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Thesis

Emergency supply chain management for controlling infectious disease outbreaks

By

Thomas K. Dasaklis

University of Piraeus, Greece

Members of the supervisory committee:

- Professor Emeritus **Costas Pappis**, University of Piraeus (supervisor)
- Professor **Luk Van Wassenhove**, The Henry Ford Chaired Professor of Manufacturing, Academic Director, INSEAD, Social Innovation Centre
- Professor Emeritus **Nikolaos Blesseos**, University of Piraeus

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Abstract

Outbreaks of communicable diseases occurred many times in the past with a devastating effect on all aspects of human life in the infected regions. The importance of addressing infectious disease outbreaks nowadays is even greater as the general framework in which they might occur has dramatically changed. New challenges have arisen and certain drivers like climate change, population density and urbanization could serve as catalysts for the acceleration of pandemic incidents. A possible outbreak combined with changes in demographic conditions like population distribution, size and density could potentially lead to a pandemic of unprecedented proportion where available capacities and control resources could be strained to their limits.

Effective control of an infectious disease outbreak calls for a rapid response. Available resources such as essential medical supplies and well-trained personnel need to be deployed rapidly and to be effectively managed in conjunction with available information and financial resources in order to contain the epidemic before it reaches uncontrollable or disastrous proportions. Therefore, the establishment and management of an emergency supply chain during the containment effort are of paramount importance.

Planning and implementing control strategies and actions, however, is not a straightforward process since outbreaks of communicable diseases are highly context-specific. For instance, disease outbreaks may occur in the context of natural causes such as the recent outbreak of novel influenza A(H1N1) virus. Outbreaks of communicable diseases are also very common in complex humanitarian emergencies. Acute respiratory infections, measles, malaria and diarrhea are the most prevalent infectious diseases in these settings and all of them are closely related to unsanitary health conditions and malnutrition of the population affected. Last but not least, deliberate bioterrorist actions and the release of biological warfare agents could also lead to disease outbreaks. Planning and implementing control strategies and actions also requires disease-specific approaches. For instance, different diseases require different control protocols to be followed and, therefore, different operational issues may arise during the containment effort. Therefore, one-size-fits-all approaches in the case of epidemics control are not suitable and special attention should be paid to both the agent triggering the outbreak as well as to the general context in which the outbreak occurs.

Based on the particularities described above, this thesis studies the influence of resource allocation and operations management on controlling infectious disease

outbreaks for three distinct cases; the first being for epidemics attributed to natural causes, the second being for disease outbreaks due to deliberate bioterrorist actions and the third being for outbreaks in the aftermath of natural or man-made disasters. Influenza, smallpox and cholera have been chosen as the main infectious agents to be studied in each case respectively.

The main contribution of this thesis is the development of mathematical modelling approaches for managing the response operations during the containment effort of infectious disease outbreaks. Several operational and resource allocation constraints like limited medical supplies or limited response capacities for performing control actions are explicitly modeled. The methodologies applied are mainly of quantitative nature and are based on operations research techniques like linear programming, combinatorial optimization, heuristic algorithms etc. Finally, some qualitative aspects of response operations are also examined.

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To the memory of my father

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Abbreviations and acronyms

IDOs	Infectious Disease Outbreaks
ESCM	Emergency Supply Chain Management
PODs	Points of Dispensing
WHO	World Health Organization
NSC	National Stockpile Centre
RSC	Regional Stockpile Centre
SNS	Strategic National Stockpile
PPE	Personal Protective Equipment
CDC	Centers for Disease Control and Prevention
CMR	Crude Mortality Rate
CHEs	Complex Humanitarian Emergencies
GIS	Geographical information systems
AHD	Administrative Health District
HIS	Health Information System
OCVs	Oral Cholera Vaccines

Chapter 1: Introduction

1.1 Key-issues regarding infectious disease outbreak control

Infectious disease outbreaks (IDOs) occurred many times in the past and they were often associated with an enormous death toll. Plague epidemics in late Medieval Europe characterized by high mortality rates caused many fatalities, while the 1918–1919 Spanish influenza pandemic killed an estimated 20 to 50 million people worldwide (Benedictow 1987; Tumpey, Basler et al. 2005). Polio, cholera, measles, tuberculosis and HIV are among the diseases that continue to pose a threat for many developing and developed countries. According to the World Health Organization, the world is facing an infectious disease crisis of global proportions, which is responsible for more than 13 million deaths and multimillion infections per year. The social impact of IDOs can be devastating in humanitarian emergencies. An estimated 12,000 refugees died of cholera in the Goma refugee camp of the Democratic Republic of Congo in 1994 (Plotkin, Shin et al. 2011; Von Seidlein, Jiddawi et al. 2013). In the aftermath of the 2009 earthquake in Haiti, thousands of people have died by the cholera outbreak and many more have been sickened (Adams 2013).

The general context in which IDOs occur may differ. For instance, an outbreak can be attributed to natural causes such as the recent influenza A(H1N1) pandemic. Disease outbreaks are also very common in the aftermath of natural or man-made disasters. Acute respiratory infections, measles, malaria and diarrheal diseases (like cholera) are the most prevalent infectious diseases after natural disasters or complex humanitarian emergencies (CHEs). Although these outbreaks are also attributed to natural causes, they are closely related to unsanitary health conditions and malnutrition of the affected population due to the initial event triggering the humanitarian emergency. Deliberate bioterrorist actions and the release of biological warfare agents could also lead to IDOs. According to (Henderson 1999) smallpox and anthrax are considered to be among the two most feared biological agents that could be used in a probable bioterrorist attack “as they have the potential to be grown reasonably easily and in large quantities and are sturdy organisms that are resistant to destruction”. The anthrax attacks of 2001 in the United States demonstrated the threat of a possible bioterrorist action and its severe impacts.

The importance of addressing IDOs nowadays is even greater as the general framework in which they may occur has dramatically changed during the last decades. New challenges have arisen and certain drivers like climate change, population density and urbanization could serve as catalysts for the acceleration of pandemic incidents. Climate change is expected to play a crucial role in the birth and transmission of specific diseases (McMichael 2003). Many studies suggest that diseases such as yellow fever, dengue and cholera are re-emerging due to climate change among other factors (Shope 1991). Specific arbovirus diseases have recently emerged outside their usual endemic range and this could be attributed to changes in climate patterns (Gould and Higgs 2009). Apart from climate change, the witnessed rapid urbanization of the world's population along with a substantial growth in general population could lead to accelerated IDOs. A possible outbreak combined with changes in demographic conditions like population distribution, size and density could potentially lead to a pandemic of unprecedented proportion where available response capacities and resources could be strained to their limits.

1.1.1 Basic epidemiology terms and preliminaries

An IDO is the occurrence of cases of a particular disease in excess of the expected. Such an outbreak is characterized as an epidemic when it is restricted to one location; however, if it spreads to several geographic regions or even continents, it may be termed a ***pandemic*** (John Hopkins Bloomberg School of Public Health and the International Federation of Red Cross and Red Crescent Societies 2008). Infectious diseases can cause death directly but also indirectly by increasing the chance that an individual will contract other diseases (Brandeau 2005). ***Epidemiology*** is the study of the distribution and determinants of chronic and infectious disease prevalence in humans (Anderson and May 1992). ***Epidemic threshold*** refers to the level of disease (ratio of infected cases/total population) above which an urgent response is required. It is specific to each disease and depends on the infectiousness, other determinants of transmission and local endemicity levels (World Health Organization 2005). For example, the threshold for meningitis is 15 cases per 100,000 people in a two-week period (John Hopkins Bloomberg School of Public Health and the International Federation of Red Cross and Red Crescent Societies 2008).

The control of IDOs may be based on measures adopted at international, national, provincial or even community level. Reducing the rate by which susceptibles become infected, reducing the mortality rate for those already infected and increasing the immunization status of the susceptible population comprise the main objectives of any control measures. Such measures demand the launching of vaccination or quarantine programs over certain geographic regions. They also call for actions that

will ensure the provision of medical supplies like antiviral drugs, antibiotics, clean water/adequate sanitation and better nutrition conditions in order that the multiplication of the infectious agent be reduced. Control measures could be adopted with the aim either to prevent the spread of an infectious disease (as pre-event measures) or to control a confirmed outbreak (post-event measures). In the first case, a certain level of medical supplies should be kept in order to be utilized immediately at the initiation of an epidemic. In the second case the deployment of all the available resources should rapidly take place providing either treatment to those already infected or prophylaxis to those susceptible to the agent triggering the outbreak (Dasaklis, Pappis et al. 2012).

The process of infection from a disease can be described by a number of stages, beginning with the exposure of a susceptible individual to the infectious agent. Once the individual has contracted the disease, specific symptoms may appear. During this period (or shortly before the onset of the symptoms) the individual is infectious, meaning that he/she can transmit the disease to other susceptible individuals. Depending on several parameters like the health status of the infected person or the levels of prior herd immunity in his/her body, the individual may recover from the disease or perish. The transition dynamics of the aforementioned stages described in brief can be expressed through the usage of mathematical models. By creating such models, diseases can be studied and the possible benefits of control actions can be assessed. 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 a specific 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 and Chowell 2009).

For capturing the transmission dynamics of a disease, several modelling approaches have been presented in the literature. These approaches range from simple compartmental models based on differential equations (Kaplan, Craft et al. 2002; Chowell, Ammon et al. 2006; Alexander, Moghadas et al. 2008; Glasser, Taneri et al. 2010; Hollingsworth, Klinkenberg et al. 2011; Lee, Golinski et al. 2012) to meta-population models (Cooper, Pitman et al. 2006; Flahault, Vergu et al. 2006; Colizza, Barrat et al. 2007; Epstein, Goedecke et al. 2007; Hall, Egan et al. 2007) and, finally, detailed stochastic agent-based models (Eubank, Guclu et al. 2004; Ferguson, Cummings et al. 2005; Burke, Epstein et al. 2006; Carrat, Luong et al. 2006; Ciofi degli Atti, Merler et al. 2008; Sander, Nizam et al. 2009; Yang, Atkinson et al. 2011). Compartmental modelling approaches are based on homogenous mixing

assumptions. Their level of complexity is relatively low and they are easy to simulate. Meta-population models are more complex as they take into account network structures of the affected population. Finally, agent-based models are very close to reality as they capture contact patterns at an appropriate temporal and spatial scale but they are extremely complex to simulate. In Figure 1 a spectrum of the complexity versus reality of the epidemic modelling approaches is presented.

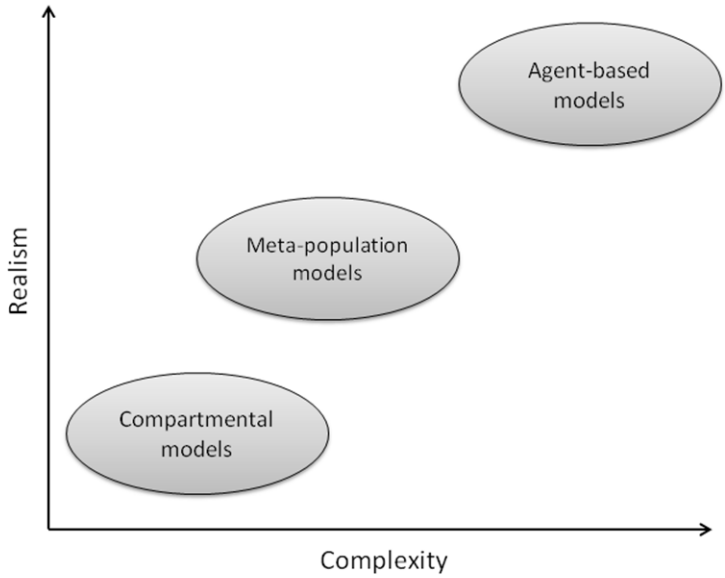


Figure 1: Realism vs complexity spectrum of epidemic modelling approaches. Source (Dimitrov and Meyers 2010)

1.2 Emergency supply chain management for controlling infectious disease outbreaks

Recent studies have demonstrated the contribution of appropriate management of disasters to save or offer relief to as many people as possible. According to (Kovacs and Spens 2007) an ***emergency*** or ***humanitarian supply chain*** encompasses a range of activities, including preparedness, planning, procurement, transport, warehousing, tracking and tracing and customs clearance. ***Humanitarian logistics*** is an umbrella term for a mixed array of operations, from disaster relief to continuous support for developing regions, and could be defined as the process of planning, implementing and controlling the efficient, cost effective flow and storage of goods

and materials as well as related information from the point of origin to the point of consumption for the purpose of alleviating the suffering of vulnerable people. As an example, one of the notable aspects of the relief effort following the 2004 Asian tsunami was the public acknowledgement of the role of logistics in effective relief (Thomas and Kopczak 2007).

The management of emergency and/or humanitarian supply chains has recently attracted the attention of both practitioners and researchers. Such supply chains have much in common with commercial supply chains but at the same time they pose significant challenges as they operate under uncertain, and many times, chaotic conditions. Research methodologies widely utilized in solving business logistics problems could be adopted in the context of emergency supply chain operations. Similarities existing between commercial and emergency supply chains offer the opportunity of transferring knowledge from the business sector to humanitarian organizations (Maon, Lindgreen et al. 2009). Even at a long-term level, strategies adopted in commercial supply chains could also be adopted in the case of emergency and/or humanitarian supply chains in an effort to match supply with demand (Oloruntoba and Gray 2006; Taylor and Pettit 2009). A very comprehensive description towards the issues of humanitarian logistics can be found in (Van Wassenhove 2006).

The control of an IDO calls for a prompt response. Certain control protocols should be followed and huge amounts of supplies together with the necessary human resources (medical and ancillary personnel) should be available in order to be utilized during the containment effort. For example, if a smallpox attack occurs, vaccination of the affected population should take place within 10 days as the incubation period of smallpox is usually 12–14 days (Strikas, Neff et al. 2008). The same holds for anthrax where the distribution of antibiotics should take place within 2 days of a possible bioterrorist event (Lee 2008). As a consequence, any control of an IDO should rely on the establishment of an emergency supply chain as a plethora of logistical issues is raised according to the control strategy adopted and the very nature of the agent triggering the outbreak. All the logistics operations such as transportation of medical supplies and commodities or the deployment of medical personnel must be managed in conjunction with available information and financial resources in order to contain the epidemic before it reaches uncontrollable proportions.

In particular, pharmaceutical companies should produce vaccines, antiretroviral drugs and complementary medical supplies. Governments and public health institutions should purchase and stockpile well in advance a plethora of such supplies for a possible outbreak. Transportation and distribution of these supplies

from central warehouses to regional store sites and then to local Points of Dispensing (PODs) will have to take place. When vaccination campaigns are implemented, a cold supply chain (i.e. a supply chain under stable temperature conditions) must be established to assure that vaccines are transported, stored and packed in accordance with manufacturers' instructions. Affected people will proceed to treatment centers where patient flow operations along with dispensing activities of medical supplies should be appropriately managed. Reverse logistics activities should also take place as dangerous waste must be treated carefully or disposed of in such a way that it doesn't pose a threat for the medical personnel and people engaged in the containment effort. In addition, coordination issues across the entire emergency supply chain arise. Manufacturers, governments, primary health care institutes and military agencies are few among several key-players for which coordination issues should be addressed. Finally, managing the information regarding the demand for medical supplies as well as the flow of funds is also critical. In Figure 2 an End-to-End approach of the epidemics control supply chain is depicted. Note that the reverse flow may refer to only a part of the medical supplies (Dasaklis, Pappis et al. 2012).

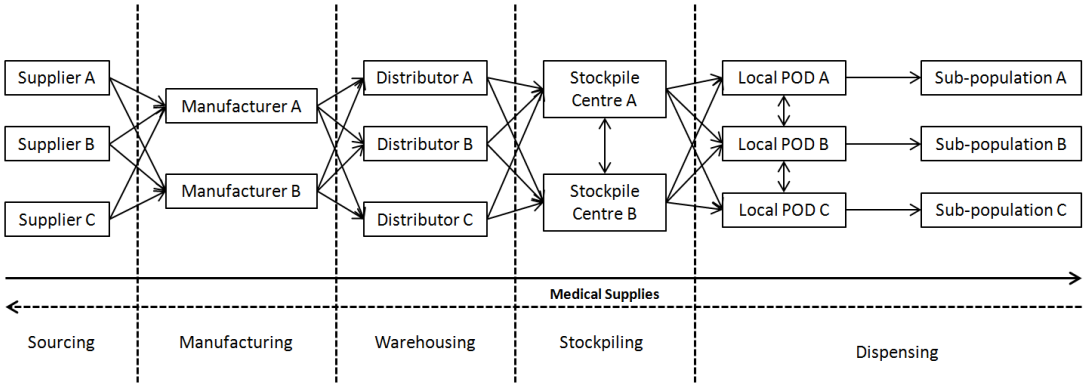


Figure 2: Materials flow of the epidemics control supply chain (End-to-End approach). Source (Dasaklis, Pappis et al. 2012)

The importance of logistics operations for controlling IDOs is recognized by several leading international health organizations like the World Health Organization and the Pan American Health Organization. A basic component of the World Health Organization's Epidemic and Pandemic Alert and Response program addresses logistic issues in order "*to provide operational assistance in the ongoing management of logistics required for epidemic and pandemic preparedness and response and for the rapid deployment of medical and laboratory supplies, transport, communications as well as the rapid deployment of outbreak response teams*" (http://www.afro.who.int/en/divisions-a-programmes/ddc/epidemic-a-pandemic-alert-and-response/programme-components/logistics.html). In the sequence, an

inventory of all the logistics operations taking place during the various phases of an epidemics' containment effort is provided. Generally, these phases could be classified as follows (World Health Organization 2005; John Hopkins Bloomberg School of Public Health and the International Federation of Red Cross and Red Crescent Societies 2008):

- Preparedness
- Outbreak investigation
- Response
- Evaluation

Preparedness

Epidemic preparedness aims at maintaining a certain level of available resources so as to reduce morbidity and mortality when an IDO occurs. Procurement and stockpiling of vaccines and medical supplies play a crucial role for successfully implementing control actions. This means that pharmaceuticals and relevant supplies should remain accessible or kept in large quantities in order to assist a prompt response, if necessary (Richards, Burstein et al. 1999). For instance, the Strategic National Stockpile (SNS) program in the United States is an indicative preparedness program with the objective to maintain large quantities of medicine and medical supplies and to provide these materials to states and communities within twelve hours in the event of a large-scale public health emergency (Esbitt 2003). In addition, a certain amount of vaccines should be available for the immunization of control teams and health-care workers. This is of great importance as medical personnel will treat the very first infected persons and should be protected against the disease that causes the outbreak. Logistics operations as well as relevant logistics-oriented decisions to be made during the phase of preparedness may include (World Health Organization 2005; John Hopkins Bloomberg School of Public Health and the International Federation of Red Cross and Red Crescent Societies 2008; World Health Organization 2008):

- Identification of sources for the procurement of medical supplies and relevant commodities
- Contract management for all the materials procured
- Inventory management for all the essential medical supplies (vaccines, antibiotics, antiretroviral drugs) and supplementary medical commodities (personal protective supplies) kept
- Periodical review and updating of medical supplies
- Facility location and capacity determination for stockpiling centers

- Network design for transportation/distribution activities and selection of appropriate means for transportation/distribution activities
- Selection of appropriate vaccination facilities/health care systems and their capacity (size, availability of rooms and designated areas, availability and scheduling of personnel etc)
- Availability of funds.

Outbreak investigation

Outbreak investigation consists of the detection of any suspected outbreak and its confirmation through laboratory testing. Surveillance mechanisms provide public health officials and decision makers with the essential information regarding any unexplained infection increases seen over a period of time through the systematic analysis of data collected. Surveillance systems provide adequate information that facilitates the development of an initial response framework where the type and magnitude of the containment effort could be determined once epidemic thresholds have been reached (World Health Organization 2005).

Leading world health organizations have developed surveillance systems covering cases like pandemic outbreaks (European Centre for Disease Prevention and Control 2009), IDOs following natural disasters (World Health Organization 2005) or even possible disease outbreaks during mass gatherings (World Health Organization 2008). Additionally, surveillance systems have been developed by the scientific community (Lombardo, Burkom et al. 2003; Dato, Wagner et al. 2004; Krause, Altmann et al. 2007) and many researchers have studied relevant issues arising during the detection and confirmation of IDOs attributed to bioterrorist attacks (Lober, Karras et al. 2002; Buehler, Berkelman et al. 2003; Pavlin, Mostashari et al. 2003; Platt, Bocchino et al. 2003; Bravata, McDonald et al. 2004) or outbreaks related to specific agents (Dietz, Gubler et al. 1990; Arita, Nakane et al. 2004; Jansson, Arneborn et al. 2005). It is worth mentioning that surveillance systems for the detection of IDOs during humanitarian crises may necessitate taking into consideration some context-specific features like the target population, the political context, the state of infrastructure and, finally, the presence of multiple partners in the field (M'ikanatha, Lynfield et al. 2007). Among the logistics activities that support the detection and confirmation mechanisms of a suspected outbreak are (World Health Organization 2005; U.S. Agency for International Development 2009):

- The provision of all the appropriate materials like report sheets to hospitals, emergency medical services and local public health departments that will be used for the collection of primary data regarding initial cases

- The training of clinical workers to recognize unexpected patterns of the occurrence of specific diseases and to promptly identify and report suspected cases using standard definitions
- The provision of all the necessary commodities and resources to the outbreak response team that will facilitate and ensure its operational deployment
- The collection of specimens and their labeling
- The secure transportation of specimens to the appropriate laboratory (using cold boxes and coolant blocks)
- The appropriate storage of specimens in the laboratory (kept within a specific temperature range)
- The procurement, handling, storing and distribution of laboratory commodities, their classification, their quality assurance and quality control etc.

