

CONTROLLING INFECTIOUS DISEASE OUTBREAKS: A DETERMINISTIC ALLOCATION-SCHEDULING MODEL WITH MULTIPLE DISCRETE RESOURCES

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Abstract

Infectious disease outbreaks occurred many times in the past and are more likely to happen in the future. In this paper the problem of allocating and scheduling limited multiple, identical or non-identical, resources employed in parallel, when there are several infected areas, is considered. A heuristic algorithm, based on Shih's (1974) and Pappis and Rachaniotis' (2010) algorithms, is proposed as the solution methodology. A numerical example implementing the proposed methodology in the context of a specific disease outbreak, namely influenza, is presented. The proposed methodology could be of significant value to those drafting contingency plans and healthcare policy agendas.

Keywords: Resource allocation, healthcare management, epidemics, heuristics

1. Introduction

Control actions in an epidemic model typically include vaccination of susceptibles, treatment or removal (e.g., quarantine) of infectious persons, and reduction of the contact rate between susceptible and infectious persons (average number of infective contacts per infected person per unit time) via restricting movement between districts, school closures, etc. (Riley et al. 2003). The key parameter for many epidemiology models is the basic reproduction number R_0 , which is defined as the average number of secondary infections produced when one infected individual is introduced into a host population where everyone is susceptible to the

disease (Hethcote 2000). When control actions are implemented, however, not all contacts will be susceptible to infection. In this case the effective reproduction number R_E is used which takes into account the time-dependent variations in the transmission potential of the agent triggering the outbreak (Nishiura & Chowell 2009). The objective of the control actions described above is to decrease the value of the effective reproduction number below one. Due to control actions infected individuals may not pass the infection to susceptible individuals during their infectious period and eventually the infection dies out.

The literature regarding epidemics

containment is vast (Coburn et al 2009, Ferguson et al. 2003). In most cases, several disease transmission modeling approaches are utilized for assessing the possible effects of control interventions. These interventions could be pharmaceutical (use of antiviral drugs or vaccines), non-pharmaceutical (closure of schools, voluntary quarantines over a wide area, social distancing and travel limitations) or any combination thereof. For modeling the progression of the disease several approaches have been presented in the literature. These approaches range from simple compartmental models based on differential equations (Alexander et al. 2008, Chowell et al. 2006, Glasser et al. 2010, Hollingsworth et al. 2011, Kaplan et al. 2002, Lee et al. 2012) to meta-population models (Colizza et al. 2007, Cooper et al. 2006, Epstein et al. 2007, Flahault et al. 2006, Hall et al. 2007) and, finally, detailed stochastic agent-based models (Aleman et al. 2011, Burke et al. 2006, Carrat et al. 2006, Ciofi degli Atti et al. 2008, Eubank et al. 2004, Ferguson et al. 2005, Sander et al. 2009, Yang et al. 2011).

Limited vaccine supplies as well as limited ancillary medical supplies are among the resources to be allocated in the case of influenza outbreak control. As vaccination remains in the forefront of any influenza control strategy, the usage of limited vaccine stockpiles and their optimal allocation among sub-populations play a crucial role (particularly vaccination of at-risk individuals). Several studies consider aspects of prioritization by using age-targeted allocation strategies (Chowell et al. 2009, Lee et al. 2010). A more specific problem of this category is the allocation of limited vaccine supplies targeting

both at-risk groups and age-dependent groups of susceptible individuals (Matrajt & Longini Jr 2010, Medlock & Galvani 2009, Meyers et al. 2009, Mylius et al. 2008, Tuite et al. 2010). In the case of pandemic influenza outbreaks, vaccines' allocation strategies among different cities or even geographical regions have also been examined (Matrajt et al. 2013, Yarmand et al. 2014). Other studies consider aspects of limited vaccine supply as well as limited vaccination administration capacities (Cruz-Aponte et al. 2011).

Apart from vaccines, other resources for controlling influenza outbreaks may refer to clinics to care for those infected (Carr & Roberts 2010) or combination of allocation of antiviral drugs, vaccines and other supplies (Das et al. 2008, Koyuncu & Erol 2010, Krumkamp et al. 2011, Stein et al. 2012, Zhou & Fan 2012). In addition, allocation of scarce resources like vaccines or antiviral drugs in conjunction with non-pharmaceutical approaches have also been developed (Hansen & Day 2011, Wallinga et al. 2010, Yaesoubi & Cohen 2011). Limited financial resources for controlling influenza outbreaks have also been developed. Budget constraints may refer to limited financial resources for the procurement of vaccines and antiviral drugs, relevant capacities for their administration etc. (Mbah & Gilligan 2011, Uribe-Sánchez et al. 2011). A concise survey regarding resource allocation for epidemic control can be found in (Brandeau 2005). The uniqueness and severity of the problem necessitates the development of dynamic, real-time and effective solutions, thus making the topic very suitable for OR/MS research.

