Ng et al. (2018a,b) proposed a multi-criterion model for evaluating the impact of targeted vaccination on the quality and efficacy of immunization

programmes. They provided a fast heuristic based on the TOPSIS scalarization of multiple criteria in combination with the Borda ranking method for finding the Pareto-optimal points.

In the following table, we summarize the main differences between the papers considered above.

Table 1. The main characteristics of the surveyed papers

Paper Authors	Solution Approach			Multiple-criteria optimization problem	Socio-economic aspects	Hybrid strategies
	Deterministic optimization	Contact network	Scenario-based			
Pastor-Satorras and Vespignani (2002)		x	x			
Holme (2004)		x				
Bansal et al. (2006)		x				x
Aballéa et al. (2007)					x	
Clements et al. (2011)					x	
Duijzer et al. (2018a,b)	x					x
Nguyen and Carlson (2016)	x					
Ng et al. (2018a,b)	x			x		
Our work	x	x	x	x	x	x

Although the cited papers provide valuable insights into the socio-economic aspects of vaccination programmes, they do not provide an integrated quantitative cost-benefit-efficacy outlook that takes into account potential variations in the three criteria of a vaccination programme over the course of the vaccination season, nor do they consider the fact that an integrated approach that mixes the vaccination strategies can be more efficient and less costly than the pure strategies. In addition, our paper suggests a different solution approach to treat the problem. Specifically, we use the deterministic linear programming optimization model rather than a simulation or a contact network model. Such an approach has several advantages. First, it does not require thorough and deep knowledge of the complex contact network as the model by Pastor-Satorras and Vespignani (2002) and Holme (2004). Second, contrary to the stochastic optimization models that are hard and computationally intractable for large instances, the linear deterministic optimization model allows a larger degree of computational tractability for large problem instances occurring in practice.

Furthermore, while there are a wide variety of optimization and heuristic approaches for solving the MCMP problem in the literature, we present in this paper a modified version of the reliable and popular solution method called the *augmented epsilon-constraint method* (Mavrotas, 2009) to address the problem.

Basing upon the above-mentioned specific features of the suggested work in comparison with earlier publications, we summarize our main contributions to the vaccine strategy selection problem as follows: (a) we focus on the problem's multi-criterion nature, (b) we formulate the problem as a new multiple criteria mathematical programming model, and (c) we provide a novel, flexible, and computationally effective solution approach oriented towards solving large-scale problem instances.

4. Problem Description and Mathematical Formulation

4.1. Problem Description

The main purpose of healthcare providers all over the world during the vaccination period is to provide a high-quality vaccination service, while keeping the total operational cost at the lowest possible level. To reach this goal, the HCO is to annually decide how many vaccine doses to buy. This decision straightforwardly stems from the optimal vaccination strategy. To address this issue, the influence of different vaccination strategies, i.e., *mass*, *random*, and *targeted*, on the disease spread in the community should be considered. For this purpose, in this paper, we study the deterministic SIR model for a closed community. By closed community, we mean a population in which there is no migration. We make this assumption in order to mimic the population structure that reflects urban settlements. The community considered in this research is divided into a number of different risk groups according to age, place of living, and profession (e.g., groups of babies, infants, teenagers, seniors). The number of members in each group may be different. However, due to the homogeneity of the group, each group includes individuals with similar rates of susceptibility, i.e., the risk to be infected, as well as the risks of morbidity and mortality. The members of each group may have contacts both inside their groups, as well as with members of other risk groups. Thus, the initial number of infected individuals in each group being known, the disease can spread in the entire community. A key point is that disease transmission occurs only when an infected individual contacts a susceptible individual. Note that, for the sake of simplicity, we assume that for each risk group, all the individuals are equally susceptible and contact all other individuals in the population in equal frequencies.

The main purpose of the proposed mathematical model is to find an optimal combination of different vaccination strategies with the intention of preventing a disease outbreak. In other words, we aim to define the optimal number of vaccine doses assigned to the members of each risk group

under different immunization programmes (adopting *mass*, *random*, *targeted* vaccination, and/or a combination of these strategies) in all stages of the influenza season. Note that a mixed strategy is possible wherein different individuals in the same risk group can be vaccinated by various vaccination strategies. For instance, certain group members can be vaccinated under the *targeted strategy*, whereas the remaining members are vaccinated under the *mass* or *random* strategy.

Assessment of the efficacy of an immunization programme is performed through the use of the following performance measures:

(i) The cost of the immunization programme.

(ii) Vaccination efficacy - measured by the post-vaccination reproduction number. This is the number of secondary cases that an initial infective can generate in a community of susceptible individuals with partial vaccine coverage. When the post-vaccination reproduction number is less than one, it means that the disease becomes endemic, i.e., the disease fades away with time without additional interventions. Otherwise, the rate of the disease spread increases and the infection becomes an epidemic.

(iii) Societal benefits - measured by the number of prevented flu cases or by the so-called prevented cost of the disease cases, as in Özaltin et al. (2011).

4.2. Mathematical Formulation

The multi-criterion vaccination planning problem belongs to the domain of MCMP. Specifically, denote by $Z(x)$, $R(x)$, and $B(x)$, the three pertinent performance measures, i.e., cost of the immunization programme, vaccination efficacy, and social benefits, respectively, where x is a vector of the decision variables. Then, we formulate the problem as follows:

$$\left(Min\ Z(x),\ \ Max\ R(x),\ \ MaxB(x)\right) \tag{1}$$

$$x \in X, X \subseteq R^n \tag{2}$$

where X is the feasible set of the variables to be defined below.

Similar to the earlier mathematical models considered by Becker and Starczak (1997) and Tanner et al. (2008), we introduce the notion of *a vaccination plan* (called a *vaccination policy index* by Becker and Starczak, and Tanner et al.). The *vaccination plan* (policy index) v defines how many people can be entirely vaccinated in each group. Since the number of people in each risk group g is known (denoted by f_g), it follows that the index v may take the following possible values in group $g: 0,1,..,\ f_g$. Furthermore, we essentially extend the Becker-Starczak model as we

explicitly introduce and evaluate several possible vaccination strategies, namely *mass*, *random*, *targeted* vaccination, and so on. To this end, combining with the just mentioned concept of vaccination policy, we introduce an additional (and meaningful) concept of *vaccine allocation strategy* φ that defines which type of vaccination strategy is applied to the individuals of a certain group.

In the following we present the notation of the mathematical model:

Sets:

G - set of risk groups, $g \in G$

Φ - set of vaccine allocation strategies, $\varphi \in \Phi$, $\varphi = 1,...,|\Phi|$

v_g^φ - the possible number of people that can be vaccinated by a strategy φ in a risk group g. The possible value of index v_g^φ may change from 0 up to the (known) number of people f_g in group g: $v_g^\varphi = 0,..., f_g$ (for the sake of simplicity, henceforth in some formulae v_g^φ we omit the indices φ and g: $v = v_g^\varphi$)

V_g - set of all possible values of index v_g^φ with respect to group g and allocation strategy φ, $\varphi \in \Phi$; $v_g^\varphi = 0,..., f_g$, $g \in G$.

Parameters:

f_g - the number of individuals in risk group g, $g \in G$

h_g - the proportion of the number of people of risk group g in the entire population

μ_G - the average size of a risk group

M - the maximum number of available vaccine doses

c_g^φ - the cost associated with vaccinating one individual in risk group g by implementing an allocation strategy φ

p - the prevented cost of flu cases (as defined in detail in Özaltin et al., 2011)

C_g - the minimally required coverage rate in risk group g

a_{gv}^φ - the impact of vaccinating v_g^φ individuals in risk group g – with the help of allocation strategy φ on the disease spread (this parameter is explained and formalized by Becker and Starczak (1997) for the case of a single vaccine allocation strategy)

n_g^{φ} - average time required to administer the vaccine to an individual in a risk-group g under the allocation strategy φ

N - total medical-personnel available hours.