Response

Once leading health agencies have confirmed an IDO, measures and control strategies must be implemented as soon as possible at a regional or national level. Treatment centers should be established and available resources such as medical supplies and personnel should be deployed rapidly in order to contain the epidemic before it reaches uncontrollable proportions. Vaccination of susceptible groups or isolation and quarantine of those infected are considered standard interventions for the containment of an epidemic. All measures taken must be based on a clear understanding of the agent's nature triggering the outbreak as some diseases necessitate specific control protocols to be followed (World Health Organization 2005). This in turn calls for the availability of additional infrastructure and medical supplies within health care premises such as isolation rooms with good ventilation systems, respiratory equipment etc. The logistics operations and relevant decisions to be made during the phase of response may include (World Health Organization 2005; John Hopkins Bloomberg School of Public Health and the International Federation of Red Cross and Red Crescent Societies 2008; World Health Organization 2008):

- the selection of facilities to serve as PODs
- the periodical review and updating of supplies and commodities needed
- the transportation/distribution of supplies and commodities from central warehouses to local POD
- the procurement of supplies/resources once depleted
- the dispensing of medical supplies, supplementary materials and commodities to the public

- the establishment of a cold supply chain for the provision of essential medical supplies like vaccines
- the daily/weekly capacity of available personnel to perform mass vaccination campaigns (for example the maximum number of people that can vaccinate per day)
- the scheduling of available vehicles to be used for transportation and distribution purposes
- adjustments to the capacity of health care facilities to hospitalize infected people
- the management of patients in triage centers (clinical flow logistics).

Evaluation

Once an IDO has been contained, decision makers and public health policy makers engaged in the control efforts should proceed to the evaluation of all the measures undertaken during the previous phases. Generally, the evaluation phase is very useful as it provides strong insights towards a series of modifications that need to be made in order to increase the resilience of the control mechanisms in future IDOs. The evaluation phase should lead to clear conclusions and, therefore, recommendations that will enhance the capabilities of the parties involved to better respond to future IDOs. Dissemination of knowledge (lessons learned) should take place among all the parties involved, from public health policy makers and health agencies to local communities. Despite the fact that the evaluation phase entails limited physical movement of medical supplies and complementary commodities, it remains important from a logistical point of view. Many useful conclusions can be drawn with respect to logistics control operations such as (Hupert, Cuomo et al. 2004; John Hopkins Bloomberg School of Public Health and the International Federation of Red Cross and Red Crescent Societies 2008):

- the identification and assessment of possible bottlenecks or delays that hindered the deployment of the available medical supplies
- the evaluation of the timeliness that should have been respected during the control of the epidemic
- the follow-up and monitoring of patients for antibiotic effectiveness or vaccine immunoresponse
- the identification of patients requiring dose modification or alternative treatment regimen due to adverse effects
- the development of indicators regarding the performance of the logistics control operations
- the assessment of coordination issues risen among the parties involved

- the establishment and operation of rehabilitation procedures in the case of disease outbreaks in the aftermath of natural disasters.

1.3 Motivation and research objectives

For clarifying and framing research questions in view of the present study a literature review was initially conducted focusing on the role of logistics operations for controlling IDOs. A comparative assessment of the suitability, advantages and disadvantages of the particular research methodologies developed so far was made (Dasaklis, Pappis et al. 2012). In general, IDOs control literature could be classified into two main streams of studies. The first stream consists of studies where several disease transmission modelling approaches are utilized for assessing the possible effects of control interventions (Ferguson, Keeling et al. 2003; Lee, Lye et al. 2009). These interventions could be pharmaceutical (use of vaccines or antiviral drugs), non-pharmaceutical (closure of schools, voluntary quarantines over a wide area, social distancing and travel limitations) or any combination thereof. For capturing the transmission dynamics of a disease simple compartmental models based on differential equations to meta-population models and, finally, detailed stochastic agent-based models have been developed (Rahmandad and Sterman 2008; Ajelli, Gonçalves et al. 2010). For assessing the possible benefits of control measures several scenarios are built based on reasonable ranges of parameters like the number of initial cases infected, levels of residual herd immunity, delays for implementing containment strategies, relevant efficiency of control measures etc. It is worth noting that the articles of this stream incorporate novel features which are of considerable biological interest. Most of these articles have been published in epidemiological/medical scientific journals.

The second stream consists of modelling approaches in which logistical prerequisites of control actions are taken into consideration. It is worth noting that this stream was the main target of the literature review conducted by (Dasaklis, Pappis et al. 2012). In particular, disease transmission models (mostly based on compartmental modelling) are coupled with OR/MS modelling approaches and the overall emergency supply chain is assessed in terms of transportation and distribution capacities (Ekici, Keskinocak et al. 2008; Ke and Zhao 2008; Zhao and Sun 2008; Herrmann, Lu et al. 2009; Jingjing, Lindu et al. 2009; Shen, Dessouky et al. 2009; Wang, Wang et al. 2009; Blecken, Danne et al. 2010; Li and Jie 2010; Zhao and Han 2010; Hu and Zhao 2011; Rottkemper, Fischer et al. 2011; Hu and Zhao 2012; Rottkemper, Fischer et al. 2012; Liu and iang 2013), facility location (Berman and Gavious 2007; Jia, Ordóñez et al. 2007; Jia, Ordóñez et al. 2007; Huang, Kim et al. 2010; Murali, Ordóñez et al. 2012), triage management and patient flow logistics

(Hupert, Mushlin et al. 2002; Kaplan, Craft et al. 2003; Wein, Craft et al. 2003; Porco, Holbrook et al. 2004; Craft, Wein et al. 2005; Giovachino, Calhoun et al. 2005; Aaby, Herrmann et al. 2006; Lee, Maheshwary et al. 2006; Miller, Randolph et al. 2006; Whitworth 2006; Patvivatsiri, Montes Jr et al. 2007; Pietz, Benecke et al. 2009; Richter and Khan 2009; Hui 2010), stockpiling of medical supplies (Balicer, Huerta et al. 2005; Cinti, Chenoweth et al. 2005; Lee, Kai et al. 2006; Liu 2007; Arinaminpathy and McLean 2008; De Laurentis, Adida et al. 2008; Siddiqui and Edmunds 2008; Arinaminpathy, Savulescu et al. 2009; DeLaurentis, Adida et al. 2009; Dhankhar, Dasbach et al. 2009; Hashikura and Kizu 2009; Lugnér and Postma 2009; Radonovich, Magalian et al. 2009; Dhankhar, Grabenstein et al. 2010; Duintjer Tebbens, Pallansch et al. 2010; Harrington Jr and Hsu 2010; Adida, DeLaurentis et al. 2011; Rebmann, Citarella et al. 2011), as well as resource allocation (Matrajt and Longini Jr 2010; Rachaniotis, Dasaklis et al. 2012; Matrajt, Halloran et al. 2013; Ren, Órdoñez et al. 2013). Research has also been directed towards the vaccine supply chain as well as the management of cold chain (Adu, Adedeji et al. 1996; Chick, Mamani et al. 2008; Hessel 2009; Mamani, Chick et al. 2013). Other studies address issues of coordination, information and communications management and general logistical impediments during the containment effort (Barbera, Macintyre et al. 2001; Brandeau, Zaric et al. 2008; Conn, Welch et al. 2008; Manley and Bravata 2009; Date, Vicari et al. 2011). Most of the articles of this stream are published in OR/MS scientific journals. In Figure 3 an analysis of the basic components of the epidemics control literature is presented where four clusters of the epidemics control supply chain are identified. These clusters refer to the epidemics logistics network configuration, stockpiling of medical supplies, triage operations and cross-functional drivers (Dasaklis, Pappis et al. 2012).

Although the studies of the first stream provide valuable insights into several aspects of IDOs control, they fail to explicitly incorporate broad operational response features. For instance, limited resources to be allocated or limited capacities for performing control actions are the main logistical features taken into account in the form of assumptions in most of these studies. Unfortunately, from an operational perspective, these underlying assumptions could lead to ambiguous conclusions with respect to the optimality of control actions, especially in real-life conditions. A typical example is smallpox control literature where the majority of the smallpox modelling approaches favors isolation of infected individuals and ring vaccination as an optimal control strategy provided that public health systems will not be compromised (Meltzer, Damon et al. 2001; Hall, Egan et al. 2007; Longini Jr, Elizabeth Halloran et al. 2007; House, Hall et al. 2009; Egan, Hall et al. 2011). However, the scalability of a possible bioterrorist attack, the inherent uncertainties for accurately estimating the value of several key parameters and the accompanying great-scale logistical implications behind control efforts have been paid little attention so far. According

to recent studies public health capabilities for managing highly infectious diseases could be easily compromised in case of large scale events (Ippolito, Puro et al. 2006; Fusco, Schilling et al. 2012). In addition, emergency exercises and drills revealed serious shortcomings in the ability of health-care personnel to rapidly detect and effectively proceed to standard response protocols in the case of highly infectious diseases like smallpox (Klein, Atas et al. 2004).

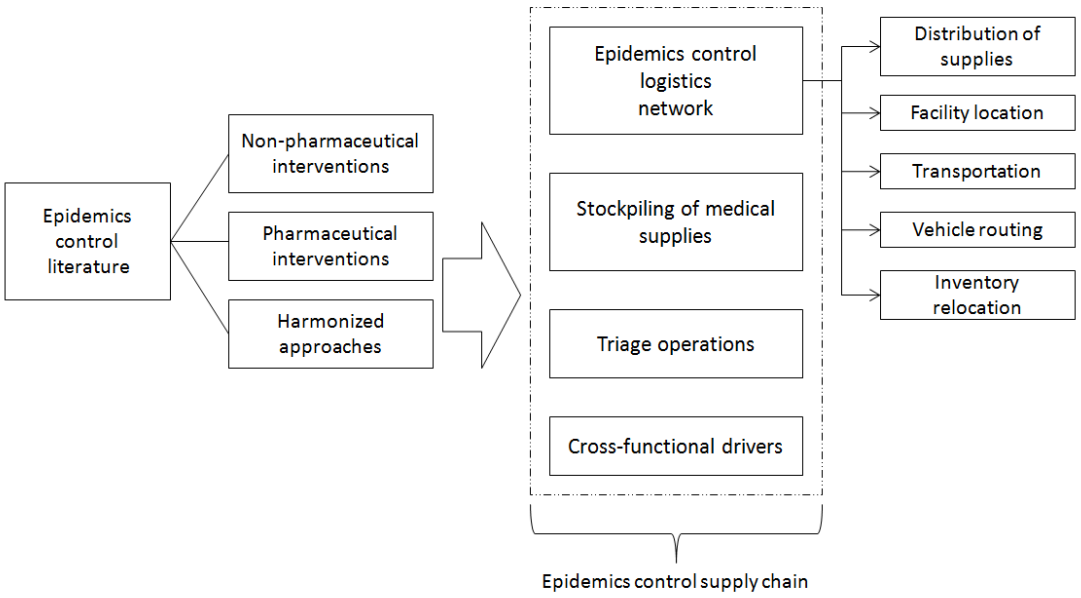


Figure 3: Epidemics control literature classification

The studies of the second stream have also some limitations. Their major defect is that they incorporate tedious epidemiological characteristics and assumptions with respect to diseases' progression and, therefore, they are unsuitable for guiding the selection of control interventions. For example, the disease transmission models coupled with OR/MS modelling approaches fail to capture the biological characteristics of the agent triggering the outbreak. In most of the cases they are simple SIR (Susceptible, Infected, and Removed) or SEIR (Susceptible, Exposed, Infected, and Removed) models that do not take into account the different stages of infection presented in different diseases. Even further, the modelling approaches of this category do not consider the way resources' allocation may affect the spread of the IDO and, therefore, the dynamics between disease's transmission and the availability of certain amount of control resources are not captured. Other aspects besides poor epidemiological characteristics are also prevalent in the studies of the second stream, such as the lack of adherence to diseases control guidelines published by national or international organizations worldwide, the absence of

robust control scenarios and their assessment, and, finally, their limited applicability (Dasaklis, Pappis et al. 2012).

In light of these findings the overall objective of this research is the development of tailor-made approaches that take into account both the biological characteristics of the agent triggering the outbreak as well as the response operations. It is worth noting that this research does not take into consideration logistical aspects arising in the context of seasonal patterns of IDOs (like seasonal influenza outbreaks) or relevant IDOs which might be expected, anticipated or last for a long period of time (like HIV outbreaks). Notice that, in the relevant extensive review of (Altay and Green Iii 2006) regarding the MS/OR research in disaster operations management, the contribution from this scientific area to epidemics control is not examined.

1.4 Research approach and contributions

The control of IDOs is not a straightforward process. In fact, the implementation of control actions should be closely related to the very nature of the agent triggering the outbreak. For instance, anthrax and smallpox could be both utilized as bioterrorists weapons. From an operational response perspective, however, their control presents huge differences. As mentioned in (Whitworth 2006), anthrax, which is not contagious, can be treated with antibiotics dispensed to heads of households (who can then dispense the antibiotics to all the family members). On the other hand, smallpox is contagious, is caused by a virus and can be only prevented by vaccination. In this case, vaccination centers should be established and each individual should be administered a fresh vaccine. Therefore, from a logistics point of view, the response to an anthrax attack doesn't resemble the response to a smallpox attack. Response time frames are also different in each case, presenting different logistical challenges for the transportation and distribution of medical supplies.

Apart from the biological characteristics of each agent, the generic context in which an IDO occurs also presents several differences. These differences are exemplified in the case where a developing country faces a humanitarian emergency situation. Death rates of over 60-fold the baseline were recorded in refugees and displaced people and most of these deaths were attributed to communicable diseases (Connolly, Gayer et al. 2004). Complete breakdown of infrastructures, population displacement, shortages of crucial medical supplies and insecurity are just a few among several impediments that public health officials are confronted with when implementing outbreak control agendas in these settings. Generally, the implementation of outbreak control measures while public health systems are

compromised, as is the case in humanitarian emergencies, can be a daunting task. On the other hand, public health systems of developed countries could face a covert bioterrorist attack. The repercussions of a possible bioterrorist attack can be chaotic since public health officials and law enforcement agencies are unaware of the breadth and depth of such an attack. A series of lessons were drawn from a senior-level exercise entitled “Dark Winter” that simulated a covert smallpox attack in the United States. This exercise revealed that state officials and lawmakers were unfamiliar with the character of a bioterrorist attack and the available policy options for its control. In addition, the exercise showed that their decision-making process was severely hindered by several resource constraints like limited vaccines or medical supplies to prevent the spread of the disease. Issues of surge capacity and prioritization also arose during the exercise (O'Toole, Mair et al. 2002). Last but not least, the emergence of a new influenza strain could trigger a pandemic outbreak of unprecedented proportions. Due to limited vaccine supplies health officials will have to prioritize control actions and apply targeted allocation strategies to specific groups of the population (individuals at high-risk etc).

Therefore, one-size-fits-all approaches in the case of IDOs control are not suitable and special attention should be paid to both the agent triggering the outbreak as well as to the general context in which the outbreak occurs. In light of these particularities, the questions addressed in this research are focused on improving the operational response of public health systems in the case of the following three types of IDOs:

- bioterrorist events
- natural outbreaks
- outbreaks in humanitarian emergencies

Smallpox, influenza and cholera have been chosen as the main infectious agents to be studied in each case. It is worth noting that this research does not intend to develop new epidemiological methods or models but rather to apply and, where necessary, modify and adapt existing epidemiological models to the context and constraints of IDOs control and, especially, from an operational point of view.

The main contribution of this thesis is the development of research methodologies for modelling the response operations of IDOs control. These methodologies are mainly of quantitative nature and are mostly based on operations research techniques. In particular, for clarifying and framing research questions a literature review was initially conducted focusing on the role of logistics operations for controlling IDOs. A comparative assessment of the suitability, advantages and disadvantages of the particular research methodologies developed so far was made (Dasaklis, Pappis et al. 2012). In the sequel, three modelling approaches were

developed for evaluating different IDOs control scenarios (for influenza and smallpox respectively):

- Two deterministic mathematical models for resource allocation (one and multiple resources) in which vaccination of the susceptible individuals has been the main control action taken into consideration.
- A linear programming model for optimally distributing a set of supplies (medical and ancillary) to affected sub-populations for controlling a smallpox outbreak.

It is worth noting that the modelling approaches presented above have been coupled with relevant epidemiological models capturing the biological characteristics of each disease (influenza and smallpox).

For studying issues of IDOs control in humanitarian emergencies both qualitative and quantitative approaches have been used:

- A systematic literature search and thematic content analysis for the identification of several factors that affect the control of IDOs in complex humanitarian emergencies.
- A multi-criteria approach (DEMATEL method) for the prioritization of these factors and the identification of their interrelationships in the case of the implementation of cholera immunization campaigns in complex humanitarian emergencies.

1.5 Structure of the thesis

This chapter introduces the key terms and issues surrounding IDOs control and the role of logistics operations in supporting the implementation of intervention strategies. Chapter 2 sets out to analyze resource allocation decisions in the case of influenza outbreaks. In particular, two distinct cases are examined with respect to resources' availability. In the first case the problem of scheduling one available resource, when there are several areas where the population is infected, is considered. A deterministic model, appropriate for large populations, where random interactions can be averaged out, is used for the epidemic's rate of spread. The problem is tackled using the concept of deteriorating jobs, i.e. the model represents increasing loss rate as more susceptibles become infected, and increasing time and effort needed for the epidemic's containment. A case study is presented for a proposed application of the model in the case of the mass vaccination against A(H1N1)v influenza in the Attica region, Greece. The second case considers the problem of allocating and scheduling limited multiple, identical or non-identical,

resources employed in parallel, where several areas are infected. A real-time synchronous heuristic algorithm is proposed as the solution methodology. A numerical example implementing the proposed methodology in the context of an influenza outbreak is presented, where a detailed epidemic transmission model capturing the biological characteristics of influenza is coupled with the proposed modelling approach.

Chapter 3 delves into the concept of bioterrorist response and the logistical implications for controlling deliberate bioterrorist attacks. In particular, the case where a large-scale deliberate smallpox attack occurs is considered. For changes in various baseline assumptions (variations to the basic reproduction number, possible delays in response etc) the logistical requirements and subsequently the flow of materials for implementing a regional mass vaccination campaign are assessed. For capturing the disease's dynamics a transmission mathematical model is used. In addition, a linear programming model for optimally distributing a predetermined vaccine stockpile to several affected subpopulations is also used. A numerical example is finally presented illustrating the methodology proposed.

Chapter 4 considers aspects of IDOs control in humanitarian emergencies. Initially, the results of a systematic literature review regarding the factors that affect the control of IDOs in humanitarian emergencies for a set of diseases are presented. In the sequence, an attempt is made for identifying operational success factors as well as the possible interrelationships among them for successfully implementing cholera vaccination campaigns in humanitarian emergencies. Several factors affecting the implementation of cholera vaccination campaigns are identified through systematically surveying the literature. Based on this survey and following experts' responses, relevant priorities are identified and the description and analysis of the interrelationships among these factors are given through the usage of the Decision Making Trial and Evaluation Laboratory (DEMATEL) method.

Finally, Chapter 5 presents the main findings of this research by summarizing the results, pointing out limitations and constraints as well as presenting a critique and an outlook for future research.

Chapter 2: Controlling infectious disease outbreaks attributed to natural causes: the case of influenza

2.1 Introduction

In this chapter resource allocation decisions in the case of influenza outbreaks control are considered. Vaccination of the susceptible individuals is the main control action taken into consideration. Two distinct cases are examined with respect to resources' availability; one being the use of a single resource, another being the use of multiple identical resources. In the first case a deterministic model, appropriate for large populations, where random interactions can be averaged out, is used for the epidemic's rate of spread. The problem is tackled using the concept of deteriorating jobs, i.e. the model represents increasing loss rate as more susceptibles become infected, and increasing time and effort needed for the epidemic's containment. A case study for a proposed application of the model in the case of the mass vaccination against A(H1N1)v influenza in the Attica region, Greece, from 11/2009 to 01/2010 is presented. The second case considers the problem of allocating and scheduling limited multiple, identical or non-identical, resources employed in parallel, where several areas are infected. A real-time synchronous heuristic algorithm is proposed as the solution methodology. For illustrating the applicability of the modelling approach a numerical example is presented. In particular, the case where several mobile medical teams implement a mass vaccination campaign for controlling an influenza outbreak is considered. Both modelling approaches presented in this chapter are novel since the literature of vaccines optimal allocation does not deal with medical teams scheduling (Ompad, Galea et al. 2006).

2.2 Related literature

Influenza control literature is vast (Germann, Kadau et al. 2006; Halloran, Ferguson et al. 2008; Coburn, Wagner et al. 2009). In most cases, several disease transmission modelling 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 modelling the progression of the disease several approaches have been presented in the literature. These approaches range from simple compartmental models based on differential equations (Chowell, Ammon et al. 2006; Alexander, Moghadas et al. 2008; Arino, Brauer et al. 2008; Glasser, Taneri et al. 2010; Hollingsworth, Klinkenberg et al. 2011; Lee, Golinski et al. 2012) to meta-population models (Flahault, Vergu et al. 2006; Colizza, Barrat et al. 2007; Balcan, Hu et al. 2009) and, finally, detailed stochastic agent-based models (Ferguson, Cummings et al. 2005; Carrat, Luong et al. 2006; Ferguson, Cummings et al. 2006; Ajelli and Merler 2008; Ciofi degli Atti, Merler et al. 2008; Sander, Nizam et al. 2009). In the sequence the logistics-oriented as well as resource allocation literature with respect to influenza outbreaks control is presented.