This paper examines the extension of the

problem described in (Rachaniotis et al. 2012) and more precisely the scheduling-allocation of limited discrete resources (mobile medical teams) employed in parallel in a time horizon to implement a vaccination campaign. The model is novel, since the literature of vaccines optimal allocation does not deal with medical teams scheduling (Ompad et al. 2006). The objective is to minimize the total number of new infections (or, equivalently, to maximize the total number of infections averted). The model captures increasing loss as more susceptibles become infected, combined with variable time and effort needed for the epidemic's control. A heuristic algorithm, based on Shih's (1974) and Pappis and Rachaniotis' (2010) algorithms, is proposed as the solution methodology, which can be coupled with any existing disease transmission model already published in the literature (from compartmental modeling to agent-based modeling approaches), thus rendering it fully compatible/extensible. The vaccination rate is time varying, synchronized with the course of the epidemic's transmission and the medical teams availability, thus R_E is adjusted at several time periods.

The remainder of the paper is structured as follows: The statement of the problem is presented in section 2. In section 3 the modelling approach is provided. A heuristic algorithm for solving the problem is proposed in section 4. A numerical example implementing the proposed methodology in the context of a specific disease outbreak (influenza) is presented in section 5, where a detailed epidemic transmission model capturing realistic disease patterns is coupled with the proposed modeling approach. In section 6 the main

findings of the study, its limitations as well as fruitful areas for further research are discussed. The paper ends with some concluding remarks.

2. Statement of the Problem

A realistic problem when health policy makers implement a mass vaccination campaign is the treatment of specific groups of the population. For example, when controlling an outbreak attributed to a deliberate bioterrorist action, public health officials should pay special attention to people unable to proceed to vaccination centres either because they are house bound (elderly, incapacitated etc.) or they are in institutions (Department of Health 2005). The same holds for disease outbreaks attributed to natural causes. For example, during the last pandemic influenza outbreak A(H1N1)v most countries launched mass vaccination campaigns. In the case of Greece, public health authorities commissioned several mobile medical teams to vaccinate certain groups of the Greek population like house bound individuals or institutionalized ones.

Allocating and scheduling limited number of resources for vaccination is a complex problem because: a) different subgroups may have different risk of infection and/or complications following it, b) epidemics of infectious diseases are nonlinear and dynamic, c) the time horizon impacts the scheduling decision, since short-term considerations may not yield the same results as long-term ones (Brandeau 2005). Regarding the second point, note that preventing one person from getting infected now could result in many individuals being saved from infection in the future.

The problem of allocating and scheduling

limited multiple, identical or non-identical, resources employed in parallel, when there are several infected areas, is considered in this paper. Mobile medical teams can be assigned to targeted populations or individuals. The following regarding the resources (mobile medical teams) to be allocated are assumed:

- The mobile medical teams can be considered as parallel (identical or non-identical) unrelated resources with constant service rates.
- More than one medical team may be allocated to a specific regional population.
- Pre-emption is not allowed. Thus, the situation where a medical team is called to visit a population in a specific region while it is employed in another one is not allowed.
- Control actions rely on vaccination of specific groups of the population (house bound and/or institutionalized individuals etc.).
- All the available medical teams at any time are employed for controlling the epidemic.
- The resources' traveling times are assumed to be negligible, since any mobile medical team can reach any population in a time period of a few hours, which is not significant compared to the control actions lasting for at least several days.

3. The Model

Let:

$P = \{P_1, P_2, \dots, P_n\}$ be the set of n populations in different regions, and let N_i be the size

of $P_i, i = 1, \dots, n$.

$t_0 > 0$ be the common for all populations time required for the resources to commence vaccination.

t be the discrete time units (days).

t_{end} be the end of the vaccination campaign in all regions. This time is not known in advance, since it depends on whether additional (resources) medical teams become available and when (time and resource-dependent problem).

m_t be the resources (medical teams) available at time t .

$(r_1(t), r_2(t), \dots, r_n(t))$ be the vector of the number of medical teams assigned for vaccination in every regional population at time t , where $r_i(t) \in \{0, 1, \dots, m_t\}$ $i = 1, \dots, n$. This is the problem's decision vector variable.

R_{Ei} be the effective reproduction number in P_i .

$I_i(r_i(t))$ be the number of new infections therefore infective in P_i at time t .

$C(r_i(t))$ be the completion time of the vaccination campaign for controlling the epidemic in P_i at time t (i.e. $R_{Ei} \leq 1$), having $r_i(t)$ medical teams assigned to region i .

The objective is to minimize the total number of new infections, given the available number of mobile medical teams:

$$\min \sum_{t=t_0}^{t_{end}} \sum_{i=1}^n I_i(r_i(t))$$

$$s.t. \quad \sum_{i=1}^n r_i(t) = m_t, t = t_0, t_0 + 1, \dots, t_{end} \quad (1)$$

$$r_i(t) \in \{0, 1, \dots, m_t\}, t = t_0, t_0 + 1, \dots, t_{end}$$

The number of new infections at any time

instance can be calculated using as input any existing disease transmission model (from compartmental modeling to agent-based modeling approaches).

4. The Heuristic Algorithm

The problem presented in the previous section is a time-dependent version of the well-known static discrete resource allocation problem with a single resource constraint, which has been thoroughly studied (Ibaraki & Katoh 1988, Shih 1974). In this problem (where $m_t=m$ and $r_i(t)=r_i$), the number of different assignments is $\binom{m+n-1}{n-1}$, thus its complexity increases rapidly as m and n increase.