For a concise definition of the latter parameter, we need the following demographic and statistical characteristics described in detail by Becker and Starczak (1997) and Tanner et al. (2008):

m - the average contact rate of infected people

u_g - the relative infectivity of individuals in risk group g

s_g - the relative susceptibility of individuals in risk group g

b - the transmission proportion

λ_g^{φ} - the vaccine efficiency for individuals in risk group g under vaccine allocation strategy φ

$$a_{gv}^{\varphi} = \frac{mh_g}{\mu_G}\left[u_g s_g\left[(1-b)\left(f_g - \lambda_g^{\varphi} v_g^{\varphi}\right) + b v_g^{\varphi}\lambda_g^{\varphi}\left(1-\lambda_g^{\varphi}\right)\right] + b u_g s_g\left(f_g - \lambda_g^{\varphi} v_g^{\varphi}\right)^2\right], \forall g \in G, \forall v \in V_g, \forall \varphi \in \Phi$$

Decision variable:

x_{gv}^{φ} - the proportion of vaccinated people within vaccine policy v in risk group g under vaccine allocation strategy φ

We formulate the mathematical model as follows:

To minimize the vaccination cost:

$$Min\ Z = \sum_{g\in G}\sum_{\varphi\in\Phi}\sum_{v\in V_g} v_g^{\varphi} c_g^{\varphi} h_g x_{gv}^{\varphi} \tag{3a}$$

To minimize the reproduction number:

$$Min\ R = \sum_{g\in G}\sum_{\varphi\in\Phi}\sum_{v\in V_g} a_{gv}^{\varphi} x_{gv}^{\varphi} \tag{3b}$$

To maximize the societal benefits:

$$Max\ B = \sum_{g\in G}\sum_{\varphi\in\Phi}\sum_{v\in V_g} p\left(f_g - v_g^{\varphi}\right) x_{gv}^{\varphi}$$

(3c)

subject to

$$\frac{\sum_{\varphi\in\Phi}\sum_{v\in V_g} v_g^{\varphi} x_{gv}^{\varphi}}{f_g} \geq C_g, \forall g \in G \tag{4}$$

$$\sum_{g\in G}\sum_{v\in V_g}\sum_{\varphi\in\Phi} v_g^{\varphi} x_{gv}^{\varphi} \leq M \tag{5}$$

$$\sum_{g\in G}\sum_{\varphi\in\Phi}\sum_{v\in V_g} n_g^{\varphi} v_g^{\varphi} x_{gv}^{\varphi} \le N \tag{6}$$

$$x_{gv}^{\varphi} \ge 0, \forall g \in G; \forall v \in V_g, \forall \varphi \in \Phi \tag{7}$$

In the above formulation, by minimizing the post-reproduction number R we aim to maximize the vaccine efficacy V. Note that the post-reproduction number R is taken in the additive form as in Becker and Starczak (1997), and Tanner et al. (2008). The main difference of (3b) in comparison with the models of R in the latter works is that the individual reproduction numbers a_{gv}^{φ} are summarized in (3b) over all the vaccine allocation strategies, $\varphi \in \Phi$, $\varphi = 1,...,|\Phi|$, as well as over all the values of index $v = v_g^{\varphi}$ and all the risk groups. The prevented costs in the societal benefits B are formalized in the expression (3c); in this notation the expression $\sum_{\varphi\in\Phi}\sum_{v\in V_g}\left(f_g - v_g^{\varphi}\right)$ presents the total number of prevented flu cases in group g under the premise that the latter number must be proportional to the number of people $f_g - v_g^{\varphi}$ in the group left unvaccinated.

Constraint (4) ensures that the total vaccination coverage for the risk-group g is no less than the predefined value C_g. Note that $\dfrac{\sum_{\varphi\in\Phi}\sum_{v\in V_g} v_g^{\varphi} x_{gv}^{\varphi}}{f_g}$ depicts the proportion of vaccinated individuals in a risk group g, in which exactly $\sum_{\varphi\in\Phi}\sum_{v\in V_g} v_g^{\varphi} x_{gv}^{\varphi}$ members are vaccinated. Since the number of vaccine doses is limited, constraint (5) is introduced, whereas the number of personnel's working hours is bound by inequality (6). Finally, constraint (7) guarantees that the decision variables are non-negative.

4.2.1. Properties of the multi-criteria vaccination planning problem

If functions $Z(x)$ and $R(x)$ are monotonically decreasing in each component of the vector decision variable x, and $B(x)$ is monotonically increasing in each component of the vector decision variable x then there always exists a Pareto-optimal solution $x = (x_{gv}^{\varphi})$, for which either all the available vaccines should be used, or the medical personnel available operates full-time, or both. In other words, we have the following result.

Property 1. If functions $Z(x)$ and $R(x)$ are monotonically decreasing in each component of the vector decision variable x, and $B(x)$ is monotonically increasing in each component of the vector

decision x, then there always exists a Pareto-optimal solution $x = (x^{\varphi}_{gv})$ for which at least one of the inequalities (5)-(6) holds as an equation.

Property 2. If functions $Z(x)$ and $R(x)$ are monotonically increasing in each component of the vector decision variable x, and $B(x)$ is monotonically decreasing in each component of the vector decision x, then there always exists a Pareto-optimal solution $x = (x^{\varphi}_{gv})$ for which $\dfrac{\sum_{\varphi\in\Phi}\sum_{v\in V_g} v^{\varphi}_{g} x^{\varphi}_{gv}}{f_g} \geq C_g, \forall g \in G$ holds as an equation.

We start with the proof of Property 1. Note that Property 2 is proved in the same way.

Proof (by contradiction). Let $x = (x^{\varphi}_{gv})$ be a Pareto-optimal solution for the problem (3)-(7), and assume that constraints (5)-(6) are treated as strict inequalities for this solution. Let y^{φ}_{gv} be another solution such that: (i) $y^{\varphi}_{gv} > x^{\varphi}_{gv}, g \in G, v \in V_g, \varphi \in \Phi$; (ii) both the constraints (5)-(6) are still valid for the y^{φ}_{gv}, and (iii) at least one of the latter constraints holds as an equation.

Further, since $y^{\varphi}_{gv} > x^{\varphi}_{gv}$, constraint (4) evidently holds for y^{φ}_{gv}. Consider now the function $Z(x)$. By the assumption, the function $Z(x)$ is monotonically decreasing, therefore, $Z(x)$ is larger than $Z(y)$, for the considered solutions x and y. Similarly, $R(x)$ is larger than $R(y)$ and $B(x)$ is smaller than $B(y)$. This implies that vector x is not Pareto-optimal. This contradiction proves the claim.

Next we consider the reciprocal property of the vaccination problem. It seems that there is no obvious direct connection between minimization of the reproduction number and maximization of the herd effect. However, Ma and Earn (2006) studied the relation between R and the herd effect for a single population group and derived that there is a one-to-one relation. Thus, in what follows, we extend this result to the case of multiple risk groups and multiple criteria.

Consider the multi-criterion problem reciprocal to the problem (1)-(2), in which the vaccination coverage determined on the left-hand-side of (4) is considered as a (new) criterion $V(x)$, which is to be minimized (instead of $B(x)$), whereas the vaccination efficiency $V(x)$ described, for instance, as the herd effect is considered as a constraint and is bounded from below by a given value M_0:

$$\left(Min\ Z(x),\ Max\ R(x),\ MaxB(x)\right) \tag{1'}$$

$$M(x) \geq M_0;\ \ x \in X, x \subseteq R^n \tag{2'}$$

Property 3. The two vaccine allocation problems (1-2) and (1'-2') are equivalent, namely finding the Pareto-optimal set (*Z, B*) that results in a critical coverage $M = M_0$ and finding the Pareto-optimal set (*Z, M*) that has a corresponding value of the herd effect, is achieved for the same set of vector *x*. The proof, along the same line of reasoning as Favati and Pappalardo (1985), is straightforward.