2.2.1 Stockpiling of medical supplies

Inventory management in the case of influenza control may relate to managing specific medical supplies like vaccines and antiviral drugs as well as ancillary medical resources like Personal Protective Equipment (PPE) etc. In some cases the problem of stockpiling of medical supplies has been treated as a joint inventory stockpiling problem for several groups of hospitals. In this case it is assumed that mutual aid agreements for inventory sharing are established among the hospitals. A game theoretical approach is adopted for the formulation of the problem (De Laurentis, Adida et al. 2008; DeLaurentis, Adida et al. 2009; Wang, de Véricourt et al. 2009; Arora, Raghu et al. 2010; Adida, DeLaurentis et al. 2011). Some researchers have also tried to determine the amounts of supplementary medical supplies like PPE to be held that could serve as a means of preventing influenza pandemics (Hashikura and Kizu 2009). Additionally, many researchers have tried to estimate the capacity of health care facilities to respond to spreading diseases in terms of materials (Radonovich, Magalian et al. 2009) and PPE needed (Rebmann, Citarella et al. 2011).

As far as antiviral drugs are concerned, logistical constraints such as a finite stockpile of drugs and limited distribution rates have been examined (Arinaminpathy and McLean 2008; Arinaminpathy and McLean 2009; Arinaminpathy, Savulescu et al. 2009; Dimitrov, Goll et al. 2011). (Lee, Kai et al. 2006) utilize cost-benefit and cost-effectiveness analyses with Monte Carlo simulations to compare strategies for stockpiling neuraminidase inhibitors to treat and prevent an influenza pandemic outbreak. (Lugnér and Postma 2009) utilize cost-effectiveness considerations when

stockpiling antiviral drugs in order to mitigate an influenza pandemic outbreak. (Siddiqui and Edmunds 2008) develop a decision analytical model to investigate the cost-effectiveness of stockpiling antiviral drugs for a potential influenza pandemic in the United Kingdom and the possible role of near-patient testing in conserving antiviral drug stocks. (Carrasco, Lee et al. 2011) make use of an epidemic-economic model to assess the effect of different antiviral stockpiles on total mortality and costs for several countries. (Balicer, Huerta et al. 2005) analyze strategies for the utilization of stockpiled antivirals for a future influenza pandemic and estimate cost-benefit ratios, while (Cinti, Chenoweth et al. 2005) provide a strategy for stockpiling certain antivirals at a reasonable cost. (Harrington Jr and Hsu 2010) examine the so-called Manufacturer Reserve Programs which are used by manufacturers to promote stockpiling of anti-viral drugs in preparation for pandemic influenza by non-governmental organizations such as hospitals. Finally, (Lee, Chowell et al. 2010) develop a modelling approach that combines the effects of non-pharmaceutical interventions (isolation) with the usage of antiviral drugs by taking into account limited resource assumptions.

In the case of vaccine inventory control, (Liu 2007) considers the case in which a sudden demand for vaccines attributed to an urgent incident like a natural outbreak or a bioterrorist attack occurs and develops mathematical models for estimating the necessary stockpile levels of vaccines in order to meet future urgent needs. (Dhankhar, Dasbach et al. 2009) examine the quantities to be held in stock and relevant economic evaluations of vaccines in accordance with their time of expiration. Vaccine control strategies in the case of secondary bacterial infections (especially pneumococcal infections) during a pandemic influenza outbreak have also been examined (Dhankhar, Grabenstein et al. 2010).

2.2.2 Vaccine supply chain

Research has also been directed towards the vaccine supply chain as well as the management of cold chain. Generally, in a possible influenza pandemic outbreak logistical challenges and difficulties such as production, stockpiling and delivering vaccines will arise (Jennings, Monto et al. 2008). For example (Adu, Adedeji et al. 1996), through an exploratory research, examine several issues that affect the efficiency of cold supply chains like mishandling of vaccines and false storage conditions. (Hessel 2009) examines issues of vaccine allocation and relevant procurement processes, the establishment of critical health systems and infrastructure required for vaccine deployment, storage aspects associated with

stockpiling pre-pandemic vaccines, and finally mutually agreed contractual arrangements between manufacturers and governments or international institutions. Other logistics aspects of the vaccine supply chain may concern vaccines' production and distribution (Collin and de Radiguès 2009). Ethical issues regarding vaccine distribution during an influenza pandemic like who will likely produce and "own" the vaccine and how vaccine distribution and administration might be accomplished are studied in (Hadler 2005).

Another important aspect of the epidemics control supply chain is the sourcing decisions to be made. Antiviral drugs as well as vaccines should be procured in order to be utilized during the containment effort. Governments around the world and public health institutes may be faced with uncertainty regarding the exact amount of medical supplies to be purchased. For instance, many times huge quantities of vaccines are procured by governments but they eventually become obsolete as the demand for vaccinating the population remains low (unwillingness of people to get vaccinated etc). (Chick, Mamani et al. 2008) examine several supply contracts that coordinate buyer (governmental public health service) and supplier (vaccine manufacturer) incentives and design a variant of the cost-sharing contract that provides incentives to both parties which ultimately leads to the improvement of the supply of vaccines in the case of annual influenza outbreaks. In (Ak, Heier Stamm et al. 2012) procurement aspects of the Pan American Health Organization's vaccine supply chain are examined and several recommendations for the improvement of demand forecast for vaccines are provided. The study also explores issues of transportation cost for vaccines and the possible implications of bundle bidding. (Mamani, Chick et al. 2013) proposes a contractual mechanism for reducing the inefficiencies in the allocation of influenza vaccines due to interdependent risk of infection across different countries. Despite the fact that the above papers address issues of seasonal influenza, they have been included in the analysis as they provide strong insights towards the issues of contract management and sourcing of epidemics control supply chain.

2.2.3 Resource allocation models

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. In particular, vaccinating at-risk individuals is of paramount importance. Several

studies consider aspects of prioritization by using age-targeted allocation strategies (Chowell, Viboud et al. 2009; Lee, Brown 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 (Mylius, Hagenaars et al. 2008; Meyers, Galvani et al. 2009; Matrajt and Longini Jr 2010; Tuite, Fisman 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, Halloran et al. 2013; Yarmand, Ivy et al. 2014). Other studies consider aspects of limited vaccine supply as well as limited vaccination administration capacities (Cruz-Aponte, McKiernan et al. 2011).

Apart from vaccines, other resources for controlling influenza outbreaks may refer to clinics to care for those infected (Carr and Roberts 2010) or combination of allocation of antiviral drugs, vaccines and other supplies (Das, Savachkin et al. 2008; Koyuncu and Erol 2010; Krumkamp, Kretzschmar et al. 2011; Stein, Rudge et al. 2012; Zhou and Fan 2012). In addition, allocation of scarce resources like vaccines or antiviral drugs in conjunction with non-pharmaceutical approaches have also been developed (Wallinga, Van Bovena et al. 2010; Hansen and Day 2011; Yaesoubi and 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 and Gilligan 2011; Uribe-Sánchez, Savachkin et al. 2011).

2.3 Resource allocation for controlling an influenza outbreak

Although infectious diseases pose a serious threat to public health, resources for controlling them are often limited. Public health officials and decision makers must determine how to allocate and schedule limited resources among subpopulations to ensure that widespread community transmission does not occur. Scheduling resources for controlling IDOs is a complex problem due to the fact that: a) different subgroups may have different risk of infection depending on their susceptibility, b) epidemics of infectious diseases is nonlinear and dynamic, since the rate of new infections is proportional to the product of the number of infected people and the number of uninfected people, and these quantities change over time, c) the time horizon has an impact on the scheduling decision, since a short term consideration may not have the same results as a long term one. 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. Consequently, the problem's

uniqueness and severe impacts demand dynamic, real-time and effective solutions, thus making the topic very suitable for OR/MS research in the area of Disaster Operations.

2.3.1 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, 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 (Greek Minister of Health, 17/09/2009, www.yyka.gov.gr). House-bound individuals or institutionalized ones formed part of these specific groups. The same holds for IDOs attributed to bioterrorist attacks. For instance, 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).

Control actions in the case of an influenza outbreak typically include prophylaxis of susceptible individuals (either by vaccination or by using antiviral drugs), 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, travel limitations etc). The objective of the control actions described above is the reduction of the value of the effective reproduction number below one. In this case infected individuals may not pass the infection on susceptible individuals during their infectious period and eventually the infection dies out (Riley, Fraser et al. 2003). 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 chapter. Mobile medical teams can be assigned to targeted populations or individuals. Mass vaccination of susceptible individuals is the main control strategy. To the best of the author's knowledge, there is no application of resource allocation-scheduling in epidemics control literature and particularly in the case of mobile medical teams scheduling.

2.3.2 The case of one processor

In this sub-section the case of an epidemic spread in several distinct communities (subpopulations) in a region is examined and the problem of scheduling a single available resource (e.g. a mobile medical team or equipment) to service the infected communities is considered as a job-scheduling problem using the concept of deteriorating jobs. In particular, a specific region with several infected distinct subpopulations or individuals (e.g. old aged citizens) is assigned to a single available mobile medical team. Vaccination of susceptible individuals is the main control strategy. The model represents increasing loss rate as more susceptibles become infected and variable time and effort needed for the epidemic's containment (Alidaee and Womer 1999; Cheng, Ding et al. 2004). The utilization of the 'deteriorating jobs' concept in order to schedule the control actions is supported by epidemiological studies, which explicitly state that strict measures implemented early (during the initial phase of an IDO) are more effective for controlling the outbreak (Lipsitch, Cohen et al. 2003). In addition, the new version of the deteriorating jobs' scheduling problem (Rachaniotis and Pappis 2006), where the objective is to find the optimal scheduling policy if the processing times increase depending on the processing starting time and the jobs' values also decrease over time, under the scheduling criterion of maximizing the total jobs' remaining value at the time that processing of all jobs is completed, is directly connected to the case examined.

Several applications of the above approach regarding states of emergency have been reported. Thus, the general machine scheduling problem has been used to solve the resource allocation problem after a severe earthquake (Fiedrich, Gehbauer et al. 2000). Besides the numerous applications in industry (Bachman, Cheng et al. 2002; Bachman, Janiak et al. 2002; Cheng, Ding et al. 2003; Janiak and Krysiak 2005; Janiak and Kovalyov 2006; Janiak and Krysiak 2007), a few have also been reported in the area of wildfire suppression (Rachaniotis and Pappis 2006; Pappis and Rachaniotis 2010; Pappis and Rachaniotis 2010), and in the field of scheduling in a contaminated area with radio-active or chemical materials (Janiak and Kovalyov 2006; Janiak and Kovalyov 2008).

Notation

Let:

n: be the number of subpopulations infected simultaneously. Under an arbitrary epidemic's control sequence (permutation) of all n! potential control sequences of

the subpopulations' set **S**={S_1 ,S_2,…,S_n}, denote the first subpopulation to be treated as $S_{[1]}$, the second as $S_{[2]}$, etc.

N_i: be the size of S_i.

$x_i(t)$: be the number of susceptible individuals in S_i at time t.

$y_i(t)$: be the number of infected individuals in S_i at time t.

$z_i(t)$: be the number of removed individuals in S_i at time t.

$\lambda_i(t)$: be the rate of contacts sufficient to cause disease transmission at time t in S_i (sufficient contact rate).

$\mu_i(t)$: be the percentage rate at which susceptibles are immunized per unit time at time t in S_i.

$\kappa_i(t)$: be the percentage rate of removal (or "therapy", e.g. quarantine) from the infected group in S_i at time t.

δ_i: be the percentage rate of entry into (and exit from) a group in S_i (replacement rate).

t_0: be the time required for the single mobile medical team to commence controlling the epidemic in the first subpopulation.

$H_i(t)$: be the cumulative number of infections in S_i at time t.

$P_i(t)$: be the processing time, i.e. the time needed to implement the actions to control the epidemic, at time t in S_i.

C_i: be the completion time of the actions to control the epidemic in S_i.

Following the previous definitions, the problem is formulated as follows:

Find $<S_{optimal}>=<S_{[1]},S_{[2]},\ldots, S_{[n]}>$ such that the total number of infections be minimized (or, equivalently, the total number of infections averted be maximized):

$$\min \sum_{i=1}^{n} H_i(C_i) \qquad (1)$$

Assumptions:

- No interactions occur between control actions and actions affecting a rate in one subpopulation do not affect the respective rate in another subpopulation. These may not always be realistic assumptions, but the

complexity of the occurring correlations and the excessive difficulty for calculating their values in an IDO make it necessary to employ such assumptions with minimum risk regarding the correctness of the solution of the problem, which otherwise would be rather intractable.

- The replacement rate δi is the same for infected, susceptible and removed individuals and is assumed to be constant. The assumption of a constant replacement rate is reasonable when the time horizon is relatively short (Brandeau, Zaric et al. 2003).
- Each subpopulation's size and control actions' rates are constant, i.e. λi(t)=λi, μi(t)=μi, κi(t)=κi. The assumption is both realistic, especially for the immunization and removal rates, and necessary in order to yield closed form solutions (instead of numerical ones) in deterministic epidemic models.
- All infected individuals are assumed to be infectious and are equally likely to mix with all uninfected individuals (homogeneous mixing). This is a very common assumption in epidemiology (Brandeau 2005).
- The resources' traveling times are assumed to be negligible, since any mobile medical team can reach any subpopulation in a time period of a few hours, which is not significant compared to the control actions lasting for many days.

2.3.2.1 The mathematical model

For capturing the biological characteristics of the agent triggering the outbreak (influenza) a simple deterministic compartmental Susceptible/Infective/Treated and/or Removed (SIR) model is used (Brandeau 2005). In Figure 4 the schematic illustration of the model is presented. Each subpopulation size is considered to be constant. Individuals enter S_i at rate $\delta_i N_i$ and exit at rate $\delta_i(x_i(t)+y_i(t)+z_i(t))$. Susceptible can become infected or immunized and infected individuals can be removed. Thus, the epidemic can be described by the following system of non-linear differential equations:

$$x_i'(t)=\delta_i N_i-\lambda_i x_i(t)y_i(t)-\delta_i x_i(t)-\mu_i x_i(t) \quad (2)$$

$$y_i'(t)=\lambda_i x_i(t)y_i(t)-\delta_i y_i(t)-\kappa_i y_i(t) \quad (3)$$

$$z_i'(t)= \mu_i x_i(t)+\kappa_i y_i(t)-\delta_i z_i(t) \quad (4)$$

$$x_i(t)+y_i(t)+z_i(t)=N_i \quad (5)$$

It is $y_i(0)=Y_{0i}$ and $z_i(0)=0$ (and consequently $x_i(0)=N_i-Y_{0i}$).

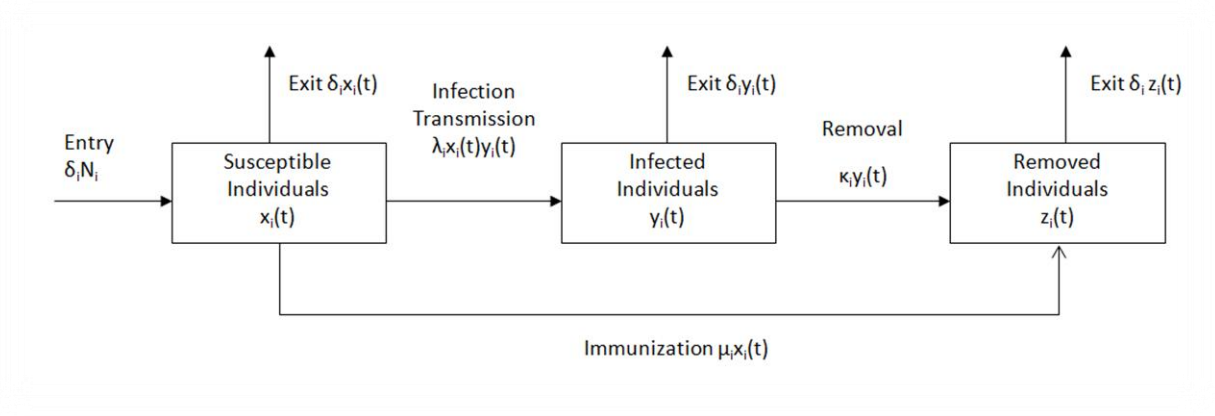


Figure 4: A simple compartmental epidemic model with control actions. Adapted from (Brandeau 2005)

Equations (2)-(4) yield the rate of change in the numbers of susceptible, infective and removed individuals according to the entries and exits illustrated in Figure 4. Equation (5) ensures that the size of each subpopulation S_i is constant.

In accordance to the law of mass action (Daley and Gani 1999; Kaplan, Craft et al. 2002), susceptibles are becoming infectives at a rate proportional to the product of the sizes of the two subpopulations. Usually the susceptibles' population is a non-increasing function and the infectives' population is a non-decreasing function. Therefore it is:

$$H_i(t)=\int_0^t \lambda_i x_i(\tau) y_i(\tau) d\tau \tag{6}$$

Solving the previous system of non-linear differential equations yields the following results:

$$x_i(t)=(N_i - Y_{0i} - B_i - \Gamma_i)e^{-\frac{\delta_i N_i}{\Gamma_i}t} + B_i e^{A_i t} + \Gamma_i \tag{7}$$

$$y_i(t)=e^{A_i t} \tag{8}$$

where A_i, B_i, Γ_i are constants depending on the previously mentioned constant rates λ_i, μ_i, κ_i, δ_i and N_i.

The mobile medical team examines the targeted subpopulations or individuals. Susceptible persons are vaccinated (subtracting a number which can not be located and a number that should not be vaccinated due to vaccine contraindications). Infected persons are isolated or quarantined/ hospitalized. Thus the processing time function (control action time function) is:

$$P_i(t)=\frac{x_i(t)}{\mu_i N_i} \tag{9}$$

and from Equations (6)-(8) the total number of new infections function is:

$$H_i(t)=\left(1+\frac{\delta_i+\kappa_i}{A_i}\right)\left(e^{A_i t}-1\right) \tag{10}$$

Consequently, after the elimination of the constant terms, the objective function (1) can be formulated as:

$$\min\sum_{i=1}^{n} H_{[i]}(C_{[i]})=\min\sum_{i=1}^{n}\frac{A_{[i]}+\delta_{[i]}+\kappa_{[i]}}{A_{[i]}}e^{A_{[i]}C_{[i]}} \tag{11}$$

where

$$C_{[i]}=\sum_{r=1}^{i} P_{[r]} \tag{12}$$

Equations (9)-(11) connect the presented single resource scheduling problem in the case of an IDO to the NP-hard deteriorating jobs' scheduling problem on a single machine (Alidaee and Womer 1999). 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. Although the assumptions listed in the previous section, combined with the simplicity of the epidemic model used, limit its applicability, this scheduling model offers a decision support tool that can assist decision makers in optimally employing a mobile medical team for controlling an IDO.

2.3.2.2 Case study: mass vaccination against A(H1N1)v influenza in Greece

As in the case of many E.U. countries, Greece developed a national influenza pandemic control plan. According to this plan, a mass vaccination of the entire population was due to start at mid-November 2009, with a specified order of priority. There was a specific prevision for mobile vaccination medical teams targeting certain sub-populations within Greek population (Greek Minister of Health, 17/09/2009, www.yyka.gov.gr).

The Hellenic Centre for Infectious Diseases is responsible for the surveillance of A(H1N1)v spread in Greece. According to its week report, issued at 21/10/2009, week 42 of the pandemic, there were 1,250 laboratorial confirmed cases in the Attica administrative region, yielding a percentage of 31 cases per 100,000 inhabitants, which was at that time the fifth among Greek regions (www.keel.gr). It should be noted here that the above data did not capture the total number of A(H1N1)v in Attica but the total numbers of laboratorial confirmed cases, which certainly underestimated its true frequency. A particular difficulty occurred from the mild nature of the disease, which means that many infections were undetected and unreported. Additionally, a laboratorial control was made only to selected incidents (mainly for hospitalized individuals).

As of 19/10/2009 there were three confirmed deaths from $A(H1N1)_v$ influenza in Greece, all in Attica region. This combined with the facts that: a) Athens, Greece's capital is located in Attica, b) influenza spread is strongly correlated to the population's density (Boni et al. 2009) and Attica region has the highest population density in Greece, were the main incentives to apply the proposed model to this region.

Attica region is divided into four prefectures, namely Athens, Piraeus, East and West Attica. In the case study a mobile medical team with a significant service rate was assigned to the region in order to vaccinate people that were not able to go to their local vaccination centers. The targeted subpopulations in this study consisted of habitants older than 80 years (living either in their homes or in residential homes) and habitants with kinetic problems. An estimation of the size of these targeted subpopulations for Attica's' four prefectures is provided in Table 1 (www.statistics.gr/portal/page/portal/ESYE/PAGE-themes?p_param=A1604).