The solution methodologies for the static discrete resource allocation problem proposed in the literature are branch-and-bound algorithms (Mjelde 1978, Shih 1977), dynamic programming techniques (Bretthauer & Shetty 1995, Ibaraki & Katoh 1988) and a greedy incremental algorithm (Shih 1974).

The heuristic for tackling the problem presented in this paper, which has not been addressed until now according to the best of the authors' knowledge, is a combination of Shih's (1974) algorithm and a variation of the algorithm used in (Pappis & Rachaniotis 2010). In the latter the problem of scheduling multiple resources employed as parallel identical or non-identical processors (multi-processor tasks) for wildfires' suppression was examined. A low-order polynomial time algorithm was proposed for scheduling resources according to their availability and the fires' severity. The selection of the proposed methodology can be justified by the fact that Shih's algorithm is very

fast to implement and yields satisfactory solutions (Ibaraki and Katoh 1988), whereas Pappis and Rachaniotis (2010) algorithm has an empirically proven satisfactory performance in the quite similar dynamic problem of wildfire containment.

An informal description of the algorithm used in this paper is the following:

- Step 1: Allocate resources to populations according to the incremental algorithm (Shih 1974) for solving the respective static discrete resource allocation problem. The vaccination time duration under the current assignment is calculated.
- Step 2: Check whether the current resource allocation should be altered. The resource allocation changes in two cases: a) arrival of additional resources, b) the region's vaccination with the shortest completion time finishes. If yes, move to Step 3. If not, then the vaccination campaign is completed (time t_{end} is reached) and the algorithm ends calculating the total number of infected people.
- Step 3: Calculate new populations' susceptibles numbers and return to Step 1.

Shih's greedy algorithm used has a complexity $O(m, \log n + n)$ (Shih 1974) and the algorithm in (Pappis & Rachaniotis 2010) has a complexity of $O(n^2)$.

Finally, it has to be explicitly stated at this point that the vaccination rate is time varying, synchronized with the course of the epidemic diffusion and the medical teams availability, thus R_E is accordingly adjusted over time.

5. Numerical Experiment

To illustrate the algorithm’s application a numerical example is presented. Reactive mass vaccination of susceptible individuals is considered as the main intervention strategy. The epidemic transmission model used is proposed by (Samsuzzoha et al. 2013). It is a vaccinated epidemic model, consisting of a system of nonlinear ordinary differential equations, where population is divided into five subgroups: susceptible (S), vaccinated (V), exposed (E),

infective (I) and recovered (R). The total population size is denoted by $N=S+V+E+I+R$ (SVEIR model, Figure 1). The reason behind the selection of the aforementioned epidemiological model is twofold. First, it adequately captures the biological properties of influenza transmission. Second, it accounts for the immunization of susceptible individuals, which is the main control action undertaken during influenza outbreaks (Samsuzzoha et al. 2013).

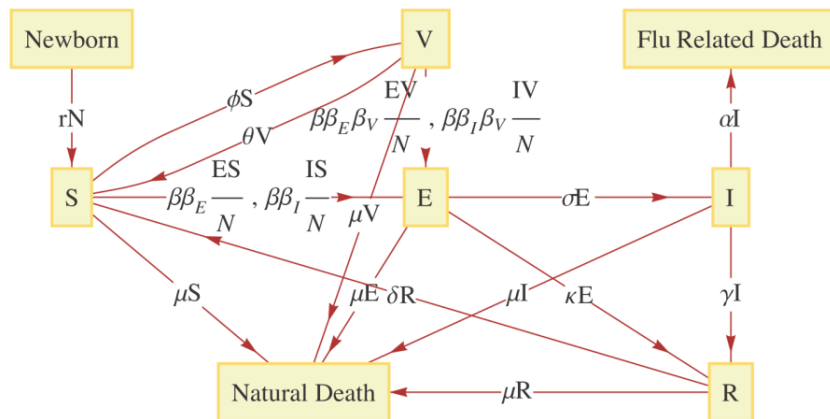


Figure 1 The SVEIR influenza model. Adapted from (Samsuzzoha et al. 2012)

The model’s parameters are the following:

- β : Contact rate
- β_E : Ability to cause infection by exposed individuals
- β_I : Ability to cause infection by infectious individuals
- $1-\beta_V$: Vaccine effectiveness
- σ^{-1} : Mean duration of latency
- γ^{-1} : Mean recovery time for clinically ill
- δ^{-1} : Duration of immunity loss
- u : Natural mortality rate

- r : Birth rate
- κ : Recovery rate of latent
- α : Flu induced mortality rate
- θ^{-1} : Duration of vaccine-induced immunity loss
- CSR: the mobile medical teams’ constant service rate
- ϕ_t : Rate of vaccination. It is $\phi_t = r(t)CSR$, which differs from the common SVEIR models’ assumption that the vaccination rate is constant during the control effort.