5. The Solution Algorithm and Experiments

A comprehensive survey of recent algorithmic approaches for solving multi-criteria optimization problems is given in many textbooks (see, e.g., Steuer, 1986; Greco et al., 2005). Finding the optimal solutions when explicitly accounting for multiple objectives in a combinatorial problem is a mathematically challenging endeavour. To this end, the *goal programming* and the *compromise programming* approaches have been widely used. The novelty of this paper is that amongst the wide variety of such methods that have been developed thus far, we select and develop the ε-constraint method (Mavrotas, 2009; Felfel et al., 2016) in combination with the method of ranking Pareto-optimal alternatives, known as the Borda method (Saari, 2000).

The idea behind the ε-constraint method is based on the well-known lexicographic optimization technique, i.e., when one criterion, namely the vaccination programme cost, is selected as the principal criterion, while the two remaining criteria are treated as constraints. The right-hand-side constraints are defined by finding the ranges of changing the two criteria, and for them, a grid of possible values in the two-dimensional space efficiency-benefits is constructed iteratively. Subsequently, different single-criterion problems are systematically solved in each grid cell whereby each solution provides a Pareto-optimal point. The grid size is selected adequately fine so that either all or most of the Pareto-optimal solutions can be found. The choice of the grid size defines the running time of the entire method. For finding the ranges of the grid for the two constraints, the corresponding single-criterion problems are solved. The optimal value of each single criterion provides one end of the range, while the other end (nadir) is usually defined by experts. However, such a procedure does not ensure that the obtained solution is always efficient. To overcome this issue, Mavotas (2009) suggested the *augmented* ε-constraint method, which is successfully implemented in our work.

In the next stage, after the algorithm finds the set of Pareto-optimal solutions, none of them can be claimed to be better than the others. Hence, we suggest adding an additional post-optimization Borda-type procedure providing their rankings that disclose the decision-makers' preferences.

It is noted that in the Borda method (see, e.g., Saari, 2000), each Pareto-optimal solution is treated as a separate alternative. There are K decision-makers, each of whom ranks the list of alternatives in order of his/her preference. For example, a decision-maker assigns the rank value 1 to his/her most preferred alternative, 2 to the second most preferred, and so on. These values, in turn, are used to compute initial information, called *Borda points*. The quantity of *Borda points* given by a decision-maker to each Pareto-optimal alternative is equal to the total number of candidate alternatives minus the assigned rank value plus 1. For instance, when there are n (Pareto-optimal) alternatives, a candidate alternative receives n points from an expert if it is the first preference, $n-1$ points for the second preference, $n-2$ for the third, and so on; it receives one point for being ranked last. Next, for each alternative, all the Borda points from the K experts are added up, and the alternative with the largest sum of Borda points wins; other alternatives are ranked correspondingly by their sums of Borda points.

Subsequently, the obtained ranks may be normalized within the range from 0 to 1 and the obtained scores are perceived as the ultimate ranks of the alternatives we are searching for. This procedure guides the search towards the most preferred Pareto-optimal solution. As a version, this ranking procedure can be performed after a number of iterations of the ε-constraint method defined by the decision-maker. This procedure can also be taken as one of the heuristic preference definition schemes in GAMS.

The main factors explaining the predominance of the suggested algorithm in comparison with the existing approaches are: (a) multi-criterion decision-making allows for a wider spectrum of obtained Pareto-solutions to be obtained, (b) the ε-constraint method permits rapid determination of the Pareto solutions, and (c) the linear deterministic optimization model leads to a larger degree of flexibility and computational tractability.

Next, we analyzed the experimental behaviour of the above algorithm. To this end, we used the commercial solver CPLEX, on the NEOS server (Czyzyk et al., 1998). The hardware specifications of the server machines were as follows: Dell Power Edge R410 servers, CPU - 2x Intel Xeon X5660 @ 2.8GHz (12 cores total), HT Enabled, 64 GB RAM. The analysis was carried out on a set of 100 test problems generated by experts at the HCO CLALIT Health Services (the largest of Israel's state-mandated health service organizations). All the test problems contained deterministic input data resembling the real-life data of the HCO, namely the test parameters were generated by the

experts on the basis of real data, with possible variations of up to ±20%. For instance, the demand in Table 2 was calculated as the average annual demand over the years 2010-2016.

In the numerical studies, we used five different risk groups with respect to age. Table 2 presents the demand of each group type divided in accordance with the vaccination season stage (note that the demand for vaccine equals the number of individuals in each risk group). This number, for each stage t, t = 1, 2, 3 (corresponding to the beginning, peak, and final stages respectively) was taken as an average across the years 2010-2016. The set of vaccine programmes included the three possible vaccination strategies of *mass*, *random*, and *targeted* vaccination. The remaining data regarding the contact rate, relative infectivity/susceptibility, and others were borrowed from Tanner et al. (2008), and Hovav and Tsadikovich (2015). To find the solution for the linear program (3)-(7), we used the commercial software GAMS along with the CPLEX algorithm.

Table 2. Demands for the vaccine in the groups

Group type	$t=1$	$t=2$	$t=3$
1 (infant - play age)	19,928	37,700	246
2 (primary school age - adolescence)	24,432	46,298	311
3 (middle age)	64,287	117,932	797
4 (senior)	51,433	97,461	636
5 (elderly)	115,080	218,066	1,432

5.1. Numerical results

The computational results of applying the suggested algorithm are graphically presented in Figures 2(*a*)-(*c*). In particular, Figure 2(*a*) presents the Pareto-optimal frontier for the case where *cost* is selected as the principal objective function, Figure 2(*b*) presents the Pareto-optimal frontier when *societal benefits* is selected as the principal objective function, and Figure 2(*c*) presents the Pareto-optimal frontier for the case where *vaccination efficacy* is selected as the principal objective function. Each point on the exhibited surface (e.g., *A*, *B* or *C*) presents a non-dominated Pareto solution corresponding to the corresponding conflicting objective functions. For instance, the coordinates of point *A* are *cost* = 0.65, *vaccination efficacy* = 0.42, and *societal benefits* = 0.41, while those of point *B* are *cost* = 0.41, *vaccination efficacy* = 0.22, and *societal benefits* = 0.72. Note that the performance measures, i.e., *cost*, *vaccination efficacy*, and *societal benefits*, are normalized. Furthermore, using the Borda method, the decision-maker selects point *A* as the preferred solution.