Prefecture	Population density (inhabitants/km^2)	Targeted subpopulation (2009 estimation)
Athens	7,375	83,000
Piraeus	583	15,000
East Attica	277	10,000
West Attica	143	3,000

Table 1: An estimation of the targeted subpopulations' prefecture-specific distribution

Parameter values

The model's parameters' values were ranged over estimated intervals. This was necessary due to the difficulties to estimate them with accuracy, given the various factors that influenced their measurement and their actual values, including, among others, social and healthcare particularities. Thus, higher disease rates were considered. There are several ways to justify such a worst-case approach. First, in the early stage of a pandemic it is reasonable to assume that disease rates are relatively high as the general population has not yet obtained herd immunity to the new strain. Second, from a public health perspective, planning for worst case scenarios is a rather common policy and overestimates of the true rates represent reasonable planning assumptions.

Sufficient contact rate

Sufficient contact rate calculation is based on: a) the key epidemiological parameter R_0, which is defined as the average number of secondary cases infected by a primary case in a susceptible population (basic reproduction number), b) the mean duration of infectiousness and c) the number of susceptibles and the population's density in the different geographical areas.

Regarding the basic reproduction number calculation for A(H1N1)v pandemic, a particular difficulty arose due to the mild nature of the disease, which means that many infections were undetected and/or unreported while only more severe incidents were likely to be captured by surveillance systems. This means that the reported numbers were likely to be biased upwards. Estimates of the basic reproductive rate worldwide can be found in (www.ecdc.europa.eu/en/healthtopics/Pages/Influenza_A(H1N1)_Outbreak.aspx). A very similar estimate has been used for model communities situated in Greece (Sypsa, Pavlopoulou et al. 2009). As would be expected for a pandemic, the number is higher than the value observed for seasonal influenza but in line with previous

pandemics. Regarding the mean duration of infectiousness, reports were used, which provide evidence that the incubation period may have a longer tail than usually observed in seasonal influenza. Finally, different rate's values have been observed in countries where transmission is intense because of the high population density, with even higher figures in some closed communities (www.ecdc.europa.eu/en/healthtopics/Pages/Influenza_A(H1N1)_Outbreak.aspx).

Immunization rate

This is the percentage rate at which susceptibles are immunized per unit time. It was assumed that this rate coincided with the percentage service rate of the mobile medical team. This resulted to a somewhat underestimated rate, since there was some evidence of asymptomatic infectious persons that were difficult for a mobile medical team to trace, and it had to be taken under consideration. The mobile medical team provided indoor examination and vaccination for the targeted population groups. A prior examination was necessary because if an individual was infected and not sensitive to the vaccine, then the vaccination is ineffective (the infection is not prevented) and useless since the vaccine is wasted (Kaplan, Craft et al. 2002).

A simulation model has been applied in Greece (Sypsa, Pavlopoulou et al. 2009) which assumes that the percentage of daily vaccinations is between 2% and 10% in a 2,000-persons community. (Kaplan, Craft et al. 2002) gives a service rate of 50-200 vaccinated persons per day/per vaccinator, depending on the procedure. According to the Hellenic Statistical Authority (ELSTAT), in Attica region there are about 3.7 doctors/1,000 habitants, 6.1 nurses/1,000 habitants and approximately 0.075 ambulances/1,000 habitants.

Removal rate

This is the percentage rate of removal from the infected group. It includes quarantine at home for mild cases and hospitalization for more severe cases. More details about estimations of the removal rate in the case of $A(H1N1)_v$ can be obtained in (http://www.ecdc.europa.eu/en/healthtopics/Pages/Influenza_A(H1N1)_Outbreak.aspx).

Replacement rate

This is the percentage rate for entering and exiting from (migration or travel rate) a group. In (Boni, Manh et al. 2009) and (Brandeau, Zaric et al. 2003) there are estimations of this rate, which were used in this study once they had been adjusted to account for Attica region particularities.

Initial infected cases

The number of initial infected cases is estimated based on the data provided by the Hellenic Center for Infectious Diseases Control (www.keel.gr). Summarizing the above, using data and formulas for the sufficient contact rate calculation from (Kaplan, Craft et al. 2002), the values' ranges for the previously discussed parameters are presented in Table 2. It is worth noting that the ranges for removal and replacement rates and the percentage number of initial infected cases were assumed to be the same for the four prefectures since there was no relevant information available regarding possible differences.

i	λ_i (infections/person·day)	μ_i (% persons/day)	κ_i (% persons/day)	Y_{0i} (cases)	δ_i (% persons/day)
Athens	$[2.065\cdot10^{-6},3.856\cdot10^{-5}]$	[0.0163, 0.065]	[0.05, 0.3]	[1,150]	[0.01,0.1]
Piraeus	$[1.143\cdot10^{-5},2.133\cdot10^{-4}]$	[0.09,0.36]	[0.05, 0.3]	[1,30]	[0.01,0.1]
East Attica	$[1.714\cdot10^{-5},3.2\cdot10^{-4}]$	[0.135, 0.54]	[0.05, 0.3]	[1,20]	[0.01,0.1]
West Attica	$[5.714\cdot10^{-5},1.067\cdot10^{-3}]$	[0.45, 1]	[0.05, 0.3]	[1,6]	[0.01,0.1]

Table 2: Model's parameters' value ranges

For each prefecture 1,000 parameters' permutations were randomly drawn from the ranges specified in Table 2 using Latin hypercube sampling (Blower and Dowlatabadi 1994). Without loss of generality (Kaplan, Craft et al. 2002), it was assumed that $t_0=0$ at the beginning of the vaccination effort. The experimental design was implemented in object oriented Pascal in Delphi7 platform, using a 1.4 GHz Centrino Pentium IV PC.

The average number of infections was 2,696 cases (standard deviation 10,159 cases), whereas the average completion time was 38 days (standard deviation 11 days). A sensitivity analysis comparing the number of total infections was performed by varying the three model's parameters that might have the most significant impact, namely, the four prefectures' average sufficient contact rate, the four prefectures' average number of initially infected cases and the mobile medical team's average

percentage service rate. The results are presented in Figures 5-7. From Figure 5 it can be derived that the total number of infected cases, even if the mobile medical team's schedule is the optimal, increases if the average sufficient contact rate increases. This is coherent with respective results from the epidemiology research area (Kaplan, Craft et al. 2002).

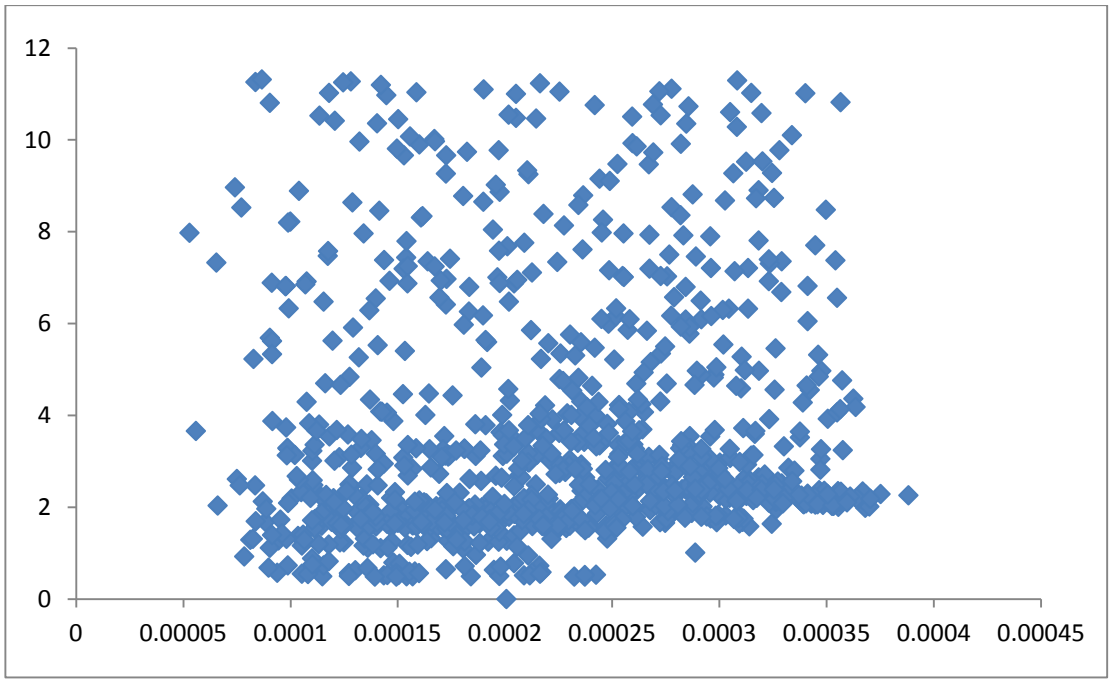


Figure 5: Total infections (vertical axis) vs. average sufficient contact rate (horizontal axis)

From Figure 6 it can be derived that the total number of infected cases does not seem to be affected by an increase of the initially infected cases for their values' range examined. This is due to the fact that persons initially infected were a very small percentage compared to the total targeted subpopulations (less than 0.2%), thus they cannot differentiate the numbers of infected persons significantly. Finally, from Figure 7 it can be derived that, as expected, the total number of infected cases is decreased if the medical team's percentage service rate is increased. It must be noticed that the vertical axes in Figures 5-7 present the natural logarithms of the total numbers of infected cases for illustration purposes.

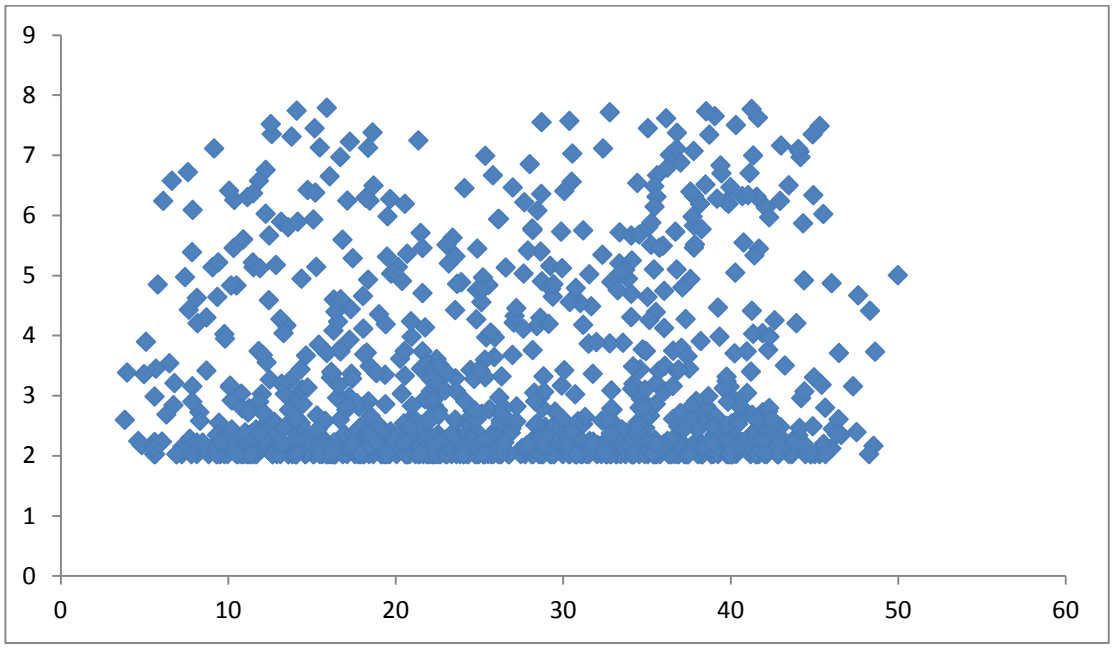


Figure 6: Total infections (vertical axis) vs. average number of initially infected cases (horizontal axis)

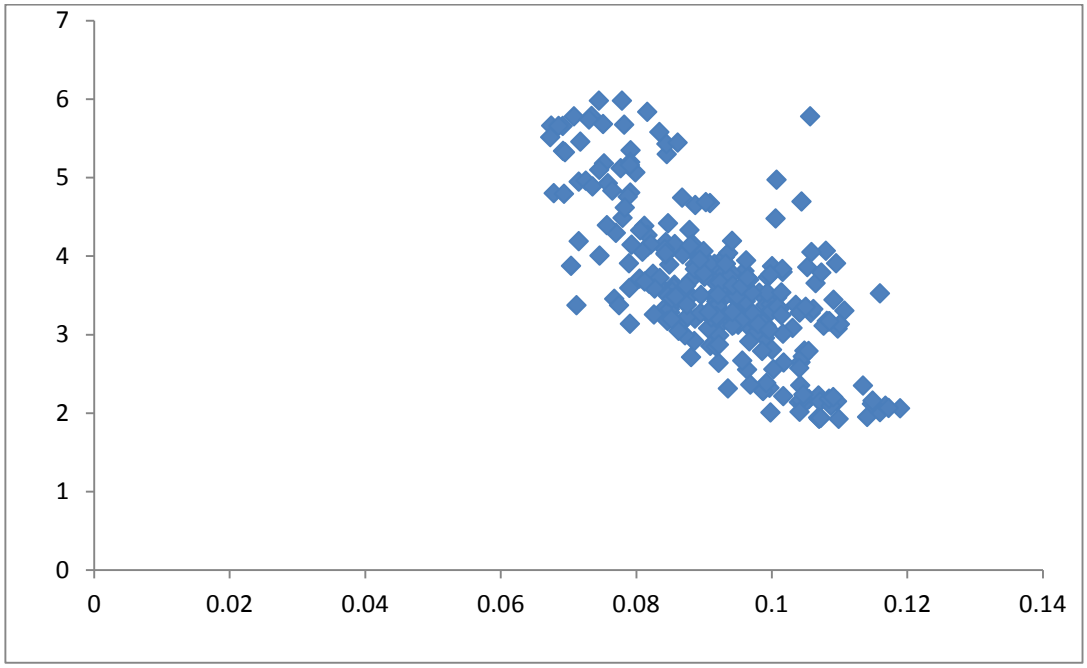


Figure 7: Total infections (vertical axis) vs. average percentage service rate of the mobile medical team (horizontal axis)

In order to compare the proposed model's efficiency to current practice, some statistics regarding the reported case study may be worth mentioning. The vaccination program against A(H1N1)$_v$ influenza virus did not have the expected

mass participation worldwide and more especially in European level. In Greece, according to the Hellenic Center for Infectious Diseases report issued at 21/04/2010, there were 18,228 laboratorial confirmed cases and 149 confirmed deaths. For Attica administrative region there were 8,484 cases and 54 confirmed deaths, yielding an overall fatality rate of approximately 0.64%. Regarding the targeted study's subpopulations, there were approximately 200 confirmed cases and 10 confirmed deaths in Greece, yielding an overall fatality rate of approximately 5%. Vaccination initiated at 16/11/2009. At 21/04/2010, almost at the end of the annual influenza alert period, only 364,559 citizens had been vaccinated countrywide (less than 3% of the total Greek population). A mobile medical team was employed in Attica region from mid-December 2009 to mid-January 2010 aiming at persons that, for some reason, would not be able or choose to visit health centers (e.g. hospitals) appointed for vaccination. The number of citizens vaccinated by the mobile medical team was very low (between ten and twenty) due to several reasons, such as abundance of vaccination places, limited duration of the team's operation (only one month), possible lack by interested persons of relevant information, limited effectiveness of the state's campaign, etc. The vaccination schedule was random, based on telephone appointments requested by the citizens.

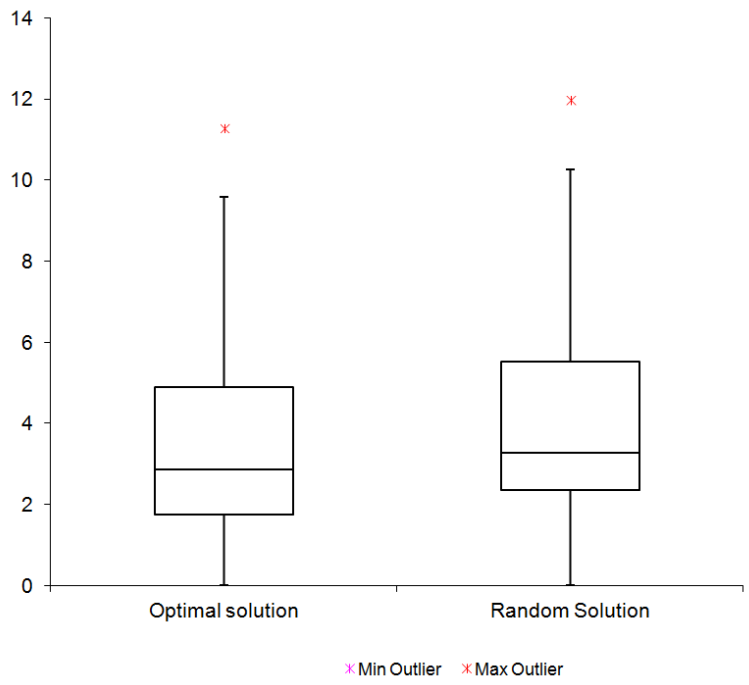
The disadvantages of the applied practice are obvious. Administrators and doctors are faced with the questions of what services to provide and how to provide them (Feldstein 1963). Usually there are not enough resources. The decision to send the mobile medical team to one subpopulation is a decision equivalent to denying this service at the same time to other patients. Selecting a particular method of health care is justified not because it is a "necessary" or "good" use of resources but because it is a better use (better than all others).

Enhancing this statement, a comparative study of the proposed model's performance vs. the applied random practice is presented. The same series of the 1,000 test problems are used and for each test the optimal solution and a random solution generated out of the 4!=24 potential sequences are captured.

The quality of these solutions in terms of the number of infections and completion time is depicted with the descriptive statistics in Table 3 and the Box-Whisker plots in Figures 8 and 9 (for illustration purposes, the vertical axis in Figure 8 presents the natural logarithms of the total numbers of infected cases).

	Infections		Completion time (days)	
	Optimal solution	***Random Solution***	***Optimal solution***	***Random solution***
Mean	2,696	5,347	37.68	55.38
s.d.	10,159	20,300.87	11.35	22.28
Min	0	0	22	31
Q_1	5.71	10.49	28.75	37.52
Median	17.48	26.21	34.61	49.09
Q_3	131.89	247.50	44.57	68.10
Max	78,993	157,986	78.32	121.68

Table 3: Optimal vs. random solution descriptive statistics



Figures 8: Box-Whisker plot for the number of total infections from the optimal and the random solutions

The descriptive statistics show that the proposed model outperforms a random solution both in terms of the number of infections (the optimal solutions' average is almost half of its counterpart yielded by a random practice) and in terms of completion time (with an average of 37.68 vs. 55.38 days). This superiority is also demonstrated in the Box-Whisker plots (the marks represent the maximum values). However, in order to determine if the differences in the solutions quality provided by

the proposed model and the random practice are statistically significant, two-sample non-parametric Kolmogorov-Smirnov tests (since the samples do not follow normal distributions) were performed (at a significance level of 5%) testing the null hypotheses that their infections' and completion times' means are equal. For both tests p-values were less than 0.0002, therefore the proposed model yields statistically significant better solutions than a random schedule.

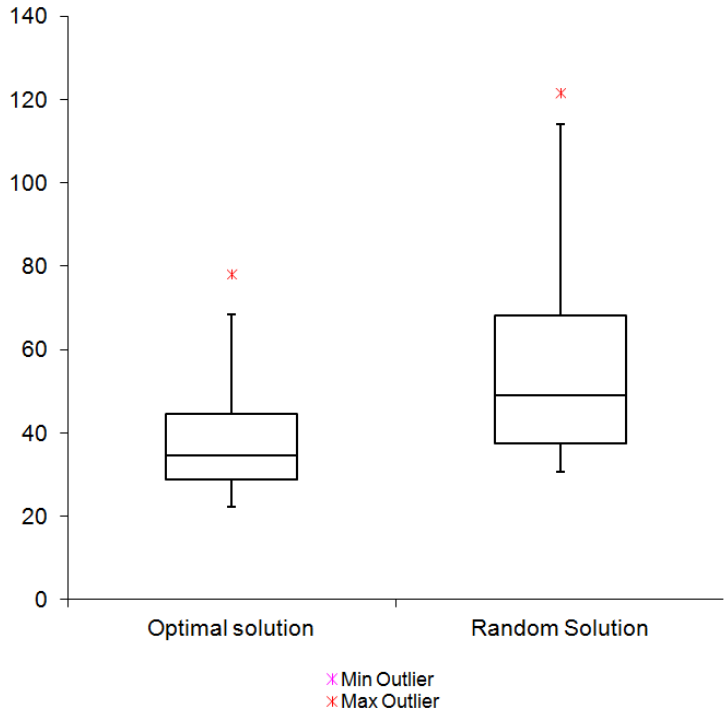


Figure 9: Box-Whisker plot for the completion time yielded from the optimal and the random solutions

Concluding, in making their decisions, doctors and health-care administrators should look for the optimal use of resources. The model presented here, embedded in a more generic decision support system, is a step towards this direction and can be used in future similar disease outbreaks.

2.3.3 The case of multiple processors

In the sequence the extension of the problem described in the previous sub-section is examined. More precisely the scheduling-allocation of limited discrete resources

(mobile medical teams) employed in parallel in a time horizon to implement a vaccination campaign is considered. A real-time synchronous heuristic algorithm is proposed as the solution methodology, which can be coupled with any existing disease transmission model already published in the literature (from compartmental to agent-based model), 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.