The model is represented by the following

system of ordinary differential equations:

$$\begin{aligned}
 S'(t) &= -\beta\beta_E \frac{ES}{N} - \beta\beta_I \frac{IS}{N} - \varphi_1 S - \mu S + \delta R + \theta V + rN, \\
 V'(t) &= -\beta\beta_E \beta_V \frac{EV}{N} - \beta\beta_I \beta_V \frac{IV}{N} - \mu V - \theta V + \varphi_1 S, \\
 E'(t) &= \beta\beta_E \frac{ES}{N} + \beta\beta_I \frac{IS}{N} + \beta\beta_E \beta_V \frac{EV}{N} + \beta\beta_I \beta_V \frac{IV}{N} - (\mu + \kappa + \sigma)E, \\
 I'(t) &= \sigma E - (\mu + \alpha + \gamma)I, \\
 R'(t) &= \kappa E + \gamma I - \mu R - \delta R.
 \end{aligned}
 \tag{2}$$

It should be noted that the aforementioned system (2) can only be solved numerically through the usage of approximation methods (like Runge-Kutta's). Therefore, there is no closed form formula for $I(t)$ and consequently model (1) cannot be solved optimally (except in the case of small instances where it can be solved numerically) but only with heuristic algorithms. The effective reproduction number due to vaccination for the previous model is

provided by the formula:

$$R_E = \frac{\beta(r\beta_E + \alpha\beta_E + \gamma\beta_E + \sigma\beta_I)(r + \theta + \beta_V\varphi_1)}{(r + \alpha + \gamma)(r + \kappa + \sigma)(r + \theta + \varphi_1)}.$$

Mobile medical teams with a significant service rate are assigned to Greece's 13 Administrative Health Districts (AHDs). Their main task is to vaccinate people unable to proceed to local vaccination centres, whereas the remainder of the population can be administered the vaccine in mass immunization centres (hospitals). The targeted subpopulations in this study consist of the following groups of individuals: a) home living people aged 80 years or older, b) institutionalized elderly people and, finally, c) housebound individuals with kinetic problems. Data regarding basic demographical characteristics (subpopulations sizes' estimations) from Greece's 13 AHDs is used as input for the model (Figure 2 and Table 1).

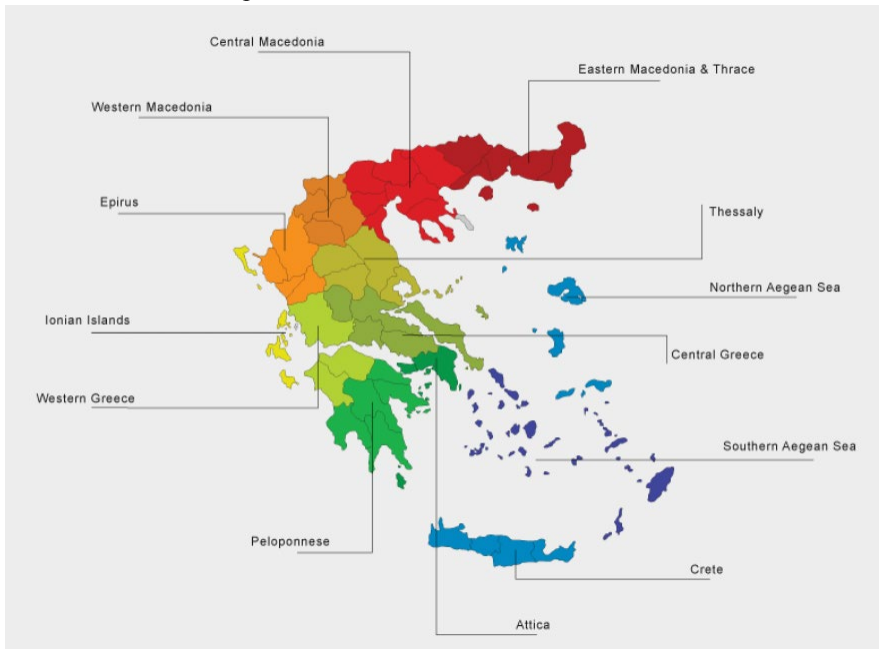


Figure 2 Map of Greece's 13 administrative health districts

Table 1 Estimation of targeted subpopulations (Total: 362,500 people)

District	Estimated targeted subpopulation N_i
East Macedonia and Thrace (AHD1)	15,000
Central Macedonia (AHD2)	43,000
West Macedonia (AHD3)	9,500
Epirus (AHD4)	14,000
Thessaly (AHD5)	25,000
West Greece (AHD6)	25,000
Central Greece (AHD7)	22,000
Attica (AHD8)	128,000
Peloponessos (AHD9)	28,000
Ionian Islands (AHD10)	9,000
North Aegean (AHD11)	10,000
South Aegean (AHD12)	9,000
Crete (AHD13)	25,000

Table 2 Model's parameter values

Parameter	Description	Value	Source
β	Contact rate	$(0.514 \text{ days})^{-1}$	Estimated (www.keelpno.gr)
β_E	Ability to cause infection by exposed individual ($0 \leq \beta_E \leq 1$)	0.25	Estimated (Samsuzzoha et al. 2012)
β_I	Ability to cause infection by infectious individuals ($0 \leq \beta_I \leq 1$)	1	Estimated (Samsuzzoha et al. 2012)
$1 - \beta_V$	Vaccine effectiveness	83.3%	(Wichmann et al. 2010)
σ^{-1}	Mean duration of latency	$(2 \text{ days})^1$	(Samsuzzoha et al. 2013, Van Der Weijden et al. 2013)
γ^{-1}	Mean recovery time for clinically ill	$(5 \text{ days})^{-1}$	(Samsuzzoha et al. 2013)
δ^{-1}	Duration of immunity loss	$(365 \text{ days})^{-1}$	(Samsuzzoha et al. 2013)
μ	Natural mortality rate	46×10^{-9} persons/day	www.statistics.gr
r	Birth rate	52×10^{-7} persons/day	www.statistics.gr
κ	Recovery rate of latent	1.857×10^{-4} persons/day	(Samsuzzoha et al. 2013)
α	Flu induced mortality rate	93×10^{-7} persons/day	(Sypsa et al. 2009)
θ^{-1}	Duration of vaccine-induced immunity loss	$(365 \text{ days})^{-1}$	(Samsuzzoha et al. 2013)
CSR	The mobile medical teams' constant service rate	50 persons/team/day	(Kaplan et al. 2002)
ϕ_t	Rate of vaccination. It is $\phi_t = r(t)CSR$, which differs from the common SVEIR	Dynamic calculation	-