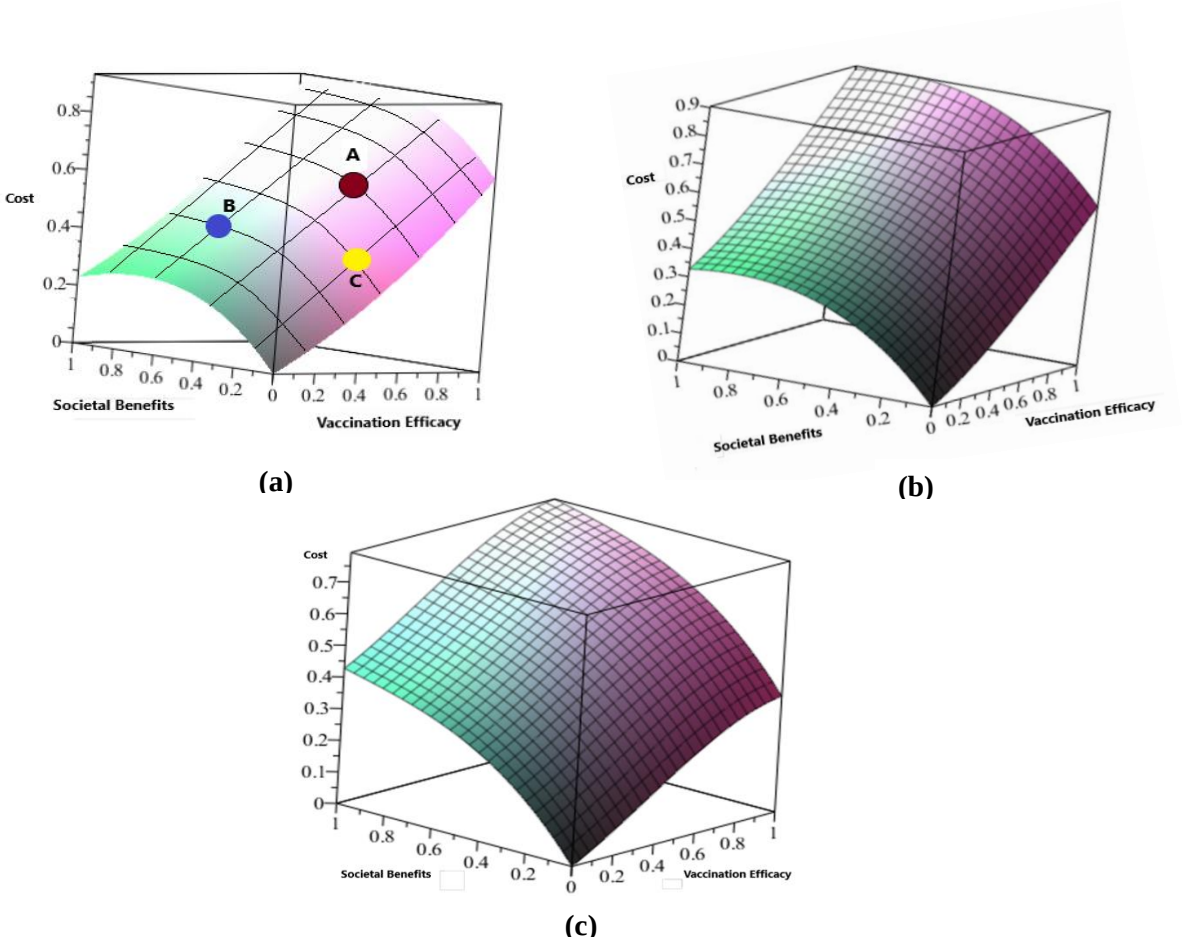
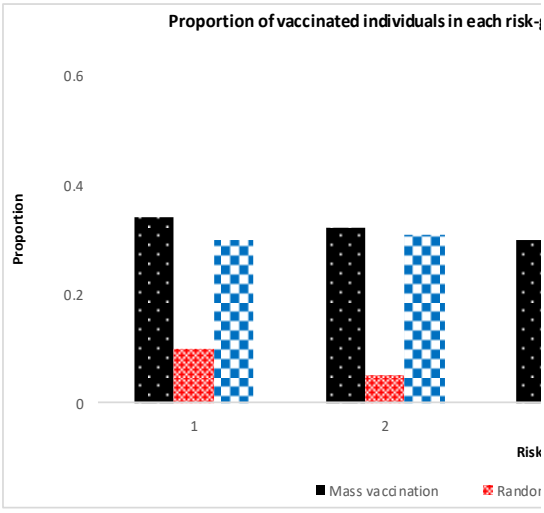


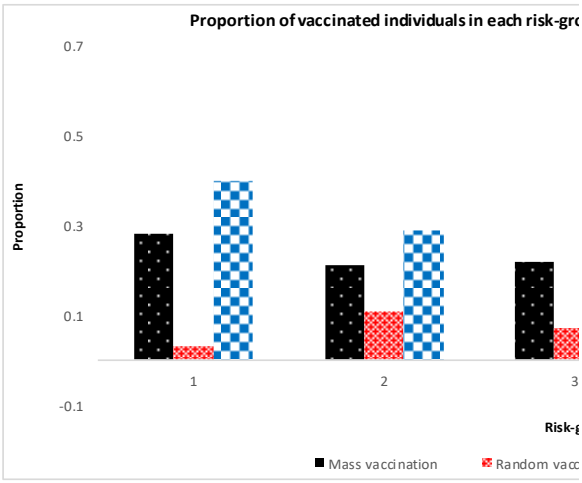
Figure 2. Pareto frontiers for three main objective functions: cost, benefits, and vaccination efficacy

The performance of the epsilon-constrained method greatly depends on the choice of the principal objective function. Our results show that a change in the principal objective function leads to new positive ideal solutions (PIS) and negative ideal solutions (NIS), so new Pareto-optimal frontiers. For instance, changing the principal objective function from *cost* (Figure 2(*a*)) to *societal benefits* (Figure 2(*b*)) increases the cost but improves the corresponding societal benefits.

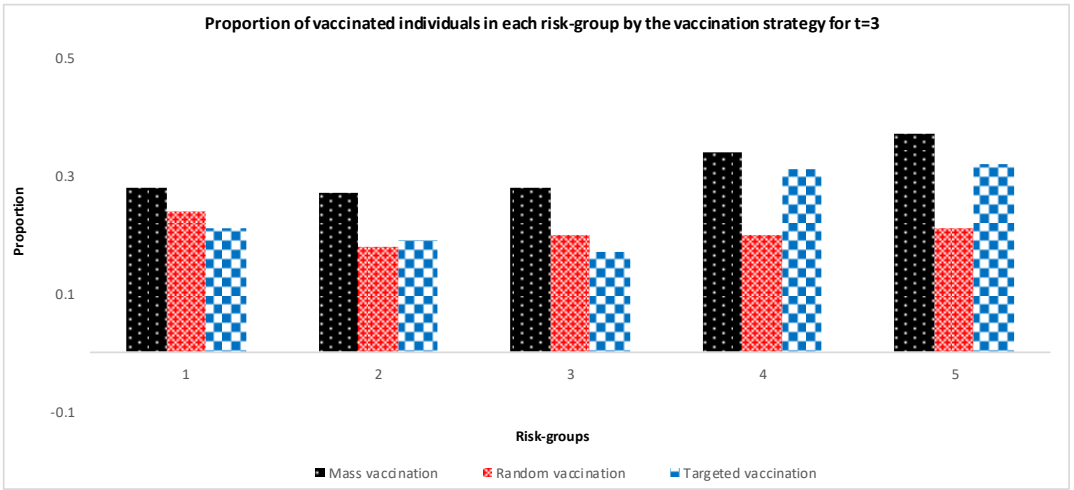
Furthermore, based on the obtained results of the numerical studies, we depict in Figure 3 the proportions of individuals in each risk-group vaccinated under each vaccination strategy for $t = 1,2,3$.



(a)



(b)



(c)

Figure 3. The proportion of the individuals in each risk-group vaccinated by each vaccination strategy for: (a) time period $t=1$, (b) time period $t=2$, and (c) time period $t=3$

From Figures 3(*a*)-(*c*), we observe that the results found are non-trivial. Specifically, at the beginning of the vaccination season, i.e., $t=1$, the fraction of individuals vaccinated by the *mass* strategy is larger than the proportion of individuals vaccinated under *targeted* and *random* vaccination. This is due to the fact that the demand for vaccination in this period is still small, so *mass* vaccination can be more effective. However, the beginning of the second period, i.e., $t=2$, is characterized by a significant increase in the required vaccine doses (see Table 2). Consequently, *mass* vaccination becomes not cost-effective. Therefore, as can be observed from Figure 3(*b*), the *targeted* vaccination strategy prevails over *mass* and *random* vaccination. Finally, during the last period of vaccination, i.e., $t=3$, the requirement for vaccination drops. This results in the preference of switching from *targeted* vaccination to the *mass* and *random* strategies (as shown in Figure 3(*c*)).

5.2. Sensitivity analysis

In order to investigate the impacts of the different parameters on the optimal solution, we conduct the sensitivity analysis. We begin with exploring the effect of the number of available vaccine doses. We summarize the results in Tables 3-5. Note that we denote *mass* vaccination as *M*, *random* as *R*, and *targeted* as *T*.