2.3.3.1 The mathematical model

Let:

P=$\{P_1,P_2,\ldots,P_n\}$ be the set of n populations in different regions, and let N_i be the size of P_i, i=1,…,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.
$(r_1(t),r_2(t),\ldots,r_n(t))$ be the vector of the number of medical teams assigned for vaccination in every regional population at time t, where $r_i(t)\in\{0,1,\ldots,m_t\}$, i=1,…,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:

$$\min \sum_{t=t_0}^{t_{end}} \sum_{i=1}^{n} I_i(r_i(t)) \tag{13}$$

$$s.t. \quad \sum_{i=1}^{n} r_i(t) = m_t, t = t_0, t_0+1, \ldots, t_{end} \tag{14}$$

$$r_i(t) \in \{0,1,\ldots,m_t\}, t = t_0, t_0+1, \ldots, t_{end} \tag{15}$$

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.

2.3.3.2 Solution approach

The problem tackled here is a dynamic version of the well-known discrete resource allocation problem. The static discrete resource allocation problem with a single resource constraint has been thoroughly studied (Shih 1974; Ibaraki and Katoh 1988). 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 (Shih 1977; Mjelde 1978), dynamic programming techniques (Ibaraki and Katoh 1988; Bretthauer and Shetty 1995) and a greedy incremental algorithm (Shih 1974). Since the problem examined here is dynamic, a heuristic algorithm is developed, using some ideas from the algorithms presented in (Shih 1974) and (Pappis and Rachaniotis 2010). The algorithm is real-time (i.e., dynamic) and synchronous (i.e., can be run online),

meaning that it builds schedules using only the information for regions that have already been infected.

Description of the algorithm

The heuristic for tackling the problem presented here is a variation of the algorithm used in (Pappis and Rachaniotis 2010), who examined the problem of scheduling multiple resources employed as parallel identical or non-identical processors (multi-processor tasks) in order to contain several wildfires. A low-order polynomial time algorithm was proposed, which schedules resources according to their availability and fires' severity.

An informal description of the algorithm 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.

Note that no information about regional populations' infections numbers in the next release time intervals is necessary to schedule the control of IDOs with release times less than R_{k+1}. Hence, the above algorithm is a real-time (dynamic) algorithm and it is synchronous (can be run on-line), meaning that it builds sub-optimal schedules using only existing information. The algorithm's computational complexity is a low order polynomial one, since the greedy algorithm used has a complexity $O(m_t \log n+n)$ (Shih 1974) and the algorithm in (Pappis and Rachaniotis 2010) has a complexity of $O(n^2)$.

2.3.3.3 Numerical experiment

To illustrate the algorithm's application a numerical example is presented. A mathematical transmission model capturing the biological characteristics of

influenza is used. Reactive mass vaccination of susceptible individuals is considered as the main intervention strategy. Data regarding basic demographical characteristics (size of subpopulations) from Greece's 13 administrative health districts (AHDs) is used as input for the model (Figure 10 and Table 4 respectively).

Figure 10: Map of Greece's 13 administrative health districts

Mobile medical teams with a significant service rate are assigned to the 13 AHDs. Their main task is to vaccinate people unable to proceed to local vaccination centres. 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. An estimation of these targeted subpopulations is provided in Table 4[1].

The epidemic transmission model used is proposed by (Samsuzzoha, Singh et al. 2013). It is a vaccinated epidemic model, consisting of a system of nonlinear ordinary

[1] www.statistics.gr/portal/page/portal/ESYE/PAGE-themes?p_param=A1604

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 $N = S + V + E + I + R$. 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 (SVEIR model, Figure 11).

District	Estimated targeted subpopulation Ni
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 4: Estimation of targeted subpopulations (Total: 362,500 people)

The model is represented by the following system of ordinary differential equations:

$$S'(t) = -\beta\beta_{\mathrm{E}}\frac{ES}{N} - \beta\beta_{\mathrm{I}}\frac{IS}{N} - \varphi_t S - \mu S + \delta R + \theta V + rN \quad (16)$$

$$V'(t) = -\beta\beta_{\mathrm{E}}\beta_V\frac{EV}{N} - \beta\beta_{\mathrm{I}}\beta_V\frac{IV}{N} - \mu V - \theta V + \varphi_t S \quad (17)$$

$$E'(t) = \beta\beta_{\mathrm{E}}\frac{ES}{N} + \beta\beta_{\mathrm{I}}\frac{IS}{N} + \beta\beta_{\mathrm{E}}\beta_V\frac{EV}{N} + \beta\beta_{\mathrm{I}}\beta_V\frac{IV}{N} - (\mu + \kappa + \sigma)\mathrm{E} \quad (18)$$

$$\mathrm{I}'(t) = \sigma\mathrm{E} - (\mu + \alpha + \gamma)\mathrm{I} \quad (19)$$

$$R'(t) = \kappa E + \gamma I - \mu R - \delta R \quad (20)$$

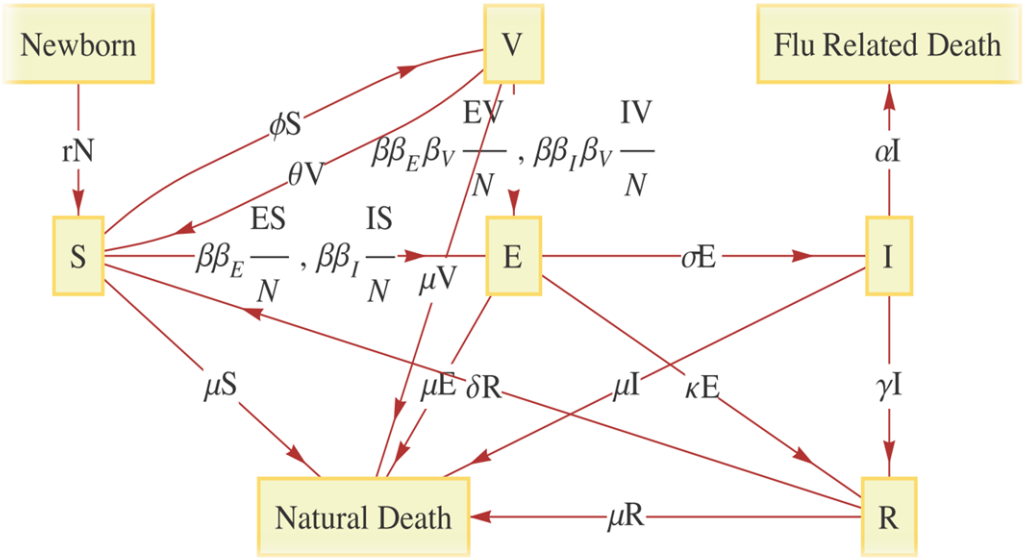


Figure 11: The SVEIR influenza model. Adapted from (Samsuzzoha, Singh et al. 2012)

The effective reproduction number due to vaccination for the previous model is provided by the next formula:

$$R_E = \frac{\beta(r\beta_E + a\beta_E + \gamma\beta_E + \sigma\beta_I)(r + \theta + \beta_V\varphi_t)}{(r + a + \gamma)(r + k + \sigma)(r + \theta + \varphi_t)} \quad (21)$$

The epidemic diffusion model is applied in all n=13 AHDs, under the assumption that all AHDs have the same basic parameters for the influenza transmission (Matrajt, Halloran 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 and 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 5.

Parameter	Description	Value	Source
β	Contact rate	0.514 $days^{-1}$	Estimated (www.keelpno.gr)
β_E	Ability to cause infection by exposed individual	0.25	Estimated (Samsuzzoha, Singh et al. 2012)
β_I	Ability to cause infection by infectious individuals	1	Estimated (Samsuzzoha, Singh et al. 2012)
$1-\beta_V$	Vaccine effectiveness	83.3%	(Wichmann, Stöcker et al. 2010)
σ^{-1}	Mean duration of latency	$(2\ days)^{-1}$	(Samsuzzoha, Singh et al. 2013; Van Der Weijden, Stein et al. 2013)
γ^{-1}	Mean recovery time for clinically ill	$(5\ days)^{-1}$	(Samsuzzoha, Singh et al. 2013)
δ^{-1}	Duration of immunity loss	$(365\ days)^{-1}$	(Samsuzzoha, Singh et al. 2013)
μ	Natural mortality rate	$46x10^{-9}$ persons/day	www.statistics.gr
r	Birth rate	$52x10^{-7}$ persons/day	www.statistics.gr
κ	Recovery rate of latent	1.857×10^{-4} persons/day	(Samsuzzoha, Singh et al. 2013)
α	Flu induced mortality rate	$93x10^{-7}$ persons/day	(Sypsa, Pavlopoulou et al. 2009)
ϑ^{-1}	Duration of vaccine-induced immunity loss	$(365\ days)^{-1}$	(Samsuzzoha, Singh et al. 2013)
CSR	the mobile medical teams' constant service rate	50 persons/team/day	(Kaplan, Craft et al. 2002)
φ_t	Rate of vaccination. It is $\varphi_t=r(t)CSR$, which differs from the common SVEIR model	50 persons/day	This research

Table 5: Model's parameter values

Generally, 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.

A simplifying assumption is that subpopulation mixing between districts is not considered. There are at least three ways 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.

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 the response scenarios examined here involve the implementation of a reactive mass vaccination campaign for different resource allocation policies (Table 6). In particular, the sensitivity of the number of casualties to two factors: amount of resources allocated and delays in implementing the vaccination campaign have been examined.

Intervention strategy	Resource allocation policy	Scenario
No intervention	-	Baseline
Reactive mass vaccination starting at day 7, 14, 21, 28 and 60 from the onset of the outbreak	Allocation of a single resource to all sub-populations	Fixed strategy
	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

Table 6: Intervention strategy, resource allocation policies and relevant scenarios built

The results generated by the numerical implementation of 3 types of resource allocation policies and relevant scenarios built for a vaccination time period of 120 days 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, Ansart et al. 2011).
- The fixed-strategy approach where a single mobile medical team is assigned to each district.
- 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.

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 to a certain subpopulation. 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 (the vaccination campaign could be politicized or become subject of contention, fair allocation of resources, etc).

Five different vaccination initiation days have been considered, i.e. 7, 14, 21, 28 and 60 days after the beginning of transmission (Matrajt, Halloran et al. 2013). The assumptions made are that the number of vaccines necessary for the targeted subpopulations is available at the vaccination 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 Greece during 2009 (www.keelpno.gr).

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_{t0} = 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 Development Core Team 2008) and MS Excel and the results are illustrated in Table 7.

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 comparing 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 8). Obviously, 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. We refer to this allocation scenario as the “maximum resources” 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.

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 in each district by using population drivers as seen in Table 8). The numbers of infected individuals under the three scenarios are presented in Table 9 and the mobile medical teams’ optimal allocation to AHDs according to the heuristic algorithm implementation is depicted in Table 10.

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
Fixed strategy scenario (initiation of vaccination at day d), one medical time	d=7	2725	7875	1738	2545	4507	4507	3974	23828	5040	1647	1828	1647	4507	66368
	d=14	2783	8050	1775	2600	4604	4604	4059	24355	5148	1682	1867	1683	4604	67814
	d=21	2844	8229	1813	2657	4705	4705	4148	24897	5261	1719	1907	1719	4705	69309
	d=28	2907	8411	1854	2716	4809	4809	4239	25446	5377	1758	1950	1758	4809	70843
	d=60	3156	9041	2001	2945	5249	5249	4622	26911	5875	1895	2106	1895	5249	76194

Table 7: Number of infected individuals under the baseline and the fixed strategy (one allocated medical team per AHD) scenarios

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

Table 8: Mobile medical teams' allocation to AHDs based on populations' size characteristics

Data from Table 9 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 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 could be translated into 15-20 less deaths (per 1,000 infective cases averted). Comparative assessments for the different vaccination's initiation day in terms of the cumulative infected cases for the three scenarios under examination are presented in Figures 12-15.

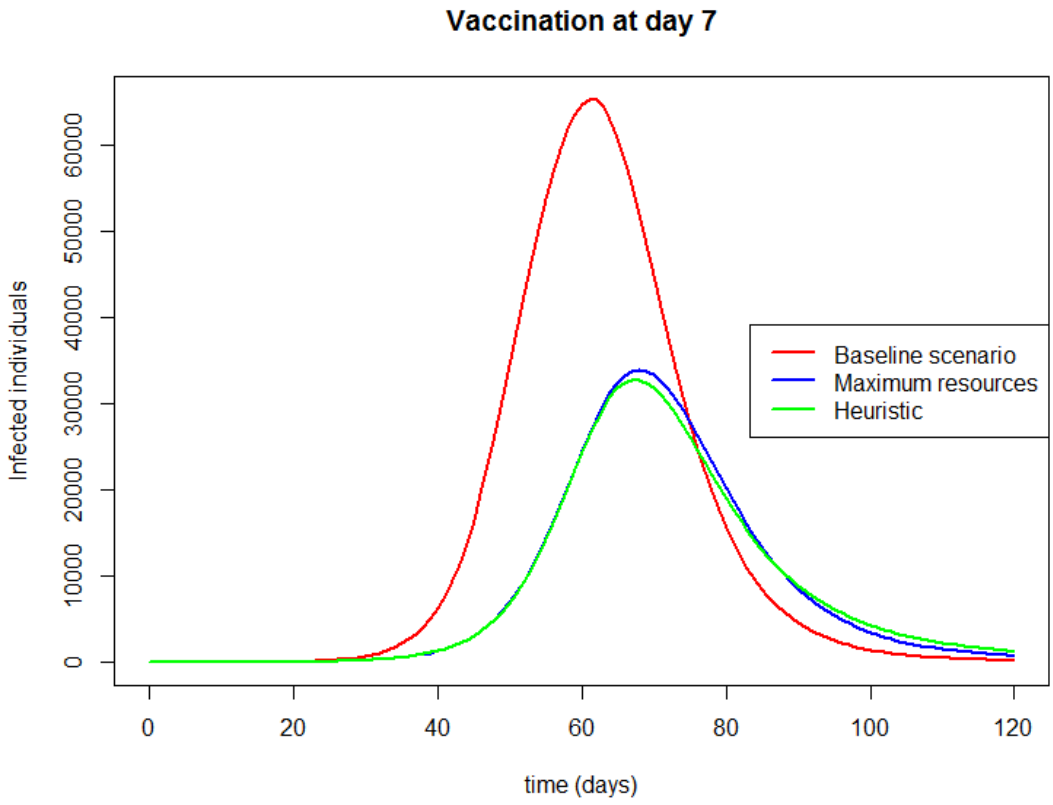


Figure 12: Cumulative infected cases for the three scenarios when vaccination starts at day 7

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
Initiation of vaccination at day d (maximum resources)	d=7	2725	4719	1738	2546	3800	3800	3358	951	3495	1648	1828	1648	3800	36056
	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 9: Numbers of infected persons under the baseline scenario, the maximum resources scenario and the heuristic algorithm solution

AHDs		AHD1	AHD2	AHD3	AHD4	AHD5	AHD6	AHD7	AHD8	AHD9	AHD10	AHD11	AHD12	AHD13	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

Table 10: Mobile medical teams' optimal allocation

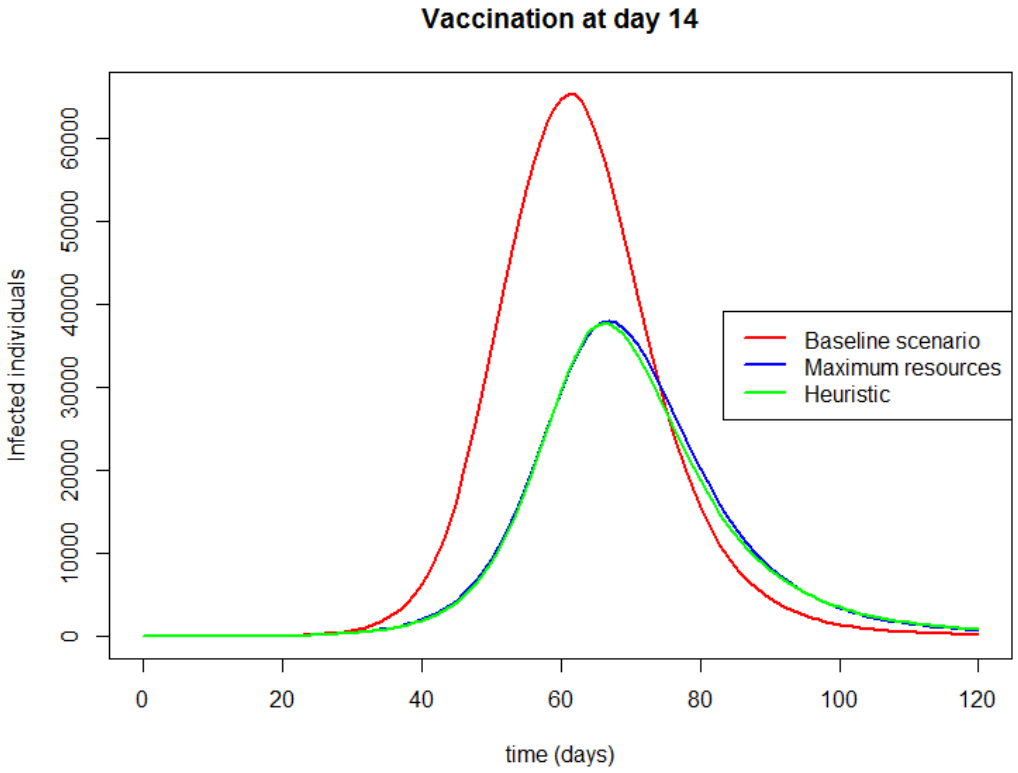


Figure 13: Cumulative infected cases for the three scenarios when vaccination starts at day 14

From Table 10 it is evident that the medical teams' optimal allocation takes place the next day after the vaccination initiates as anticipated if the law of diminishing returns is considered. 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 subpopulations.

The results show that the optimal strategy found 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 obvious since the effects of a delayed immunization campaign don't 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 the results have proven that this does not yield the optimal use of resources. In fact, the modelling approach presented here 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 scheduling mobile medical teams to perform control actions (vaccination) has not been broadly tackled so far.

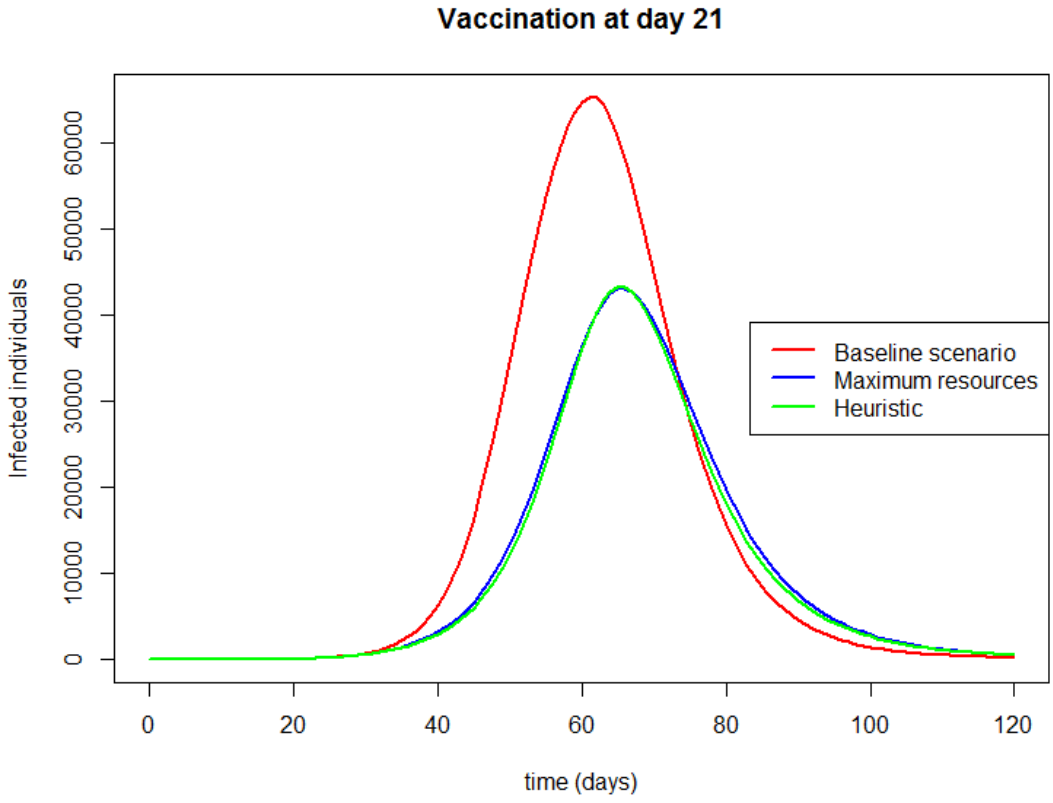


Figure 14: Cumulative infected cases for the three scenarios when vaccination starts at day 21

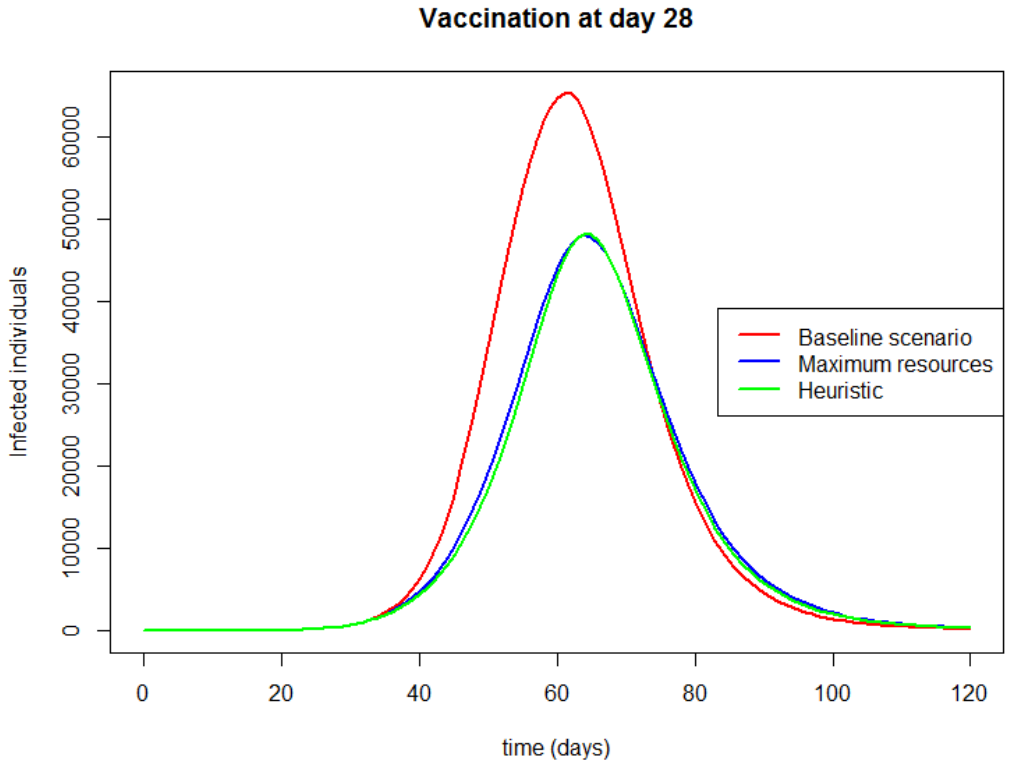


Figure 15: Cumulative infected cases for the three scenarios when vaccination starts at day 28

2.4 Summary

Available resources to tackle an IDO are usually limited, while time and effort required for controlling the outbreak depend on the starting time of the containment effort. Therefore, efficient utilization of a set of limited resources is of paramount importance when controlling IDOs. In this chapter the problem of allocating discrete resources for controlling an influenza outbreak has been considered for two distinct cases. In the first case, the problem of scheduling a single available resource, when there are several areas where the population is infected, is considered. A deterministic model, appropriate for large populations, where random interactions can be averaged out, has been used for the epidemic's rate of spread. The problem has been tackled by using the concept of deteriorating jobs, i.e. the model represents increasing rate of loss as more susceptibles become infected, and variable time and effort needed for the epidemic's containment. The modelling approach presented is theoretical, based on field research from the literature but

also novel. It helps to give an insight and stimulation for future, more realistic approximations of epidemic control management situations. Its application in the case of Attica region in Greece presents a rough picture of what might happen, but it includes some assumptions, uncertainties and un-modelled heterogeneities which require that the results be interpreted with caution. However, it is a quite helpful decision support tool that can assist decision makers in scheduling a mobile medical team in case of a future influenza outbreak. Notice that the case study presented has been treated using an enumerative approach, as the number of affected subpopulations is limited. Nevertheless, in cases of a medium number of infected subpopulations (approximately between 20 and 50), a simple B&B algorithm has been developed for solving this job-scheduling problem, which may be applied in such cases.