The epidemic diffusion model is applied in all $n=13$ AHDs, under the assumption that all influenza transmission parameters' values are the same for all AHDs (Matrajt et al. 2013). Susceptible (S), vaccinated (V), exposed (E), infective (I) and recovered (R) are divided into two groups, namely the targeted population (elderly and/or housebound individuals) and the rest of the population (Matrajt & Longini Jr 2010). Parameters' values of the SVEIR epidemiological model have been carefully selected to reflect the particularities of the targeted population. In particular, a literature search was initially conducted for the identification of a range of plausible influenza parameter values based on data collected during the influenza A(H1N1) 2009 pandemic (Boëlle et al. 2011, Van Der Weijden et al. 2013, Wichmann et al. 2010). In the sequel, epidemiological data from the Hellenic Center for Disease Control & Prevention as well as census data from the Hellenic Statistical Authority were used for narrowing down this range of parameter values. The estimated parameters' values of the SVEIR epidemiological model may be seen in Table 2.

A simplifying assumption is that subpopulation mixing between districts is not considered. There are at least three arguments to justify this assumption. First, subpopulations' mixing is negligible compared to mixing within districts. Second, the time lag between the initial cases countrywide and the first cases in the remaining districts is captured by the different epidemic outbreak times. Third, targeted population consists of individuals that are not highly movable (since they are either elderly people or house-bound individuals). Therefore,

from an epidemiological point of view, the interactions of these sub-groups of individuals between different regions may be considered as negligible.

There were difficulties in the accurate estimation of model's parameters', given:

- The various factors affecting their measurement and their actual values.
- The fact that the real burden of the disease (number of influenza cases) is not captured. For example, many infections are undetected due to the usually mild nature of the disease. Individuals with these symptoms do not usually seek medical attention. In addition, laboratory testing by the Hellenic Center for Disease Control & Prevention (www.keelpno.gr) focuses mainly on selected incidents (hospitalized cases). As a consequence, the surveillance data reported do not necessarily reflect the true incidence of the disease, which is likely to be underestimated.

Scenarios and sensitivity analysis

In the event of an influenza outbreak, public health authorities should try to ensure that widespread community transmission does not occur. All of the response scenarios examined here involve the implementation of a targeted reactive vaccination campaign for different resource allocation policies (Table 3). In particular, the sensitivity of the number of infected individuals to two factors: amount of resources allocated and delays in implementing the vaccination campaign have been examined.

Table 3 Intervention strategy, resource allocation policies and relevant scenarios built

Intervention strategy	Resource allocation policy	Scenario
No intervention	-	Baseline
	Allocation of a single resource to all sub-populations	Fixed strategy
Reactive mass vaccination starting at day 7, 14, 21, 28 and 60 from the onset of the outbreak	Allocation of a constant amount of resources by using the size of each sub-population as the main driver	Maximum resources
	Dynamic reallocation of resources	Heuristic

The results generated by the numerical implementation of 3 types of control scenarios for a time period of 120 days for the targeted subpopulations are presented:

- The baseline scenario where no intervention (vaccination) takes place. The R_0 value is constant and approximately equal to 2.826, which is inside the limits used in the influenza epidemics literature (Boëlle et al. 2011).
- The fixed-strategy approach where a single mobile medical team is assigned to each district. This is used only to prove that vaccination is mandatory for the targeted subpopulation, therefore the mobile medical teams' allocation, which is the only way of vaccinating them, is essential.
- The maximum resources scenario where each district is assigned a constant number of medical teams by using the size of each districts' population as the main driver.
- The heuristic approach that allows the dynamic re-allocation of teams between districts.

For the second scenario five different

vaccination initiation days are considered, i.e. 7, 14, 21, 28 or 60 days after the beginning of transmission (Matrajt et al. 2013). The assumptions made are that the number of vaccines necessary for the targeted subpopulations is available at the vaccination's initiation day and that the epidemic initiates in Attica region with 1 case, then in Central Macedonia with 1 case in day 10 and in all other districts with 5 cases in day 25, similar to the initial cases' pattern that appeared in the last pandemic influenza outbreak A(H1N1)v in 2009. This is quite reasonable, since Greece is a country with isolated mountainous areas and hundreds of habited islands.

Initially, for each possible vaccination initiation day, the solution (number of infective individuals) yielded by the fixed strategy scenario where the number of available mobile medical teams is $m_{t_0} = 13$ and one team is allocated per district, is compared to the baseline scenario, where no vaccination takes place. All numerical solutions of the model were obtained using R programming language (R Core Team 2013) and MS Excel and the results are illustrated in Table 4.