Table 3. Effect of the number of vaccines on the optimal solution for $t=1$

Amount of available vaccines (as a % from the total demand)/Groups	Infant - play age			Primary school age - adolescence			Middle age			Senior			Elderly		
	M	R	T	M	R	T	M	R	T	M	R	T	M	R	T
60%	0.19	0.01	0.38	0.15	0	0.29	0.11	0	0.31	0.18	0.01	0.48	0.19	0.02	0.5
80%	0.32	0.09	0.33	0.34	0.05	0.25	0.35	0.04	0.24	0.38	0.03	0.4	0.4	0.05	0.42
90%	0.49	0.1	0.22	0.43	0.11	0.21	0.42	0.1	0.19	0.5	0.04	0.27	0.51	0.05	0.28

Table 4. Effect of the number of vaccines on the optimal solution for $t=2$

Amount of available vaccines (as a % from the total demand)/Groups	Infant - play age			Primary school age - adolescence			Middle age			Senior			Elderly		
	M	R	T	M	R	T	M	R	T	M	R	T	M	R	T
60%	0.01	0	0.43	0.03	0	0.32	0.01	0	0.33	0.01	0	0.68	0	0	0.78
80%	0.27	0.05	0.41	0.22	0.1	0.3	0.22	0.08	0.29	0.21	0.01	0.58	0.25	0.02	0.62
90%	0.5	0.08	0.31	0.45	0.05	0.22	0.44	0.1	0.26	0.52	0.01	0.31	0.55	0.02	0.32

Table 5. Effect of the number of vaccines on the optimal solution for $t = 3$

Amount of available vaccines (as a % from the total demand)/Groups	Infant - play age			Primary school age - adolescence			Middle age			Senior			Elderly		
	M	R	T	M	R	T	M	R	T	M	R	T	M	R	T
60%	0.21	0.19	0.24	0.21	0.16	0.19	0.23	0.16	0.19	0.27	0.2	0.38	0.29	0.21	0.39
80%	0.29	0.21	0.23	0.29	0.18	0.18	0.3	0.17	0.17	0.31	0.21	0.35	0.33	0.22	0.36
90%	0.54	0.15	0.13	0.5	0.12	0.11	0.49	0.14	0.12	0.6	0.16	0.14	0.61	0.15	0.14

Our computational results show that for the high-demand periods, i.e., $t = 1$ and $t = 2$ (see Table 2), reduction in the number of the available vaccine is reflected in a decrease in the vaccinated individuals under the *random strategy* (see Tables 3-4). This is due to the fact that this strategy implies random vaccination, so when the vaccine stock is limited, the available vaccine should be used in a more effective way, i.e., by either *mass* or *targeted* vaccination. In addition, we observe that as the vaccine stock increases, the percentage of the individuals vaccinated under the *mass strategy* increases. This result can be explained as follows: if the amount of vaccine is enough to cover the entire population, there is no advantage in using either the *random* or *targeted strategy*. On the other hand, when the vaccine stock is low, targeted vaccination becomes more cost-beneficial.

Moreover, it follows from Table 6 that, with a decrease in the initial vaccine stock, the number of vaccinated individuals in the low-risk groups (e.g., *primary school age–adolescence* and *middle age*) diminishes more rapidly than in the high-risk groups (e.g., *senior* and *elderly*).

Table 6. Effect of the number of vaccines on the vaccination rates

Period/ Group	Infant - play age			Primary school age - adolescence			Middle age			Senior			Elderly		
	60%	80%	90%	60%	80%	90%	60%	80%	90%	60%	80 %	90%	60%	80%	90%
$t = 1$	0.58	0.74	0.81	0.44	0.64	0.75	0.42	0.63	0.71	0.67	0.81	0.81	0.71	0.87	0.84
$t = 2$	0.44	0.73	0.89	0.35	0.62	0.72	0.34	0.59	0.8	0.69	0.8	0.84	0.78	0.89	0.89
$t = 3$	0.64	0.73	0.82	0.56	0.65	0.73	0.58	0.64	0.75	0.85	0.87	0.9	0.89	0.91	0.9

No less interesting and non-trivial result is found when comparing the consumption rates with the available amount of vaccine in stock (see Table 7 and Figure 4). We observe that with an increase in the number of available vaccine doses, the inventory-consumption rate decreases. This

means that during the vaccination period, the total amount of purchased vaccine may not be fully utilized. Such a result has a non-trivial managerial insight and allows the decision maker to re-consider their current inventory policies by ordering less vaccine in comparison with the existing demand. Note that a similar result is observed in Hovav and Tsadikovich (2015).

Table 7. Consumption rates

Amount of available vaccines (as a % from the total demand)	Vaccine inventory	Consumption	Inventory-consumption rate
60%	477623.4	477513.5	100%
80%	636831.2	613265.8	96%
90%	716435.1	658504.2	92%

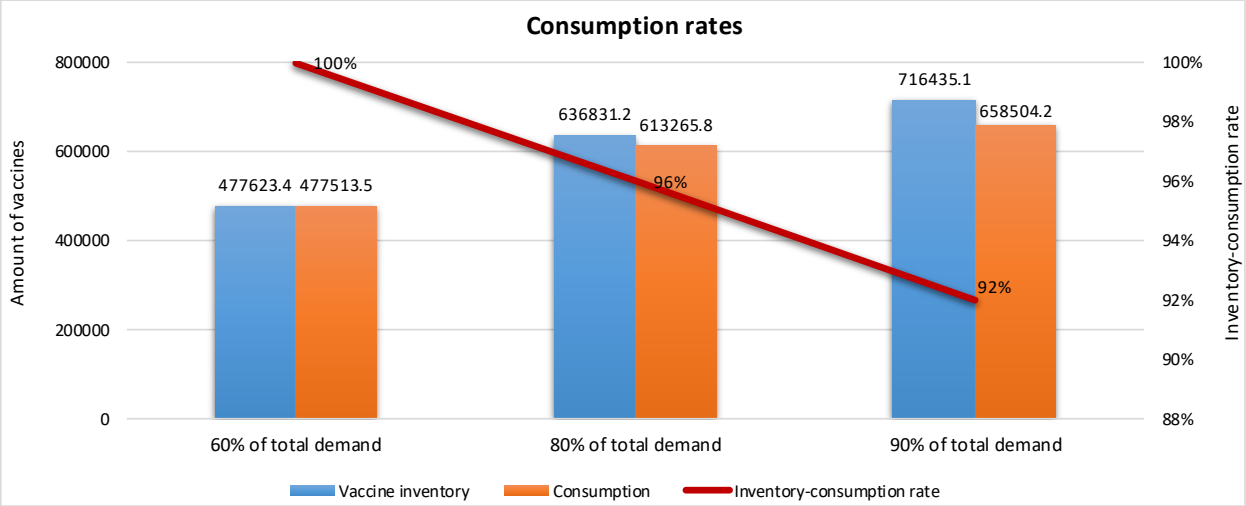


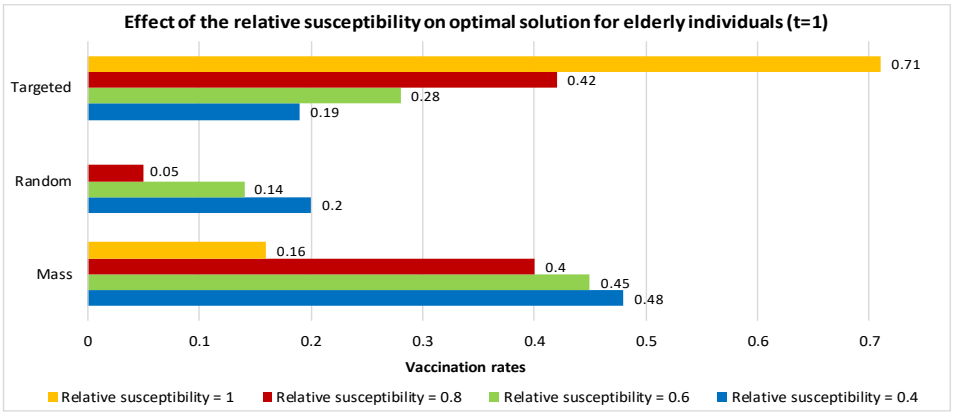
Figure 4. Consumption rates as functions of stocks

Next, we continue with exploring the impact of the relative susceptibility of individuals s_g on the optimal solution. Specifically, we conduct an analysis on the elderly risk group. Recall that $s_5 = 1$ means that the elderly individuals are highly susceptible to the disease. In the sensitivity analysis, we range s_5 from the level of 0.4 to 1 with a step size of 0.2. We assume that the amount of available vaccine is 80% of the entire demand. We report the results in Table 8 and Figure 5.