The second case considers the problem of allocating several discrete resources (mobile medical teams) for controlling an influenza outbreak. The possible benefits of a reactive mass vaccination campaign of certain groups of the population (incapacitated, house bound, institutionalized etc.) have been assessed. A disease transmission model parameterized for capturing the biological characteristics of influenza has been coupled with a mathematical model for allocating a set of mobile medical teams to certain sub-populations. Several scenarios have been built based on different vaccination initiation days as well as different resource allocation policies. A real-time synchronous heuristic algorithm has been proposed as the solution methodology, which could serve as a helpful decision support tool for assisting decision makers in order to schedule mobile medical teams in case of influenza outbreaks. The proposed methodology was exemplified in the context of an influenza outbreak in Greece and the results are encouraging.

Chapter 3: Responding to bioterrorist attacks: the case of smallpox

3.1 Introduction

Smallpox is considered one of the most feared bioterrorist agents with a case-fatality rate ranging from 15 to 30% (Henderson, Inglesby et al. 1999; Gani and Leach 2001). Although the disease has been eradicated since 1978, defense officials have expressed their concerns that the virus could be used as a possible biological weapon (Hull, Danila et al. 2003). These concerns give rise to a wider range of issues related to smallpox control. For example, due to the eradication of the disease, routine vaccination has gradually diminished, rendering a substantial portion of global population susceptible to the virus (Gani and Leach 2001; Halloran, Longini Jr et al. 2002). Modern and historical populations present several differences in terms of herd immunity and, therefore, extrapolating past data to current populations regarding disease transmission would be a difficult task if control measures were to be implemented (Ferguson, Keeling et al. 2003; Kerrod, Geddes et al. 2005). In addition, vaccination strategies against smallpox are not straightforward since vaccination of the population is accompanied by serious side-effects (Hall, Egan et al. 2007). It is estimated that 250 out of every 1 million people vaccinated are likely to experience an adverse reaction whereas 60 out of approximately 100 million people vaccinated will probably have fatal reactions (Sato 2011). Several research and development projects for developing safer and rapidly manufactured vaccines are under way (Artenstein 2008). However, rigorous testing of new vaccines is still needed with respect to their potential to induce immunity compared to conventional smallpox vaccines (Kennedy, Ovsyannikova et al. 2009). Last but not least, public health authorities are completely unaware of the breadth and depth of a possible bioterrorist attack and the subsequent health-care response capacities required to deal with such an event. A senior-level exercise simulating a covert smallpox attack in the United States revealed numeral challenges public officials and policy-makers would be faced with during the containment effort of such an attack. According to the results of the exercise, state officials and decision-makers were unfamiliar with the character and nature of the attack, the available policy options, and their consequences. Management options were further limited due to limited amount of crucial medical suipplies like vaccines and drugs (O'Toole, Mair et al. 2002).

Responding to bioterrorist attacks: the case of smallpox

A public-health system could respond to a bioterrorist smallpox attack by adopting a set of non-pharmaceutical and pharmaceutical interventions like isolation and quarantine of exposed and vaccination of susceptible individuals. The most prevalent and recommended strategy for controlling a smallpox outbreak is targeted or ring vaccination (Porco, Holbrook et al. 2004; House, Hall et al. 2009). In this case, public health authorities will immediately isolate infectious individuals and will trace and vaccinate their close contacts. In addition, public health authorities should also trace and vaccinate the contacts of the close contacts of infected individuals, if logistically possible (Kaplan, Craft et al. 2003). Pre-emptive vaccination of a larger part of the population (targeted mass vaccination) might also take place as a supplementary intervention (Hall, Egan et al. 2007; Egan, Hall et al. 2011). Finally, in the presence of a larger number of index cases or higher values of the basic reproduction number R_0 regional or even national mass vaccination may be a preferable response for controlling a smallpox outbreak (Kaplan, Craft et al. 2002; Ohkusa, Taniguchi et al. 2005).

Despite the fact that ring vaccination is highly recommended for controlling a smallpox outbreak, in realistic circumstances implementing such a campaign might not yield the expected results. In fact, the relative effectiveness of ring vaccination is highly sensitive to several parameters like the size of the initial attack, time to intervention, proportion of contacts traced, response capacities, levels of prior herd immunity in the population affected etc. As a consequence, an inconclusive debate in the academic literature exists with respect to the optimality of control interventions and especially the generic context in which ring vaccination outperforms mass vaccination and vice versa. According to simulation results, isolation along with targeted vaccination seems an adequate control practice as long as the number of index cases remains low (Hall, Egan et al. 2007). In addition, targeted or ring vaccination can control a smallpox outbreak as long as intervention measures are very effective (Kretzschmar, Van Den Hof et al. 2004; Legrand, Viboud et al. 2004; Porco, Holbrook et al. 2004; Longini Jr, Elizabeth Halloran et al. 2007). On the contrary, a large-scale smallpox outbreak with a larger number of index cases would necessitate the adoption of a more aggressive response like a mass vaccination campaign (Kaplan, Craft et al. 2002). Delayed outbreak detection, ineffectiveness of ring vaccination and lack of prior herd immunity in the population affected present complementary drivers (in conjunction with large number of index cases), favoring also a wider vaccination campaign (Halloran, Longini Jr et al. 2002; Ohkusa, Taniguchi et al. 2005; Riley and Ferguson 2006; Egan, Hall et al. 2011). Finally, in the event of a covert bioterrorist attack crisis, managers and health officials will also be faced with political or public imperatives (mass panic) and broader responding actions like a mass vaccination campaign might be adopted for calming public fears.

Implementing a mass vaccination campaign, however, poses significant logistical challenges, especially when strict time lines apply (vaccination of the whole population of a district or region within certain time-frames). Many countries have drafted emergency response plans and operational frameworks for immediately implementing mass vaccination strategies within 24 hours of the confirmation of a smallpox outbreak (Hupert, Cuomo et al. 2004; Department of Health 2005). From a logistical point of view, the implementation of a broader vaccination campaign should rely on the establishment of an emergency supply chain and a series of decisions should be made regarding the location, number and capacity of both the stockpile centers and final Points of Dispensing (PODs), the inventory level of medical supplies and commodities held within these facilities as well as the replenishment policies adopted, the assignment of these facilities to serve certain sub-populations and, finally, the selection of modes of distribution and relevant capacities.

This chapter discusses the logistical implications for actually implementing a large-scale vaccination campaign for controlling a deliberate smallpox outbreak in a large urban area. In particular, the dynamics of the spread of a smallpox outbreak and its interactions with resource allocation decisions are considered. A modelling approach is presented consisting of two modules. The first module relates to disease's progression whereas the second one relates to optimally distributing a set of supplies (medical and ancillary) to affected sub-populations. For predicting the course of the outbreak a deterministic mathematical model parameterized to capture several biological properties of smallpox is developed which makes use of the above modules while simultaneously evaluates the effects of a reactive regional mass vaccination campaign. A linear programming model is developed for formulating the emergency supply chain problem where multiple commodities are distributed using a set of multi-modes within a number of time periods. Several logistical aspects are taken into consideration like predetermined levels of health care capacities (in terms of facilities available to care for those infected and relevant health-care personnel), limited number of vehicles for transportation/distribution activities, limited vaccine supply etc.

The assessment of the approach presented is based upon scenarios and variations to several key parameters like the magnitude of the attack rate and possible delays for actually implementing the control actions, limited response capacities (number of facilities available to care for those infected and relevant health-care personnel, number of vehicles for transportation/distribution activities and limited vaccine supply). Simulations are performed for assessing the different scenarios in terms of the total number of people infected and perished. For certain scenarios it is assumed

that the vaccination process is limited to the number of available health-care workers as well as vaccines' availability and several vaccination capacity thresholds are derived from (Centers for disease control and prevention 2002).

For illustrating the applicability of the proposed methodology a numerical experiment is provided. Several benefits and pitfalls for implementing the mass vaccination campaign are further discussed. It is worth noting that the modelling approach presented here could be coupled with any other epidemiological model (first module), thus allowing replication with any change in assumptions, parameter values' range and scenarios.

3.2 Related literature

A considerable amount of literature exists with respect to smallpox control. The main body of this literature could be classified into two main streams of studies, as seen in Figure 16. The first stream consists of disease transmission modelling approaches utilized for assessing the possible effects of control interventions (Ferguson, Keeling et al. 2003). These interventions could be pharmaceutical (use of vaccines), non-pharmaceutical (closure of schools, voluntary quarantines over a wide area, social distancing and travel limitations) or any combination thereof. In order to capture the transmission dynamics of smallpox simple compartmental models based on differential equations to meta-population models and, finally, detailed stochastic agent-based models have been developed. Comparisons between ring and mass vaccination campaigns form the main objective in several studies (Halloran, Longini Jr et al. 2002; Kaplan, Craft et al. 2002; Kaplan, Craft et al. 2003; Eidelson and Lustick 2004; Eubank, Guclu et al. 2004; Porco, Holbrook et al. 2004; Ohkusa, Taniguchi et al. 2005; Hall, Egan et al. 2007; House, Hall et al. 2009; Egan, Hall et al. 2011). Other studies consider quarantine options (Barbera, Macintyre et al. 2001), combination of pharmaceutical and non-pharmaceutical interventions like, for instance, vaccination and closure of schools or voluntary quarantines (Meltzer, Damon et al. 2001; Bozzette, Boer et al. 2003; Eichner 2003; Kretzschmar, Van Den Hof et al. 2004; Legrand, Viboud et al. 2004; Aldis and Roberts 2005; Kress 2005; Burke, Epstein et al. 2006; Riley and Ferguson 2006; Longini Jr, Elizabeth Halloran et al. 2007; Glasser, Foster et al. 2008; Zenihana and Ishikawa 2010; Sato and Sakurai 2012; Finin, Kosaraju et al. 2013; Mizumoto, Ejima et al. 2013), and, finally, the possible benefits of prior levels of herd immunity combined with control measures (Nishiura and Tang 2004). In order to assess the possible benefits of control measures, several scenarios are built based on reasonable ranges of parameters like the number of initial cases infected, levels of residual herd immunity, delays for implementing containment strategies, relevant efficiency of control measures etc. It is worth noting that the

articles of this stream incorporate novel features of biological interest and most of them have been published in epidemiologic/medical scientific journals.

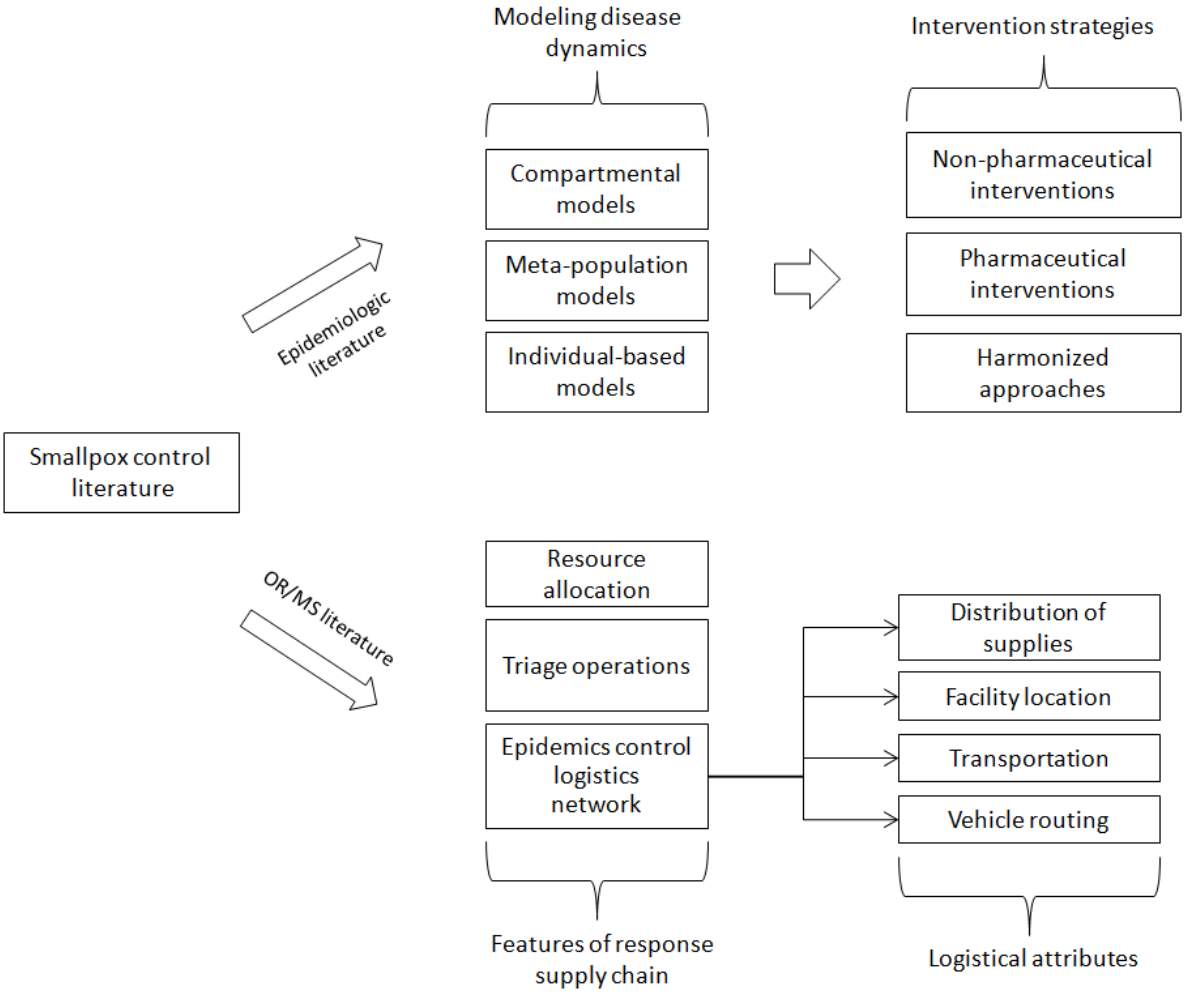


Figure 16: Classification of smallpox control literature

The second stream consists of modelling approaches in which logistical prerequisites of control actions are taken into consideration (Dasaklis, Pappis et al. 2012). In particular, disease transmission models (mostly based on compartmental modelling) are coupled with Operations Research/Management Science (OR/MS) modelling approaches and the overall emergency supply chain is assessed in terms of transportation and distribution capacities (Wang, Wang et al. 2009; Liu and Zhao 2011; Liu, Zhao et al. 2011). Other approaches consider aspects of facility location (Berman and Gavious 2007; Jia, Ordóñez et al. 2007; Jia, Ordóñez et al. 2007), triage management and patient flow logistics (Aaby, Herrmann et al. 2006; Pietz, Benecke et al. 2009), as well as resource allocation (Ren, Órdoñez et al. 2013). Most of the articles of this stream are published in OR/MS scientific journals. In Figure 16 a breakdown of the available smallpox control literature (both streams) is presented.

Other approaches that fall outside the classification scheme presented in Figure 16 but deserve mentioning deal with the estimation of baseline parameters like R_0 (based on historical data) as well as the effectiveness of public health interventions for controlling a smallpox outbreak (Gani and Leach 2001; Eichner and Dietz 2003; Kerrod, Geddes et al. 2005; Nishiura, Brockmann et al. 2008). In addition, operational framework plans for containing a smallpox outbreak have also been presented (Kim-Farley, Celentano et al. 2003; Strikas, Neff et al. 2008). Finally, (Hull, Danila et al. 2003) provide a review of the clinical presentation and epidemiology of smallpox and describe a qualitative public health response for its containment.

Although the aforementioned studies provide valuable insights into several aspects of smallpox control, there are several oversimplifying assumptions that could lead to ambiguous conclusions. A key problem with much of the literature of the first stream relates to the underlying assumptions that favor ring vaccination as an optimal control policy. For instance, the majority of the modelling approaches favors isolation of infected individuals and ring vaccination as an optimal control strategy provided that public health systems will not be compromised (Meltzer, Damon et al. 2001; Hall, Egan et al. 2007; Longini Jr, Elizabeth Halloran et al. 2007; House, Hall et al. 2009; Egan, Hall et al. 2011). Despite the fact that some of these studies incorporate resource constraints (limited vaccination rates or limited capacities for performing ring vaccination), broad logistical considerations are not explicitly modeled (Kaplan, Craft et al. 2003; Eubank, Guclu et al. 2004; Porco, Holbrook et al. 2004; Riley and Ferguson 2006; Egan, Hall et al. 2011). Generally, the scalability of a possible bioterrorist attack, the inherent uncertainties for accurately estimating the value of several key parameters and the accompanied great-scale logistical implications behind control efforts have been paid little attention so far. According to recent studies, public health capabilities for managing highly infectious diseases could be easily compromised in case of large-scale events (Ippolito, Puro et al. 2006; Fusco, Schilling et al. 2012). In addition, emergency exercises and drills revealed serious shortcomings in the ability of health-care personnel to rapidly detect and effectively proceed to standard response protocols in the case of highly infectious diseases like smallpox (Klein, Atas et al. 2004). Therefore, in real life the optimality of ring vaccination might be called into question and a shift to more aggressive responses like a targeted mass vaccination campaign would deem necessary.

The studies of the second stream have also some limitations. Their major defect is that they incorporate tedious epidemiological characteristics and assumptions with respect to smallpox. For example, the disease transmission models coupled with OR/MS modelling approaches fail to capture the biological characteristics of smallpox. In most of the cases they are simple SIR (Susceptible, Infected and Removed) models that do not take into account the different stages of infection

presented in smallpox. In addition, their assumptions regarding the control strategies implemented (for instance, vaccination of susceptible individuals) are not suitable in the case of smallpox. In particular, any vaccination campaign against smallpox should take place within 10 days because the incubation period of smallpox is usually 12–14 days (Strikas, Neff et al. 2008). Other weak aspects, besides the poor description of epidemiological characteristics, of these studies are the lack of adherence to smallpox control guidelines published by national or international organizations worldwide, the absence of robust control scenarios and their assessment, and, finally, their limited applicability.