Table 4 Number of infected individuals under the baseline and the fixed strategy (one allocated medical team per AHD) scenarios

AHD'S		AHD1	AHD2	AHD3	AHD4	AHD5	AHD6	AHD7
Baseline scenario		3157	9041	2001	2947	5260	5260	4629
Fixed strategy scenario (initiation of vaccination at day d), one medical team	d=7	2725	7875	1738	2545	4507	4507	3974
	d=14	2783	8050	1775	2600	4604	4604	4059
	d=21	2844	8229	1813	2657	4705	4705	4148
	d=28	2907	8411	1854	2716	4809	4809	4239
	d=60	3156	9041	2001	2945	5249	5249	4622
AHD'S		AHD8	AHD9	AHD10	AHD11	AHD12	AHD13	Total
Baseline scenario		26911	5891	1895	2106	1895	5260	76253
Fixed strategy scenario (initiation of vaccination at day d), one medical team	d=7	23828	5040	1647	1828	1647	4507	66368
	d=14	24355	5148	1682	1867	1683	4604	67814
	d=21	24897	5261	1719	1907	1719	4705	69309
	d=28	25446	5377	1758	1950	1758	4809	70843
	d=60	26911	5875	1895	2106	1895	5249	76194

The fixed strategy scenario outperforms the baseline scenario (the percentage difference of total infective cases ranges from 7.1% to 13%), even when the minimum number of a single mobile medical team is allocated per AHD, as long as the vaccination starts early (i.e. vaccination initiates until the 28th day after the beginning of transmission), thus rendering the vaccination necessary. In the case where the vaccination starts 60 days after the beginning of the transmission it seems that the number of infections averted is very small (only 59 cases) compared to a no vaccination policy. This happens due to the fact that the peak of the epidemic takes place around day 60 in most of the districts and any vaccination effort beyond this time window is deemed unnecessary. Therefore this vaccination initiation day is not considered when the third and fourth scenarios are examined.

For building the third and fourth scenarios it has been considered that the number of mobile medical teams allocated to the AHDs is proportional to their population size. More precisely, the smallest sub-population has been used as the main driver for proportionally assigning vaccination units to the rest of the sub-populations (Table 5). The smallest sub-population has been assigned a single vaccination unit. The total number of teams in this case is equal to 35, assuming, of course, that such a capacity will be available for controlling a massive influenza outbreak. This is the “maximum resources” allocation scenario. The rationale behind this comparison (third and fourth scenario) is to find a better way to allocate the same amount of resources while reducing the cumulative number of infected individuals in each district.

Table 5 Mobile medical teams' allocation to AHDs

AHD1	AHD2	AHD3	AHD4	AHD5	AHD6	AHD7
1	4	1	1	2	2	2
AHD8	AHD9	AHD10	AHD11	AHD12	AHD13	
14	3	1	1	1	2	

For each possible vaccination initiation day, the solution (number of infective cases) yielded by the heuristic algorithm is compared to the baseline scenario, (no vaccination) and the maximum resources scenario (constant number of allocated mobile medical teams to each district by using population drivers as seen in Table 5). The numbers of infected individuals

under the three scenarios are presented in Table 6 and the mobile medical teams' initial allocation to AHDs at a specific allocation day according to the heuristic algorithm implementation is depicted in Table 7. Finally, the cumulative infected cases for the three scenarios are depicted in Figure 3.

Table 6 Number of infected persons under the baseline scenario, the maximum resources scenario and the heuristic algorithm solution

AHD's	HD1	AHD2	AHD3	AHD4	AHD5	AHD6	AHD7	AHD8	AHD9	AHD10	AHD11	AHD12	AHD13	Total	
Baseline scenario	3157	9041	2001	2947	5260	5260	4629	26911	5891	1895	2106	1895	5260	76253	
d=7	2725	4719	1738	2546	3800	3800	3358	951	3495	1648	1828	1648	3800	36056	
Initiation of vaccination at day d (maximum resources)	d=14	2784	5334	1775	2601	3981	3981	3517	2871	3776	1683	1867	1683	3981	39834
d=21	2845	5981	1814	2658	4173	4173	3686	6300	4080	1720	1908	1720	4173	45231	
d=28	2907	6654	1854	2716	4375	4375	3864	11002	4408	1758	1950	1758	4375	51996	
Initiation of vaccination at day d (heuristic approach)	d=7	2725	1612	1738	2546	3800	3800	3975	1917	3495	1648	1828	1648	4508	35240
d=14	2784	2485	1775	2601	4605	4605	4060	2871	3776	1683	1867	1683	4605	39400	
d=21	2845	3510	1814	2658	4705	4705	4148	4854	5261	1720	1908	1720	4705	44553	
d=28	2907	5601	1854	2716	4810	4810	4240	8318	5378	1758	1950	1758	4810	50910	

Table 7 Mobile medical teams' initial allocation according to the proposed heuristic algorithm