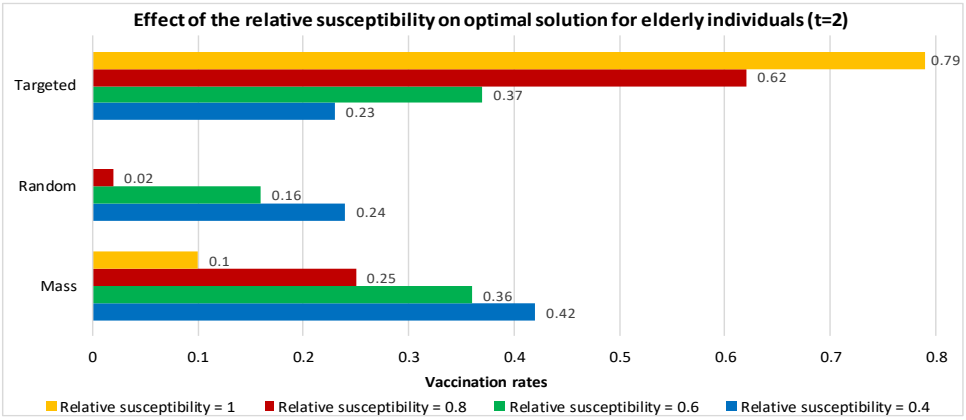
Table 8. Effect of the relative susceptibility on the optimal solution for s_5

Relative susceptibility (s_5)	$t=1$			$t=2$			$t=3$		
	M	R	T	M	R	T	M	R	T
0.4	0.48	0.2	0.19	0.42	0.24	0.23	0.48	0.29	0.14
0.6	0.45	0.14	0.28	0.36	0.16	0.37	0.39	0.27	0.25
0.8	0.4	0.05	0.42	0.25	0.02	0.62	0.33	0.22	0.36

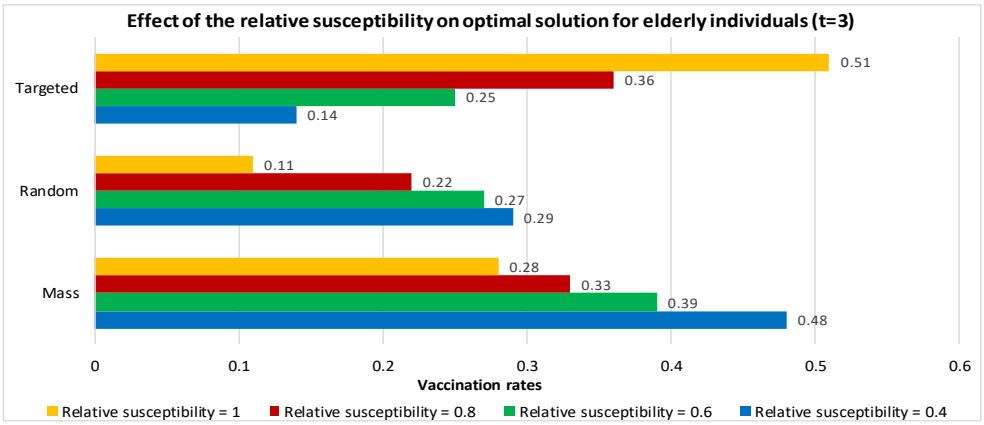
1	0.16	0	0.71	0.1	0	0.79	0.28	0.11	0.51



(a)



(b)



(c)

Figure 5. Effect of the relative susceptibility on the optimal solution for elderly individuals for: (a) time period $t=1$, (b) time period $t=2$, and (c) time period $t=3$

An increase in relative susceptibility of the elderly population means that they are more exposed to the disease and can transmit it to the remaining individuals in the community. Thus, to control the disease spread, when the vaccine stock is limited, *targeted* vaccination becomes more effective in comparison with the *mass* and *random strategies*, as it follows from our observations summarized in Table 8.

6. Operational and Managerial Insights

The contribution and innovation of this paper consist of the following aspects:

I. We consider the multi-criteria problem of optimal vaccine distribution in different groups of a population as an MCMP problem, and solve it using the standard ε-constraint method of finding the Pareto-optimal solutions in conjunction with the Borda method for prioritizing the Pareto-optimal solutions.

II. We find that the *targeted* vaccination strategy is more effective than the *mass* and *random* vaccination strategies, especially when the demand is high and the supply of available vaccine is limited.

III. We use the commercial GAMS solver CPLEX to solve large-sized problem instances based on statistical data provided by experts. Computational experiments within the considered study reveal that our approach outperforms the empirical approach currently adopted for vaccination planning in practice. Specifically, the annual costs of the immunization programmes derived from the proposed mathematical model are about 10% less than the average annual vaccination costs estimated by experts.

IV. From the operations research perspective, the proposed mathematical model can be used as an effective decision-making tool for determining the optimal vaccination strategy in different healthcare organizations around the world. This tool allows the decision-maker to define the principal strategy or the optimal combination of the strategies over the vaccination period. As a result, the operation of the entire VSC can be significantly improved by reducing the operational costs, while providing acceptable customer satisfaction.

7. Conclusion

We develop a mathematical model for determining the optimal vaccination strategy embracing the conflicting performance measures of cost, vaccination efficacy, and societal benefits for a susceptible population that comprises distinct sub-groups of customers, having different cost and benefit characteristics. The optimization model returns an overall minimum cost, while ensuring that the recommended strategy complies with the required standards of societal benefits. The

rationale for the proposed approach is given in Section 4. HCOs can use this model as a decision support tool for determining various aspects of the vaccination process, including the optimal distribution of vaccines among clinics and different population sub-groups. Furthermore, the model permits the conduct of post-optimization sensitivity analysis that provides additional insights on how costs vary once critical parameters change.

The suggested mathematical model differs from those known in the current literature; however, the numerical results obtained in this study are close and similar to earlier research results. Specifically, the targeted vaccination strategy seems to be superior to both the mass and random vaccination strategies. It is worth noting that the suggested model permits the decision-maker to find the best combination of several vaccination strategies.

In future research we intend to add the factor of time, breaking the vaccination season into several stages. By extending the *SIR* model, we intend to study the so-called *SEIR* model that has an additional compartment *E* containing the individuals that are exposed and hence infected, but not yet infectious. Another prospective study is to add stochastic conditions and design a solution method for the stochastic multi-criteria vaccination planning problem.

Directions for future research can also include incorporating additional stakeholders into the model, such as governmental and public entities, and optimization of the clustering of clinics, as mentioned above. Moreover, although age-based segmentation is commonly used in practice, it would be useful to optimize the segmentation of the population while taking into account additional characteristics, such as occupation, gender, income, health, or ethnicity; this could improve the accuracy and applicability of the model. An additional challenging perspective is to design efficient solution algorithms for the problem in more general environments, including multiple manufacturers, multiple governmental and public agencies, and multiple DCs.

Acknowledgements

We wish to thank the Editor and anonymous reviewers for their constructive and very useful suggestions. The work was supported in part by the University Grant Council under grant number PolyU 152629/16E.

References

Aballéa, S., Chancellor, J., Martin, M., Wutzler, P., Carrat, F., Gasparini, R., Toniolo-Neto, J., Drummond, M. and Weinstein, M. (2007) The cost-effectiveness of influenza vaccination for people aged 50 to 64 years: An international model. *Value in Health*, 10(2), 98-116.