3.3 Problem description

Although ring vaccination is highly recommended for controlling a smallpox outbreak, it is questionable whether such an intervention would yield optimal results in the case of a large-scale bioterrorist attack. For managing such a public health incident it is believed that more aggressive countermeasures would have to take place such as a targeted regional mass vaccination campaign. The implementation of a mass vaccination campaign should rely on the establishment of an emergency supply chain. Crucial medical supplies like vaccines as well as other emergency supplies (personal protective equipment, food, water, blankets) held in central storage sites must be distributed to regional stockpile centers and then to local PODs. Once the medical supplies have been positioned, susceptible individuals will be administered the vaccines. In addition, several facilities like hospitals and primary health-care premises might need to be converted into vaccination centers.

With respect to facilities, the configuration of the network used in this chapter has much in common with FEMA's (Federal Emergency Management Agency U.S. Department of Homeland Security) complex logistics structure (Afshar and Haghani 2012). In addition, published guidelines from several health care organizations addressing bioterrorist attacks have also been used for the development of the proposed emergency logistics network (Hupert, Cuomo et al. 2004). In particular, all supplies are initially held in a central stockpiling centre (permanent facility). Regional Stockpiling Centres (RSCs) also exist where supplies from the central stockpiling centre are received. Some of the RSCs may be permanent (hospitals) while others may be temporary. Local PODs also exist, where patients will be eventually administered treatment. Each POD is considered to be a temporary facility and has one vaccination centre (VC) within it. Each VC consists of several vaccination stations (VS). In Figure 17 the described epidemics control logistics network is illustrated.

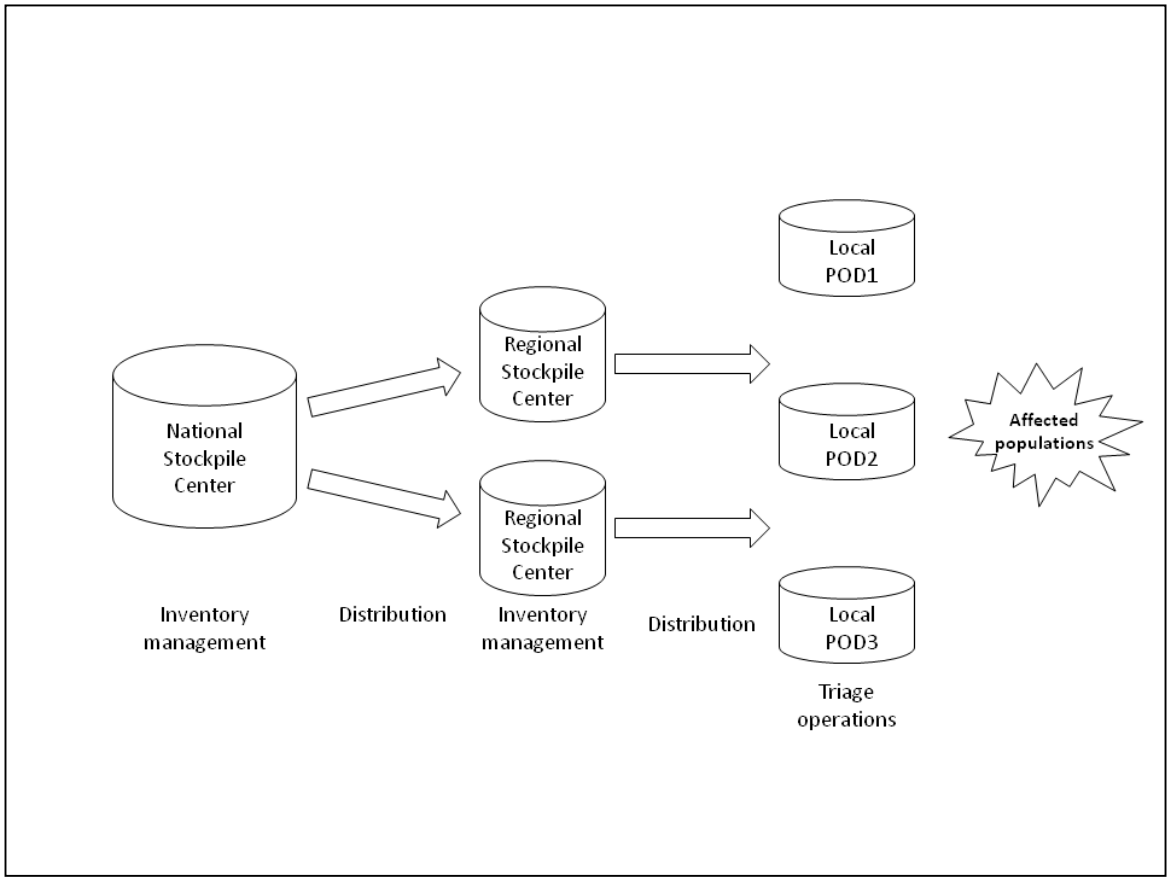


Figure 17: Smallpox control logistics network configuration

Two types of supplies should be transported from a central warehouse to RSCs and then to local PODs. The first type consists of crucial medical supplies like vaccines, which should be administered to those susceptible to the disease. For these supplies certain transportation protocols should be followed (fully monitored conditions) and, therefore, separate vehicles should be used. The second category consists of vaccine administration supplies (smallpox vaccine coolers/refrigerators, vaccine diluents, sterilized bifurcated needles etc), general supplies and equipment (tables, chairs, water and cups, paper, telephones, Fax machines etc) and other emergency supplies (blankets, food meals etc). Contrary to essential medical supplies, these supplies could be bundled together. Different types of vehicles (in terms of capacity) and different modes of transportation should be used (according to the type of commodity transported/distributed). The objective is the minimization of the total amount of unsatisfied demand over all types of commodities, final demand points (Points of Dispensing), for all periods.

3.4 Problem formulation

The modelling approach consists of two parts. The first part is the compartmental modelling approach related to the disease's progression. The second part relates to the epidemics control logistics network configuration model.

Notation

Let
T: be the planning horizon. Its magnitude can vary depending on the outbreak
t: time period, t-1,…,T. Although any time period can be used, a suitable unit of measurement during epidemic control operations is a day
C_M: be the set of different essential medical commodities (vaccines)
C_S: be the set of different ancillary supplies (bifurcated needles, food, blankets etc)
C: be the set of commodities in total. It is $C=C_M \cup C_S$
NSC: be the set of National Stockpiling Centres
RSC: be the set of Regional Stockpiling Centres
POD: be the set of local Points of Dispensing
N=NSC+RSC+POD: be the union of nodes in the network

Parameters

Let
$S_{ic}(t)$: be the supply of commodity type c in time period t at the National Stockpiling Centre i, $i \in NSC$, $c \in C$, t=1,…,T
M(t): be the set of kinds of transportation means $\{M_1(t),\ldots, M_K(t)\}$ in time period t, i.e. there are K different kinds (subsets) of non-identical transportation means with $|M_k(t)|$ identical means of each kind, k=1,…,K
V_{kc}: be the capacity of transportation mean k for commodity type c, k=1,…,K, $c \in C$. If transportation mean of kind k cannot be used for a commodity type c (e.g. vaccines must be carried in vehicles with specific equipment), then $V_{kc}=0$
v_c: be the volume of commodity type c, $c \in C$
G(N,E): be a graph, where E is the set of edges (i,j,k), $i,j \in N$, k=1,…,K
$d_{ic}(t)$: the demand for commodity type c in time period t at dispensing point i, $i \in POD$, $c \in C$, t=1,…,T
$U_{ik}(t)$: Unloading capacity for the facility in node i for transportation mean of kind k in time period t, $i \in N$, k=1,…,K, t=1,…,T
$SC_i(t)$: Storage capacity for the facility in node i in time period t, $i \in N$, t=1,…,T
$LC_{ik}(t)$: Loading capacity for the facility in node i for transportation mean k in time period t, $i \in N$, k=1,…,K, t=1,…,T

Decision variables

$x_{ijck}(t)$: amount of commodity type c transported from node i to node j by the k-th kind of transportation in period time t, $i,j \in N$, $i \neq j$, $c \in C$, $k=1,\ldots,K$, $t=1,\ldots,T$.
$u_{ic}(t)$: unsatisfied demand of commodity type c at node i in period time t, $i \in POD$, $c \in C$, $t=1,\ldots,T$
$I_{ic}(t)$: Inventory of commodity type c at node i in period time t, $i \in N$, $c \in C$, $t=1,\ldots,T$

3.4.1 Modelling the progression of smallpox

For modelling the progression of the disease a modified approach of the model presented in (Kaplan, Craft et al. 2003) has been used (Figure 18). In particular, the main modifications made are as follows:

- The compartment of susceptible individuals is divided into two sub-compartments (see equations 22 and 23)
- The effects of the targeted vaccination campaign are explicitly modelled (see equations 31 and 32)

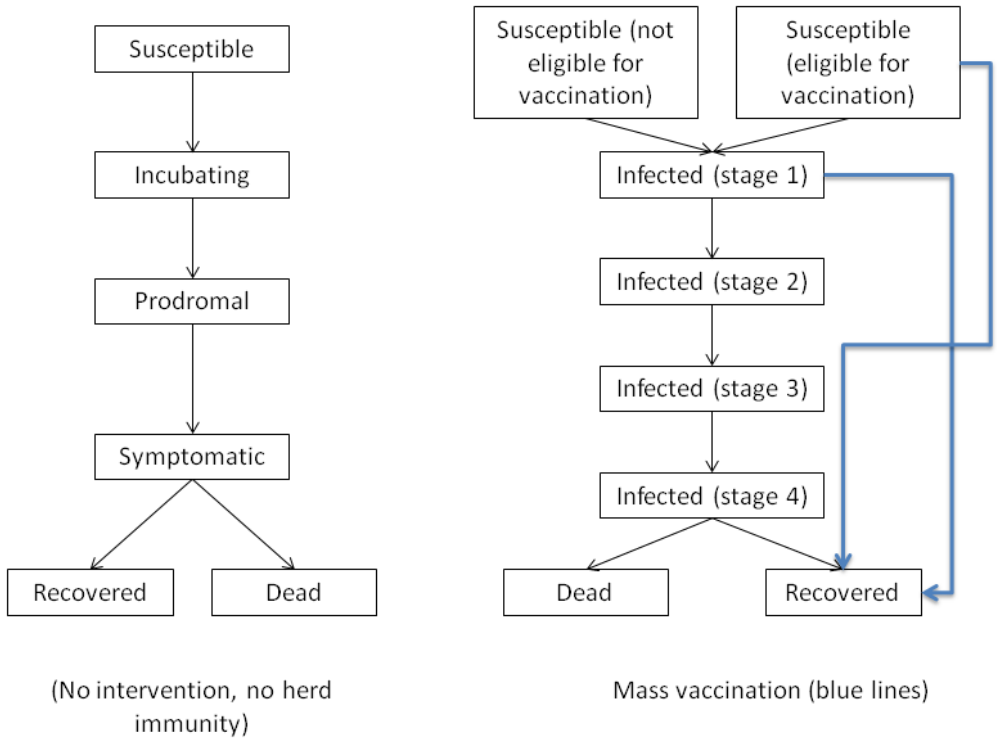


Figure 18: Biological depiction of Smallpox

The total population of size N is divided into three compartments: susceptibles, infected and removed. For capturing the biological properties of smallpox, the compartment of infected individuals consists of four sub-compartments, each of one characterising different stages of infection: (1) infected but asymptomatic, non-infectious, and vaccine-sensitive; (2) infected but asymptomatic, non-infectious, and vaccine-insensitive; (3) infected but asymptomatic, and infectious; and (4) symptomatic and isolated. The compartment of susceptible individuals consists of two sub-compartments: (1) those who can't be vaccinated (S_1) because they are immune-compromised individuals or at high risk for complications (pregnant women) and (2) those eligible for a fresh vaccine (S_2).

Since all symptomatic infectious individuals of stage 4 are isolated, the disease can be transmitted to susceptibles only from infectious individuals at stage 3. Therefore, mass-action law sets the rate of new infections equal to $\beta S_1(t) I_3(t)$ and $\beta S_2(t) I_3(t)$ at time t where β is the disease transmission parameter (Kaplan, Craft et al. 2003). In the absence of any other intervention but case isolation, the aforementioned state can be described by the following set of ordinary differential equations (ODEs):

$$\frac{dS_1(t)}{dt} = -\beta S_1(t) I_3(t) \quad (22)$$

$$\frac{dS_2(t)}{dt} = -\beta S_2(t) I_3(t) \quad (23)$$

$$\frac{dI_1(t)}{dt} = \beta S_1(t) I_3(t) + \beta S_2(t) I_3(t) - r_1 I_1(t) \quad (24)$$

$$\frac{dI_2(t)}{dt} = r_1 I_1(t) - r_2 I_2(t) \quad (25)$$

$$\frac{dI_3(t)}{dt} = r_2 I_2(t) - r_3 I_3(t) \quad (26)$$

$$\frac{dI_4(t)}{dt} = r_3 I_3(t) - r_4 I_4(t) \quad (27)$$

$$\frac{dR(t)}{dt} = r_4 I_4(t) \quad (28)$$

As mentioned in (Kaplan, Craft et al. 2003), this SEIR-like system is governed by the basic reproductive ratio R_0, where $R_0 = \beta \left[\frac{S_1(0) + S_2(0)}{r_3} \right]$ (29)

$S_1(0)$ and $S_2(0)$ represent the number of initial susceptible individuals (t=0). In the case where regional mass vaccination applies the aforementioned system of ODEs can be written as follows:

$$\frac{dS_1(t)}{dt} = -\beta\, S_1(t) I_3(t) \tag{30}$$

$$\frac{dS_2(t)}{dt} = -\beta\, S_2(t) I_3(t) - v_s \alpha(t) \sum_{i=1}^{n} I_{ic}(t) S_2(t) \tag{31}$$

$$\frac{dI_1(t)}{dt} = \beta\, S_1(t) I_3(t) + \beta\, S_2(t) I_3(t) - r_1 I_1(t) - v_1 \gamma(t) \sum_{i=1}^{n} I_{ic}(t) \mathrm{I}_1(t) \tag{32}$$

$$\frac{dI_2(t)}{dt} = r_1 I_1(t) - r_2 I_2(t) \tag{33}$$

$$\frac{dI_3(t)}{dt} = r_2 I_2(t) - r_3 I_3(t) \tag{34}$$

$$\frac{dI_4(t)}{dt} = r_3 I_3(t) - r_4 I_4(t) \tag{35}$$

$$\frac{dR(t)}{dt} = r_4 I_4(t) + v_s \alpha(t) \sum_{i=1}^{n} I_{ic}(t) S_2(t) + v_1 \gamma(t) \sum_{i=1}^{n} I_{ic}(t) \mathrm{I}_1(t) \tag{36}$$

The quantity $\sum_{i=1}^{n} I_{ic}(t)$ expresses the amount of medical supplies available at all PODs for each time period that affect the course of the outbreak (vaccines). As all asymptomatic individuals may present themselves to the vaccination queue, the available vaccines $\sum_{i=1}^{n} I_{ic}(t)$ might be allocated to those susceptible to the disease and eligible for vaccination (S_2) and to those infected in stages 1, 2 and 3 respectively. However, vaccinators are unaware of the susceptible/infectious status of all the asymptomatic individuals. It is assumed that these sub-groups (S_2 and those infected in stages 1, 2 and 3) are proportional to the numbers of population compartment in the model in any time period. Thus, the coefficients α and γ are used for normalizing the respected value of vaccines' administration to each asymptomatic sub-group, based on their size, for those compartments in which the vaccine has an effect (that affects the course of the outbreak). The values of coefficients α and γ are, respectively:

$$\alpha(t) = \frac{S_2(t)}{S_2(t) + I_1(t) + I_2(t) + I_3(t)} \tag{37}$$

$$\gamma(t) = \frac{I_1(t)}{S_2(t) + I_1(t) + I_2(t) + I_3(t)} \quad (38)$$

Since vaccines are administered to all asymptomatic individuals, for a given period t the actual demand for vaccines in all PODs will be:

$$\sum_{i=1}^{n} d_{ic}(t) = \mathrm{S}_2(\mathrm{t}) + \mathrm{I}_1(t) + \mathrm{I}_2(t) + \mathrm{I}_3(t) \quad (39)$$

As the vaccine provides protection to those susceptible to the disease and to those at stage 1 of infection there will be a quantity $V_w(t)$ of vaccine wasted per period:

$$V_w(t) = \left[\frac{I_2(t) + I_3(t)}{S_2(t) + I_1(t) + I_2(t) + I_3(t)} \right] \sum_{i=1}^{n} I_{ic}(t) \quad (40)$$

3.4.2 Logistics network configuration model

Assumptions

The following assumptions hold**:**

- NSC, RSC and POD are disjoint sets, e.g. a RSC cannot serve as local POD, etc.
- The time to transfer commodities from a transportation mean to another is considered negligible.
- Travelling time between the two most distanced nodes of the network do not exceed the period of one day (24 hours).

Objective function

The objective of the logistics network configuration model is the minimization of the total amount of unsatisfied demand over all types of commodities, PODs, and time periods:

$$\min \sum_{\mathrm{i}\in\mathrm{POD}} \sum_{\mathrm{c}\in\mathrm{C}} \sum_{\mathrm{t}=1}^{\mathrm{T}} \mathrm{u}_{\mathrm{ic}}(\mathrm{t}) \quad (41)$$

Constraints

$$\mathrm{I}_{\mathrm{ic}}(\mathrm{t}) = \mathrm{I}_{\mathrm{ic}}(\mathrm{t}\text{-}1) + \mathrm{S}_{\mathrm{ic}}(\mathrm{t}) - \sum_{\mathrm{j}\in\mathrm{RSC}} \sum_{\mathrm{k}=1}^{\mathrm{K}} \mathrm{x}_{\mathrm{ijck}}(\mathrm{t}) \text{ , } \mathrm{i}\in\mathrm{NSC}, \mathrm{c}\in\mathrm{C}, \mathrm{t}=1,\ldots,\mathrm{T} \quad (42)$$

$$\mathrm{I}_{\mathrm{ic}}(\mathrm{t}) = \mathrm{I}_{\mathrm{ic}}(\mathrm{t}\text{-}1) + \sum_{\substack{\mathrm{j}\in\mathrm{NSC} \\ \mathrm{j}\neq\mathrm{i}}} \sum_{\mathrm{k}=1}^{\mathrm{K}} \mathrm{x}_{\mathrm{jick}}(\mathrm{t}) - \sum_{\substack{\mathrm{j}\in\mathrm{POD} \\ \mathrm{j}\neq\mathrm{i}}} \sum_{\mathrm{k}=1}^{\mathrm{K}} \mathrm{x}_{\mathrm{ijck}}(\mathrm{t}) \text{ , } \mathrm{i}\in\mathrm{RSC}, \mathrm{c}\in\mathrm{C}, \mathrm{t}=1,\ldots,\mathrm{T} \quad (43)$$

$$I_{ic}(t)-u_{ic}(t)=I_{ic}(t-1) - u_{ic}(t-1) - d_{ic}(t) + \sum_{\substack{j\in RSC \\ j\neq i}} \sum_{k=1}^{K} x_{jick}(t)\,,\ i\in POD,\ c\in C,\ t=1,\ldots,T \quad (44)$$

$$\sum_{c\in C} I_{ic}(t) \le SC_i(t)\,,\ i\in N,\ t=1,\ldots,T \quad (45)$$

$$\sum_{\substack{i,j\in N \\ i\neq j}} v_c x_{ijck}(t) \le V_{kc} \left|M_k(t)\right|\,,\ k=1,\ldots,K,\ c\in C,\ t=1,\ldots,T \quad (46)$$

$$\sum_{\substack{j\in RSC+POD \\ j\neq i}} \sum_{c\in C} x_{ijck}(t) \le LC_{ik}(t)\,,\ i\in N,\ k=1,\ldots,K,\ t=1,\ldots,T \quad (47)$$

$$\sum_{\substack{j\in N \\ j\neq i}} \sum_{c\in C} x_{jick}(t) \le UC_{ik}(t)\,,\ i\in RSC+POD,\ k=1,\ldots,K,\ t=1,\ldots,T \quad (48)$$

$$x_{ijck}(t),\ u_{ic}(t),\ I_{ic}(t)\ge 0,\ \ i,\ j\in N,\ c\in C,\ k=1,\ldots,K,\ t=1,\ldots,T \quad (49)$$

Constraints (42-44) ensure the conservation of commodities' flow among the various nodes of the network for all periods. Constraint (45) ensures that the total amount of inventory held on each node cannot exceed the storage capacity of each node respectively. Constraint (46) ensures that vehicles' capacity cannot be exceeded. For example, the total volume of commodities transported between nodes cannot exceed the total capacity of all modes of transportation. Constraints (47) and (48) relate to both loading and unloading capacity of each node. For instance, constraint (47) ensures that the loading capacity of each node cannot be exceeded while constraint (48) ensures that the total amount of commodities to be received from each node do not exceed the unloading capacity of each node. Finally, constraint (49) ensures that the amount of unsatisfied demand as well as the commodities transported and stored are positive numbers.

3.5 Numerical experiment

In order to validate the proposed methodology several numerical experiments have been conducted. Data for the numerical experiments and relevant source code can be seen in Annexes C, D, E, F and G. It is considered that a covert bioterrorist attack with aerosolized smallpox takes place (during e.g. a football game) in Athens, Attica region, Greece. Attica region is a large urban area of approximately $4x10^6$ inhabitants which consists of 7 regional units as seen in Table 11. The number of initially infected persons is taken to equal $5x10^2$. Public health authorities become aware of the outbreak 2 weeks onwards the attack (during the end of the prodromal phase). Following confirmation of the outbreak and due to the large number of initially infected cases, a voluntary, large-scale, post-event smallpox vaccination campaign takes place. As the outbreak takes place within several weeks any birth/death

process (it normally affects the dynamics of endemic diseases over several years) it has been excluded from the disease progression model. Several parameters' values expressing the transmission dynamics of smallpox have been retrieved from the literature and can be seen in Table 12.