AHDs		1	2	3	4	5	6	7	8	9	10	11	12	13	Day of allocation a
Initiation of vaccination at day d ("heuristic approach")	d= 7	1	8	1	1	2	2	1	12	3	1	1	1	1	a=8
	d=14	1	8	1	1	1	1	1	14	3	1	1	1	1	a=15
	d=21	1	8	1	1	1	1	1	16	1	1	1	1	1	a=22
	d=28	1	6	1	1	1	1	1	18	1	1	1	1	1	a=29

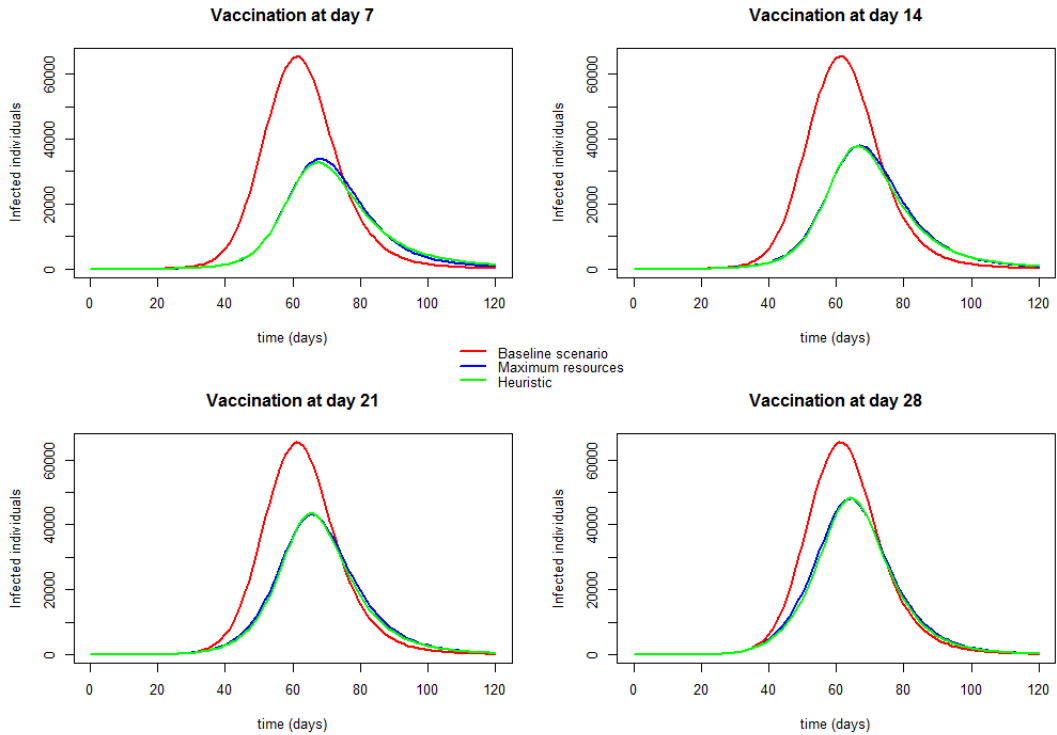


Figure 3 Cumulative number of infective cases under the baseline scenario, the maximum resources scenario and the heuristic algorithm solution

The Gantt chart in Figure 4 illustrates the number of allocated mobile medical teams that dynamically changes and the vaccination completion time for every AHD in the case of applying the heuristic algorithm when the vaccination initiates at day $d=7$. The entire

vaccination campaign is completed in 66 days, which is an acceptable limit in order for it to be considered necessary and helpful, taking into account the already mentioned fact that the epidemic peak is around day 60.

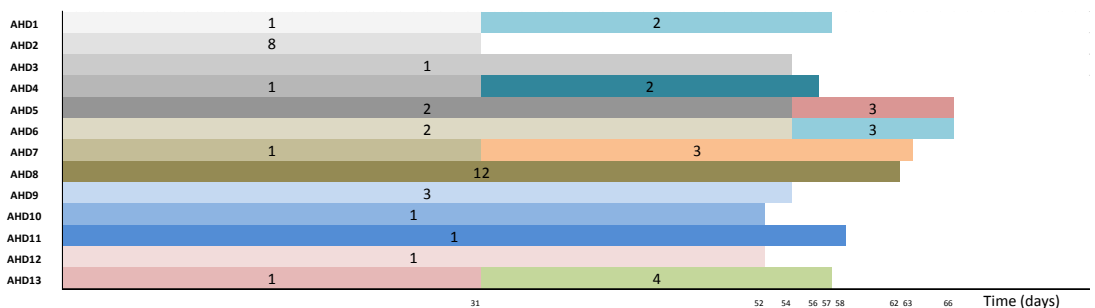


Figure 4 Heuristic algorithm's solution Gantt chart for $d=7$

Data from Table 6 suggests that the maximum resources scenario clearly outperforms the baseline (no vaccination) scenario. The percentage difference of total infective cases ranges from 31.8% to 52.7% respectively, increasing when the vaccination campaign initiates earlier. The heuristic algorithm's solution also outperforms the maximum resources scenario where the percentage difference of total infected cases ranges from 1.1% to 2.3% respectively. Although this percentage reduction is small, in practice it could be translated into 15-20 less deaths per 1,000 infective cases averted.