Andre, F.E., Booy, R., Bock, H.L., Clemens, J., Datta, S.K., John, T.J., Lee, B.W., Lolekha, S., Peltola, H., Ruff, T.A., Santosham, M. and Schmitt, H.J. (2008) Vaccination greatly reduces disease, disability, death and inequity world wide, *Bulletin of the WHO*, 86(2), 140-146.

Bansal, S., Pourbohloul, B. and Meyers, L.A. (2006) A comparative analysis of influenza vaccination programs. *PLoS Medicine*, 3(10), e387.

Becker, N. G. and Dietz, K. (1996). Reproduction numbers and critical immunity levels for epidemics in a community of households. In *Athens Conference on Applied Probability and Time Series Analysis* (pp. 267-276). Springer, New York, NY.

Becker, N.G. and Starczak, D.N. (1997) Optimal vaccination strategies for a community of households. *Mathematical Biosciences*, 139(2), 117-132.

CDC (Center for Disease Control and Prevention) (2013) Seasonal influenza vaccine supply for the U.S 2012-13 influenza season, available at: www.cdc.gov/flu/about/qa/vaxsupply.htm.

Chen, Y., Paul, G., Havlin, S., Liljeros, F. and Stanley, H.E. (2008) Finding a better immunization strategy. *Physical Review Letters*, 101(5), 058701.

Chick, S.E., Mamani, H. and Simchi-Levi, D. (2008) Supply chain coordination and influenza vaccination, *Operations Research*, 56, 1493-1506.

Clements, K.M., Chancellor, J., Nichol, K., DeLong, K. and Thompson, D. (2011) Cost-effectiveness of a recommendation of universal mass vaccination for seasonal influenza in the United States. *Value in Health*, 14, 800-811.

Cohen, R., Havlin, S. and Ben-Avraham, D. (2003) Efficient immunization strategies for computer networks and populations. *Physical Review Letters*, 91(24), 247901.

Czyzyk, J., Mesnier, M.P. and Moré, J.J. (1998) The NEOS server. *Computational Science and Engineering*, 68-75.

Dasaklis, T.K., Pappis, C.P. and Rachaniotis, N.P. (2012) Epidemics control and logistics operations: A review. *International Journal of Production Economics*, 139(2), 393-410.

Diekmann, O., Heesterbeek, H. and Britton, T. (2013) *Mathematical Tools for Understanding Infectious Disease Dynamics*. Princeton University Press.

Duijzer, L. E., van Jaarsveld, W. L., Wallinga, J. and Dekker, R. (2018a) Dose-optimal vaccine allocation over multiple populations. *Production and Operations Management*, 27(1), 143-159.

Duijzer, E., van Jaarsveld, W. and Dekker, R. (2018b) The benefits of combining early aspecific vaccination with later specific vaccination. *European Journal of Operational Research*.

Duncan, I.G., Taitel, M.S., Zhang, J. and Kirkham, H.S. (2012) Planning influenza vaccination programs: A cost benefit model. *Cost Effectiveness and Resource Allocation*, 10(1), 10.

El-Sherbiny, M.M. and Alhamali R.M. (2013) A hybrid particle swarm algorithm with artificial immune learning for solving the fixed charge transportation problem, *Computers and Industrial Engineering*, 64(2), 610-620.

Fathollahi-Fard, A. M., and Hajiaghaei-Keshteli, M. (2018). A stochastic multi-objective model for a closed-loop supply chain with environmental considerations. *Applied Soft Computing*, 69, 232-249.

Fathollahi-Fard, A. M., Hajiaghaei-Keshteli, M. and Tavakkoli-Moghaddam, R. (2018) The social engineering optimizer (SEO). *Engineering Applications of Artificial Intelligence*, 72, 267-293.

Favati, P. and Pappalardo, M. (1985) On the reciprocal vector optimization problems. *J. Optimization Theory and Applications*, 47(2), 181-193.

Ferguson, N.M., Cummings, D.A., Fraser, C., Cajka, J.C., Cooley, P.C. and Burke, D.S. (2006) Strategies for mitigating an influenza pandemic. *Nature*, 442(7101), 448.

Felfel, H, Ayadi, O., Masmoudi, F. (2016) Multi-objective stochastic multi-site supply chain planning under demand uncertainty considering downside risk. *Computers and Industrial Engineering*, 102, 268-279.

Fine, P., Eames, K. and Heymann, D.L. (2011) "Herd immunity": A rough guide. *Clinical Infectious Diseases*. 52(7), 911–916.

Gerdil, C. (2003) The annual production cycle for influenza vaccine. *Vaccine*, 21, 1776-1779.

Glasser, J., Taneri, D., Feng, Z., Chuang, J.H., Tüll, P., Thompson, W., McCauley, M.M. and Alexander, J. (2010) Evaluation of targeted influenza vaccination strategies via population modeling. *PLoS One*, 5(9), e12777.

Greco, S., Figuera, J. and Ehrott, M. (2005) *Multiple Criteria Decision Analysis: State of the Art Surveys*, Springer.

Hajiaghaei-Keshteli, M. and Fathollahi-Fard, A.M. (2018) A set of efficient heuristics and metaheuristics to solve a two-stage stochastic bi-level decision-making model for the distribution network problem. *Computers & Industrial Engineering*, 123, 378-395.

Halloran, M.E., Struchiner, C. and Longini, I.M. (1997) Study designs for evaluating different efficacy and effectiveness aspects of vaccines. *American Journal of Epidemiology*, 146(10), 789-803.

Herlin, H. and Pazirandeh, A. (2012) Nonprofit organizations shaping the market of supplies. *International Journal of Production Economics*, 139(2), 411-421.

Holme, P. (2004) Efficient local strategies for vaccination and network attack. *Europhysics Letters*, 68(6), 908.

Hovav, S. and Herbon, A. (2017) Prioritizing high-risk sub-groups in a multi-manufacturer vaccine distribution program. *The International Journal of Logistics Management*, 28(2), 311-331.

Hovav, S. and Tsadikovich, D. (2015) A network flow model for inventory management and distribution of influenza vaccines in a healthcare supply chain. *Operations Research for Health Care*, 5, 49-62.

Hovav, S., Tell, H., Levner, E., Ptuskin, A. and Herbon, A. (2017) Health care analytics and big data management in influenza vaccination programs: Use of information–entropy approach, Ch. 11 in *The Analytic Process, Strategic and Tactical Steps*, ed. E. Rodriguez, CRC Publ.

Keeling, M.J. and Shattock, A. (2012) Optimal but unequitable prophylactic distribution of vaccine. *Epidemics*, 4(2), 78-85.

Kermack, W.O. and McKendrick, A.G. (1991) Contributions to the mathematical theory of epidemics--I. 1927. *Bulletin of Mathematical Biology*, 53(1-2), 33-55.

Levner, E., Hovav, S., Tell, H., Ptuskin, A. and Herbon, A. (2014) Using entropy for healthcare analytics and risk management in influenza vaccination programs, in: E. Rodriguez and G. Richards (eds), *Proceedings of the International Conference on Analytics Driven Solutions (ICAS 2014)*, Ottawa, Academic Conferences Publication, 63-72.

Longini Jr, I.M. and Halloran, M.E. (2005) Strategy for distribution of influenza vaccine to high-risk groups and children. *American Journal of Epidemiology*, 161(4), 303-306.

Ma, J. and Earn, D.J.D. (2006) Generality of the final size formula for an epidemic of a newly invading infectious disease. *Bulletin of Mathematical Biology*, 68(3) 679-702.

Mavrotas, G. (2009). Effective implementation of the ε-constraint method in multi-objective mathematical programming problems. *Applied Mathematics and Computation*, 213(2), 455-465.

Medlock, J. and Galvani, A.P. (2009) Optimizing influenza vaccine distribution. *Science*, 325(5948), 1705-1708.

Meltzer, M.I., Neuzil, K.M., Griffin, M.R. and Fuduka, K. (2005) An economic analysis of annual influenza vaccination of children. *Vaccine*, 23(8), 1004-1014.

Muller, J. (1997) Optimal vaccination strategies – for whom? Mathematical Biosciences, 139(2), 133-154.

Ng, C.T., Levner, E., Cheng, T.C.E. and Hovav, S. (2018a) Impact of targeted vaccination on quality and efficacy of immunization programs. *Proceedings of ISERD International Conference Colombo*, Sri Lanka, IRAJ Publishers, pp. 9-15.

Ng, C.T., Cheng, T.C.E., Tsadikovich, D., Levner, E., Elalouf, A. and Hovav, S. (2018b) Optimal immunization strategies for groups at risk in vaccine supply chain management. *Proceedings of the 14th International Conference on Industrial Logistics*, ICIL-2018, Beer-Sheva, Israel, May 9-15, Z.Sinuany-Stern and Y. Cohen (Eds.). BGU Publisher, pp. 151-157.

Nguyen, C. and Carlson, J.M. (2016) Optimizing real-time vaccine allocation in a stochastic SIR model. *PloS One*, 11(4), e0152950.

Nichol, K.L. (2008) Efficacy and effectiveness of influenza vaccination. *Vaccine*, 26 (Suppl. 4), D17-D22.

Nichol, K.L. (2011) Cost-effectiveness and socio-economic aspects of childhood influenza vaccination. *Vaccine*, 29, 7554-7558.

Özaltın, O.Y., Prokopyev, O.A. and Schaefer, A.J. (2018) Optimal design of the seasonal influenza vaccine with manufacturing autonomy. *INFORMS Journal on Computing*, 30(2), 371-387.

Özaltin, O.Y., Prokopyev, O.A., Schaefer, A.J., Roberts, M.S. (2011) Optimizing the societal benefits of the annual influenza vaccine: A stochastic programming approach. *Operations Research*, 59(5), 1131-1143.

Pastor-Satorras, R. and Vespignani, A. (2002) Immunization of complex networks. *Physical Review E*, 65(3), 036104.

Patel, R., Longini, I.M. Jr. and Halloran, E.M. (2005) Finding optimal vaccination strategies for pandemic influenza using genetic algorithms. *Journal of Theoretical Biology*, 234(2), 201-212.

Plans-Rubió, P. (2012) The vaccination coverage required to establish herd immunity against influenza viruses. *Preventive Medicine*, 55(1), 72-77.

Pourbohloul, B., Meyers, L.A., Skowronski, D.M., Krajden, M., Patrick, D.M. and Brunham, R.C. (2005) Modeling control strategies of respiratory pathogens, *Emerging Infectious Disease*, 11(8), 1249-1256.

Saari, D.G. (2000) Mathematical structure of voting paradoxes: II. Positional Voting. *Economic Theory*, 15(1), 55-102.

Sahebjamnia, N., Fathollahi-Fard, A.M., and Hajiaghaei-Keshteli, M. (2018). Sustainable tire closed-loop supply chain network design: Hybrid metaheuristic algorithms for large-scale networks. *Journal of Cleaner Production*. 196, 273-296.

Steuer, R.E. (1986) *Multiple Criteria Optimization: Theory, Computation and Application*. New York: Wiley.

Tanner, M.W., Sattenspiel, L. and Ntaimo, L. (2008) Finding optimal vaccination strategies under parameter uncertainty using stochastic programming. *Mathematical Biosciences*, 215(2), 144-151.

Turner, D., Wailoo, A., Nicholson, K., Cooper, N., Sutton, A. and Abrams, K. (2003) Systematic review and economic decision modelling for the prevention and treatment of influenza A and B. *Health Technology Assessment*, 7(35), 1-170.

WHO (World Health Organization) (2011) Developing a vision for immunization supply systems in 2020. Landscape analysis summaries. URL http://www.path.org/publications/files/TS_opt_vision_2020.pdf.

Wu, J.T., Wein, L.M. and Perelson, A.S. (2005) Optimization of influenza vaccine selection. *Operations Research*, 53(3), 456-476.

Yamin, D., Jones, F.K., DeVincenzo, J.P., Gertler, S., Kobiler, O., Townsend, J.P. and Galvani, A.P. (2016) Vaccination strategies against respiratory syncytial virus. *Proceedings of the National Academy of Sciences*, 113(46), 13239-13244.

Appendix: Basic definitions from immunization theory

The SIR model. The first widely known work in the field of immunization modelling is by Kermack and McKendrick (1927, reprinted in 1991), who suggested a mathematical model describing how a disease spreads through a population. This model type, called *compartmental*, divides the population into three main compartments, each containing people that are in the same state of disease, namely susceptible (*S*), infected (*I*), and removed, i.e., recovered (*R*) individuals. According to the capital letters, this model called the SIR model consists of a family of three deterministic differential equations that describe the transition in the population from one compartment to the other as follows:

$$\frac{ds_j}{dt} = -\beta_j s_j i_j$$
$$\frac{di_j}{dt} = \beta_j s_j i_j - \gamma_j i_j$$
$$\frac{dr_j}{dt} = \gamma_j i_j$$

The following notation is used in the SIR-type model:

Table A1: Notation used in the SIR model

J or G	the set of population groups
$s_j(t), i_j(t), r_j(t)$	fractions of the population, respectively, susceptible, infected and removed in population group j at time t
β_j and γ_j	transmission rate and the rate of recovery in population j
β_{jl}	transmission rate between susceptible people from population group j and infected people from population group l
$s_j(0) = s_j^o, i_j(0) = i_j^o, r_j(0) = r_j^0$	given initially boundary conditions

However, despite their simplicity, sophisticated compartmental models cannot be solved analytically due to their nonlinear dynamics nature. This is the reason why in the model described below we consider simplified algebraic equations and inequalities.

Herd immunity (Fine et al., 2011). This term denotes the protection of susceptible individuals against infection because they are surrounded by a sufficient number of immune individuals. The immunity of the latter group may result either from vaccination or recovery from infection.

Herd effect (or *indirect effect of vaccination*) is defined as the proportion of all the people who are saved from infection because of herd immunity. In other words, this is precisely the proportion of people who are still susceptible when the epidemic has died out. The final fraction $G_j(f_j)$, i.e., when $t \to \infty$, of the people susceptible in population j after vaccinating a fraction f_j of the susceptible people in group j at time t. Thus, $G_j(f_j)$ measures the herd effect in population j.

Health benefit HB is defined as the total number of people who escaped infection. *HB* =

$$\overbrace{\sum_{j \in J} N_j G_j(f_j)}^{\text{herd effect}} + \overbrace{\sum_{j \in J} N_j f_j}^{\text{direct effect}}$$

where N_j denotes the size of population group j and f_j the fraction of susceptible people in group j. The sum reflects that there exist two benefit types of vaccination: either the direct effect when the individuals escape infection because they are vaccinated or indirect (herd) effect when they escape infection (in a crowd of vaccinated people) without being vaccinated.

The *vaccination coverage* is the proportion of individuals who are vaccinated (Becker and Starczak, 1997). *Critical vaccination coverage CVC* (Keeling and Shattock, 2012, Plans-Rubió, 2012) is defined as the smallest vaccination fraction that results in a decrease in infections directly after vaccination. CVC is denoted by f^*. Expanding the coverage beyond f^* actually reduces the herd effect. The f^* value not only maximizes the herd effect, but also directly results in a decrease in the infected individuals at any time t.

Basic reproduction ratio, denoted by R_0, is defined as the number of new infections caused by a single infectious individual in a completely susceptible population. For compartmental models, R_0 can be determined from the differential equations of *SIR* (Diekmann et al., 2013).

Post-reproduction number, denoted by R_v, reflects the effects of vaccination and vaccination strategies on a basic reproduction number R_0 (see, e.g. Becker and Starczak, 1997). Several formal presentations of R_v are known but all of them lead to the same critical vaccination coverage (see, e.g., Becker and Dietz, 1996). In this paper we use the form given by Becker and Starczak (1997) because it is suitable for our model.