From Table 7 it is evident that the medical teams' allocation takes place the next day after the vaccination initiates. Moreover, when vaccination's initiation is delayed, the number of teams allocated to AHDs with larger targeted subpopulations (AHD2 and predominantly AHD8, Athens' district) is increased. This was expected, since the marginal benefit (averted infective cases) in these areas when one additional team is allocated is higher than the corresponding loss from allocating one team less in areas with smaller sub-populations, as anticipated if the law of diminishing returns is considered.

Finally, it has to be explicitly stated here that at least one team is allocated per district during the whole vaccination period, even if the algorithm would yield less infections in the case where no team is allocated. This is due to the fact that no AHD's targeted subpopulation can be left without treatment at any circumstance for social, political and humanitarian reasons (for instance, the vaccination campaign could be politicized or become subject of contention, fair

allocation of resources, etc.). In addition, this is the only way for the elderly and/or housebound individuals to actually receive protection against influenza virus (through immunization). Therefore, the allocation of just one medical team per district reflects the minimum health care standards provided to this group of people.

6. Discussion

A mathematical model and a heuristic algorithm have been presented for facilitating in-context evaluation of alternative resource allocation policies when infectious disease outbreak control decisions are to be made. The present study contributes to the body of knowledge by taking into account mobile medical teams scheduling and by allowing the possibility of dynamic re-allocation of resources during the course of the outbreak. To the best of the authors' knowledge this is among the first attempts where the general resource allocation problem is concerned with mobile medical teams scheduling (Rachaniotis et al. 2012). Several resource allocation scenarios have been simulated. In particular, a passive (do nothing) 'baseline' and three active responses have been considered. Apart from straightforward resource allocation practices (one mobile medical team per district), the effects of proportionally allocating medical teams to each health district based on demographic criteria (populations' size), as proposed in several public health planning guides (Hupert et al. 2004), have also been examined.

The results show that the strategy proposed by the heuristic algorithm always outperforms a pro rata resource allocation strategy and significant differences exist with respect to the

cumulative number of infected individuals. Under the conditions presented, the results could be used to set general a priori guidelines for control actions on certain sub-populations for other infectious disease outbreaks. The results are very sensitive to the assumptions regarding the initiation day of the immunization campaign, i.e. the longer the delay for initiating the vaccination campaign, the worst the performance of all the resource allocation scenarios. This is largely attributable to the fact that the effects of a delayed immunization campaign do not proceed at the pace of the epidemic and, thus, more people become eventually infected. Although a resource allocation policy where resources are distributed according to population criteria is presumably the fairest strategy, our results have proven that this does not yield the optimal resources utilization. In fact, the modeling approach presented gives preference to the more populated health districts. Unfortunately, the results obtained in this study are not comparable to any other study as the problem of allocating discrete resources (like mobile medical teams) to perform control actions (vaccination) has not been broadly tackled so far.

Some limitations of the framework presented in this article should be kept in mind. Most of them are closely related to the inherent uncertainties surrounding any infectious disease outbreak and especially the dynamics of disease transmission. The SVEIR model used in this study and its deterministic nature comes with several simplifying assumptions, especially the ones related to disease's transmission rates and vaccine's immunogenicity thresholds. For instance, social networks and contact processes

that dictate disease transmission patterns or age-specific differences in the pathogenicity and transmissibility of influenza have not been considered. The usage of an individual-based model would have yielded more accurate results as it would have captured more realistic disease patterns and contact structures among all individuals in the sub-populations. It is worth noting, however, that the inclusion of a large degree of detail and heterogeneity in any epidemiological model comes at a computational cost. Compartmental models are more computationally tractable and allow extensive sensitivity analysis (Kaplan et al. 2003). In addition, epidemic models based on free mixing give larger disease outbreaks and from a public health perspective developing tools for the "worst-case" approach might be preferable. The disease progression model used in this study is not extremely complex and it might be unsuitable for guiding the selection of control interventions. However, it has been mainly used for illustrating the applicability of the proposed modeling approach which it is believed to be broadly applicable.

Apart from the usage of a more detailed disease transmission model, another fruitful area for further research is the utilization of the proposed methodology in combination with non-pharmaceutical intervention for controlling an outbreak. In this case social distancing and travel limitations could be coupled with pharmaceutical interventions (like an immunization campaign). Aspects of cost for actually implementing the targeted vaccination campaign could also be considered and particularly how implementation costs scale up with the resource allocation policy provided by

the heuristic algorithm. The approach presented could also be used in the case of infectious disease outbreaks in humanitarian emergencies. In particular, the model could be used for allocating mobile medical units to perform immunization campaigns to populations with limited access to healthcare services (due to lack of security). Finally, logistical constraints for delivering the targeted vaccination campaign like limited vaccine supply or daily administration constraints and their interaction with the disease process could also be examined.

7. Conclusions

Efficient utilization of a set of limited resources is of paramount importance when controlling infectious disease outbreaks. In this paper the problem of allocating several discrete resources (mobile medical teams) for controlling an outbreak has been considered. Vaccination of certain groups of the population (incapacitated, house bound, institutionalized etc.) has been the main control action adopted. A real-time synchronous heuristic algorithm has been proposed as the solution methodology. The modeling approach presented could serve as a decision support tool for assisting decision makers in allocating mobile medical teams for infectious disease outbreak control. The proposed methodology has been exemplified in the context of a specific disease outbreak (influenza) in Greece and the results are encouraging.

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