Regional units	Population
Central Athens	1,029,520
North Athens	591,680
West Athens	489,675
South Athens	529,826
Piraeus	448,997
East Attica	502,348
West Attica	160,927
Total	**3,752,973**

Table 11: Administrative division of the Attica Region and population size

Parameter	Description	Value	Source
β	Infection rate	10^{-7}	This study
$\mathbf{r_1}$	Disease stage 1 rate	$(3 \text{ days})^{-1}$	(Kaplan, Craft et al. 2003)
$\mathbf{r_2}$	Disease stage 2 rate	$(8 \text{ days})^{-1}$	(Kaplan, Craft et al. 2003)
$\mathbf{r_3}$	Disease stage 3 rate	$(3 \text{ days})^{-1}$	(Kaplan, Craft et al. 2003)
$\mathbf{r_2}$	Disease stage 4 rate	$(12 \text{ days})^{-1}$	(Kaplan, Craft et al. 2003)
$\mathbf{v_s}$	Vaccination rate (susceptible individuals)	$\alpha(t)\sum_{i=1}^{n} I_{ic}(t)$	This study
$\mathbf{v_{I1}}$	Vaccination rate (disease stage 1)	$\gamma(t)\sum_{i=1}^{n} I_{ic}(t)$	This study
θ	Death rate	0.15	(Gani and Leach 2001)
$\mathbf{v_s}$	Vaccine efficacy (susceptibles eligible for vaccination)	1	(Kaplan, Craft et al. 2003)
$\mathbf{v_1}$	Vaccine efficacy (disease stage 1)	1	(Kaplan, Craft et al. 2003)

Table 12: Model's parameter values

With respect to the emergency logistics network it is assumed that a central stockpiling centre located near to Athens serves as the NSC. RSCs are evenly

distributed across the large urban area based on an administrative basis. They are hospitals that at the same time act as sentinel sites for disease's surveillance. Several PODs are assigned to each RSC. A pre-defined clustering-based approach for transporting medical supplies is used. In addition, the numbers of PODs assigned to each district implies the control of the outbreak within a certain time-frame for the first two broad sets of scenarios (where the vaccination campaign lasts 4 and 9 days respectively). For the last two sets of scenarios it is assumed that the number of PODs to be opened is limited due to administrative/logistical impediments.

Vaccination goals set by several health agencies vary. For instance, for the Scottish government the principal aim is to complete vaccination within five days of any decision to commence such a control measure (Department of Health 2005). On the other hand, the United States Centers for Disease Control and Prevention (CDC) has set an overall vaccination administration goal of 1 million persons over 10 days (Centers for disease control and prevention 2002). This means that approximately 100,000 persons per day should be vaccinated. Certain variations of the aforementioned vaccination administration goal have been adopted in this study. In particular, it has been considered that within PODs vaccination clinics (VC) operate at a 24-hour basis and each one consists of 8 vaccination stations (VS). Based on data from the CDC an overall vaccination rate of 8,640 persons per day/POD has been adopted for the two first sets of scenarios. For building the last two sets of scenarios it has been considered that the overall vaccination rate is 5,900 persons per day/POD. In this case and following the guidelines presented in (Centers for disease control and prevention 2002) PODs operate on a 16-hour basis. Data for estimating the aforementioned vaccination rates (for all sets of scenarios) may be seen in Table 13.

Number of VS	8 per VC
Number of vaccinators	1 per VS
Vaccination rate	30 to 60 vaccinations per VS/ hour
Hours of operation for VC	24 hours/16 hours
Estimated overall vaccination rate per day/POD	8,640/5,900

Table 13: Overall vaccination administration thresholds

Although smallpox vaccination is accompanied by serious side effects in this study it has been considered that the number of vaccine-related deaths is negligible. This assumption is based on the fact that individuals contraindicated for vaccination have been totally excluded from the vaccination queue (compartment S_1). Vaccine's efficacy has been considered to be 100% for those susceptible individuals eligible for vaccination (compartment S_2) and for those individuals at stage 1 of infection (Kennedy, Ovsyannikova et al. 2009).

Scenarios and sensitivity analysis

For controlling the outbreak the effects of case isolation (of symptomatic infectious individuals) and a reactive regional mass vaccination campaign are considered. Several scenarios have been built based on both resource constraints as well as possible delays for initiating the large-scale vaccination campaign, as seen in Table 14. For all the sets of scenarios developed five different vaccination initiation days have been considered, i.e. 22, 29, 36, 43 and 50 from the onset of the outbreak. All numerical solutions of the epidemiological model have been obtained using R programming language by using a time step of 0.001 (R Development Core Team 2008). The GNU Linear Programming Kit has been used for finding the optimal solution of the logistics network problem (as outlined in the fourth set of scenarios).

Intervention policy	Scenario	Resource allocation policy
Case isolation	Baseline	-
Reactive regional mass vaccination within 4 days starting at days 22, 29, 36, 43 and 50 from the onset of the outbreak.	A_1	Unconstrained
	A_2	
	A_3	
	A_4	
	A_5	
Reactive regional mass vaccination within 9 days starting at days 22, 29, 36, 43 and 50 from the onset of the outbreak.	B_1	
	B_2	
	B_3	
	B_4	
	B_5	
Reactive regional mass vaccination starting at days 22, 29, 36, 43 and 50 from the onset of the outbreak with limited vaccine supply.	C_1	Constrained
	C_2	
	C_3	
	C_4	
	C_5	
Reactive regional mass vaccination starting at days 22, 29, 36, 43 and 50 from the onset of the outbreak where limited transportation capacity as well as limited vaccine supply are considered.	D_1	
	D_2	
	D_3	
	D_4	
	D_5	

Table 14: Scenarios for controlling a smallpox outbreak

Two very aggressive control actions have been modelled in the first two broad sets of scenarios: one being a mass vaccination campaign taking place within 4 days; the second being a mass vaccination campaign taking place within 9 days. The rationale behind the selection of the aforementioned time-frames has its roots in vaccine's intrinsic aspects to induce immunity as well as in smallpox's dynamics of infection.

For instance, it is widely accepted that the available smallpox vaccine can provide protection even to an infected individual provided that he/she is administered the vaccine within 4 days after his/her infection. By adopting such a vaccination policy, there will be more people (even infected) that will eventually develop immunity to smallpox virus. In the second case, given the 9–17-days incubation period for smallpox, one would argue that any vaccination campaign should take place within 9 days so that the next generation of infectious individuals is halted and, by this way, the infection eventually dies out. Generally, past experinece has shown that the economic costs of an outbreak scale along with the proportion of infected individuals and, therefore, reducing the total duration of a smallpox outbreak might also be a key factor when control strategies are formulated (Ferguson, Keeling et al. 2003).

Results of the sets of scenarios

The results of the two broad categories of scenarios can be seen in Tables 15 and 16 respectively. It is worth noting that the implementation of the vaccination campaign within 4 days requires the establishment and operation of a large amount of PODs. The same holds for the number of people that should be vaccinated within the certain timeframe so that the effective reproduction number drops below 1. It is worth noting that in both cases (vaccination within 4 and/or 9 days) any delay in vaccination's initiation day has a detrimental effect on the total number of infected individuals, as seen in Figure 19 and Figure 21, respectively. On the other hand, the total number of individuals that should be vaccinated doesn't dramatically change for the different vaccination's initiation days (Figure 20 and Figure 22). From day 36 onwards one would argue that the immunization campaign might be counterproductive as its incremental benefits are outweighed by the pace of the outbreak. Therefore, from a policy perspective it seems that health officials have a very narrow time frame to make decisions regarding the scale and magnitude of the immunization campaign that should be implemented. Obviously, this time frame is relevant to the very dynamics of the disease (reproductive ratio) as well as to the response capacities available each time (vaccination rate, number of PODs etc).

Vaccination's initiation day	Number of persons vaccinated per day	Number of PODs to open	Number of infected individuals
22	625,004	72	1,915
29	624,284	72	3,810
36	622,931	72	7,568
43	620,247	72	14,983
50	614,747	72	29,484

Table 15: Data when vaccination lasts for 4 days

Vaccination's initiation day	Number of persons vaccinated per day	Number of PODs to open	Number of infected individuals
22	277,543	32	2,408
29	277,071	32	4,788
36	276,113	32	9,503
43	274,187	31	18,790
50	270,287	31	36,876

Table 16: Data when vaccination lasts for 9 days

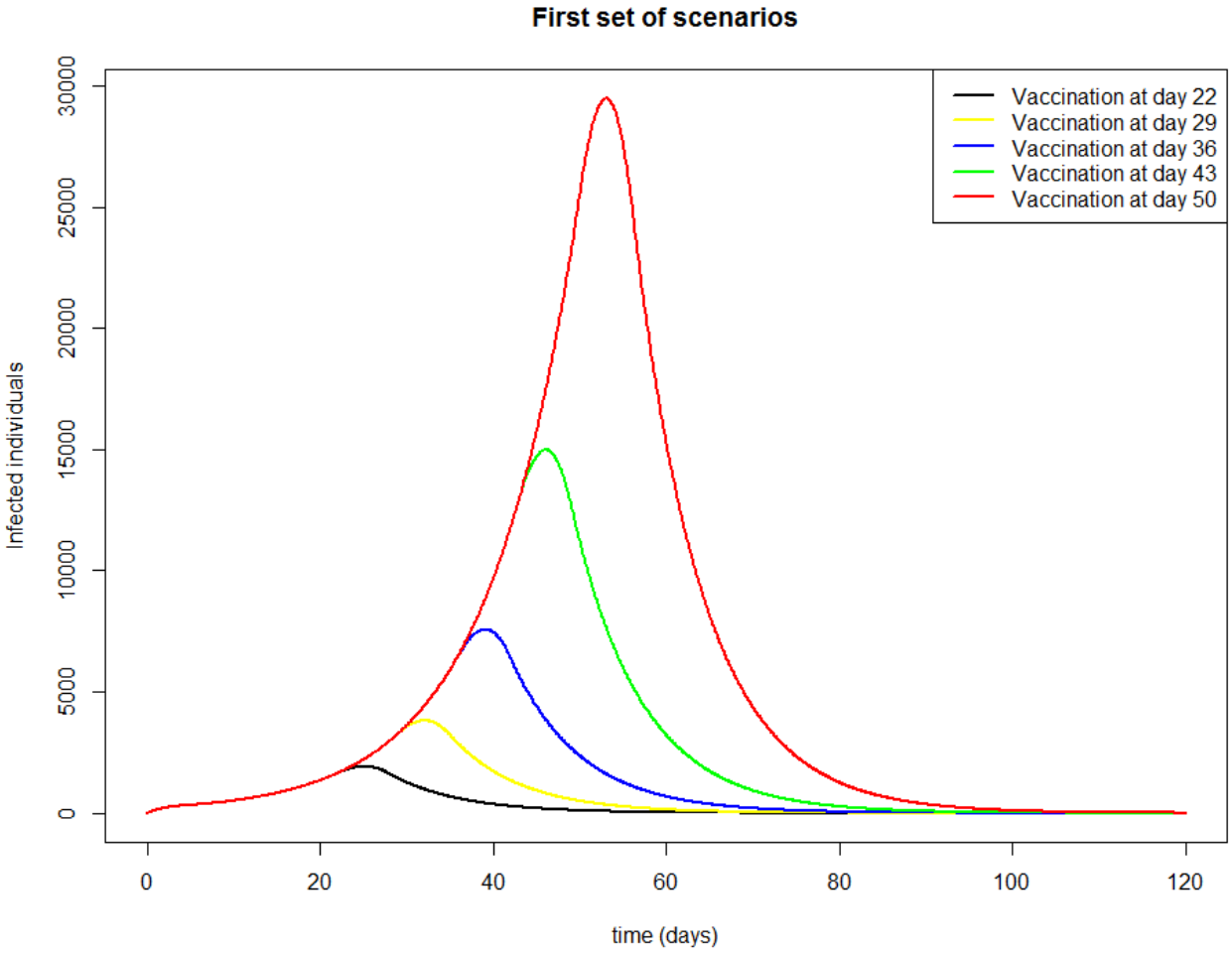


Figure 19: Cumulative number of infected individuals for the first set of scenarios

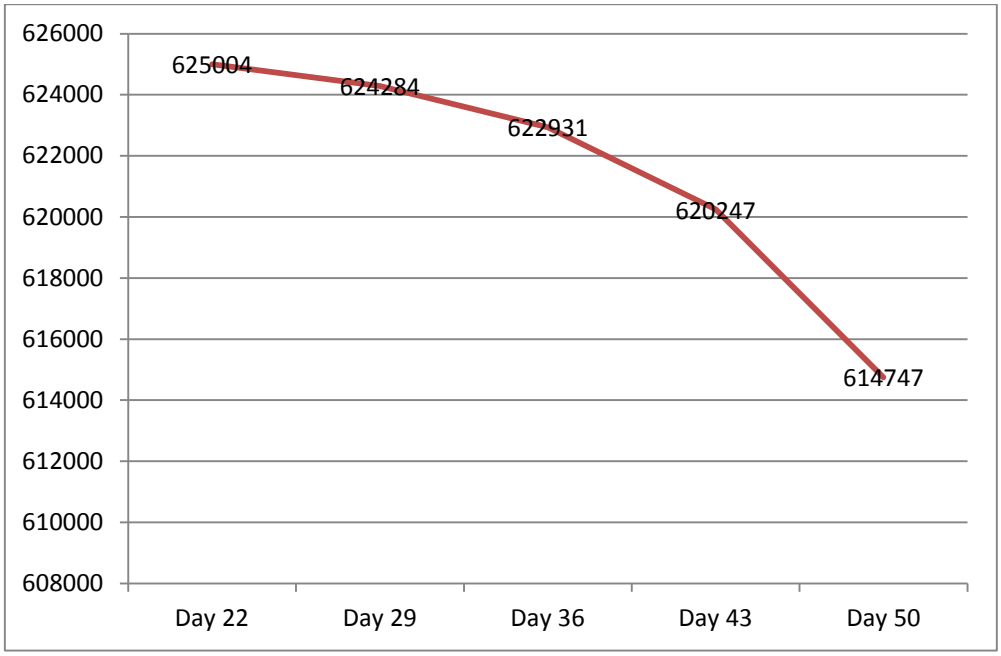


Figure 20: Total Individuals vaccinated/day when the campaign lasts 4 days

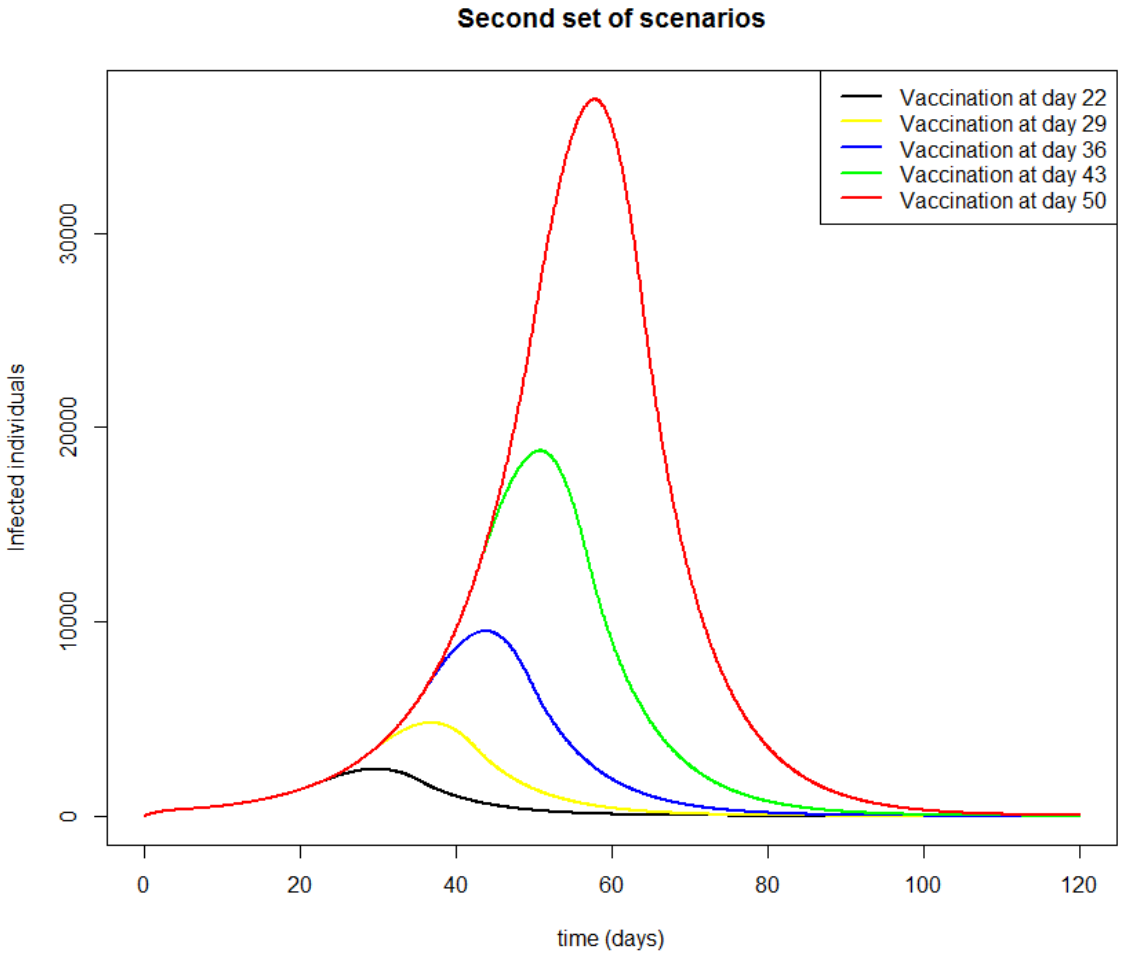


Figure 21: Cumulative number of infected individuals for the second set of scenarios

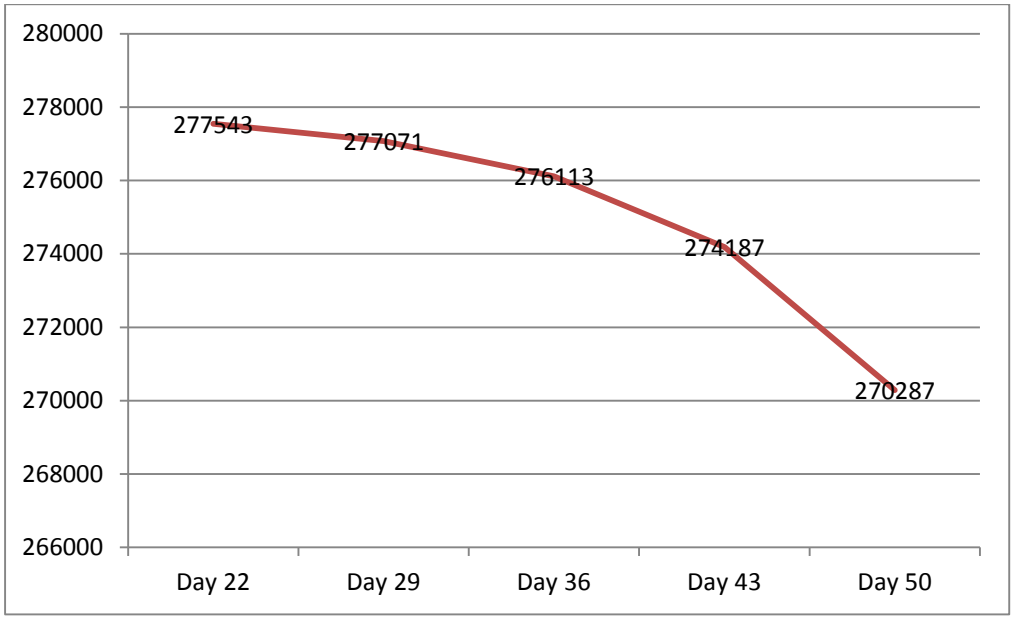


Figure 22: Total Individuals vaccinated/day when the campaign lasts 9 days

For building the third and fourth set of scenarios (constrained) it has been considered that the overall resources for responding to the outbreak are limited (limited vaccine supply, limited number of vehicles for distributing the vaccine and limited number of facilities to serve as PODs). In particular, for the third category of scenarios it has been considered that the overall vaccination rate is 5,900 per day/POD (Centers for disease control and prevention 2002) and that vaccines' availability is limited. In this case, the number of PODs to be opened per regional unit may be seen in Table 17. In addition, the vaccine supply is the following and covers all the eligible population: 40% in the initiation of the vaccination campaign and 60% ten days after. Details regarding vaccines' allocation and availability are given in Annex E.

Regional units	Population	PODs required
Central Athens	1,029,520	13
North Athens	591,680	7
West Athens	489,675	6
South Athens	529,826	7
Piraeus	448,997	6
East Attica	502,348	6
West Attica	160,927	2
Total		**47**

Table 17: Allocated PODs per regional unit for the constraint set of scenarios

Vaccination's initiation day	Vaccination's termination day	Day when effective reproduction number drops below 1	Infected individuals
22	39	35	2,833
29	46	42	5,623
36	53	49	11,119
43	60	56	21,826
50	67	62	42,238

Table 18: Results of the third set of scenarios

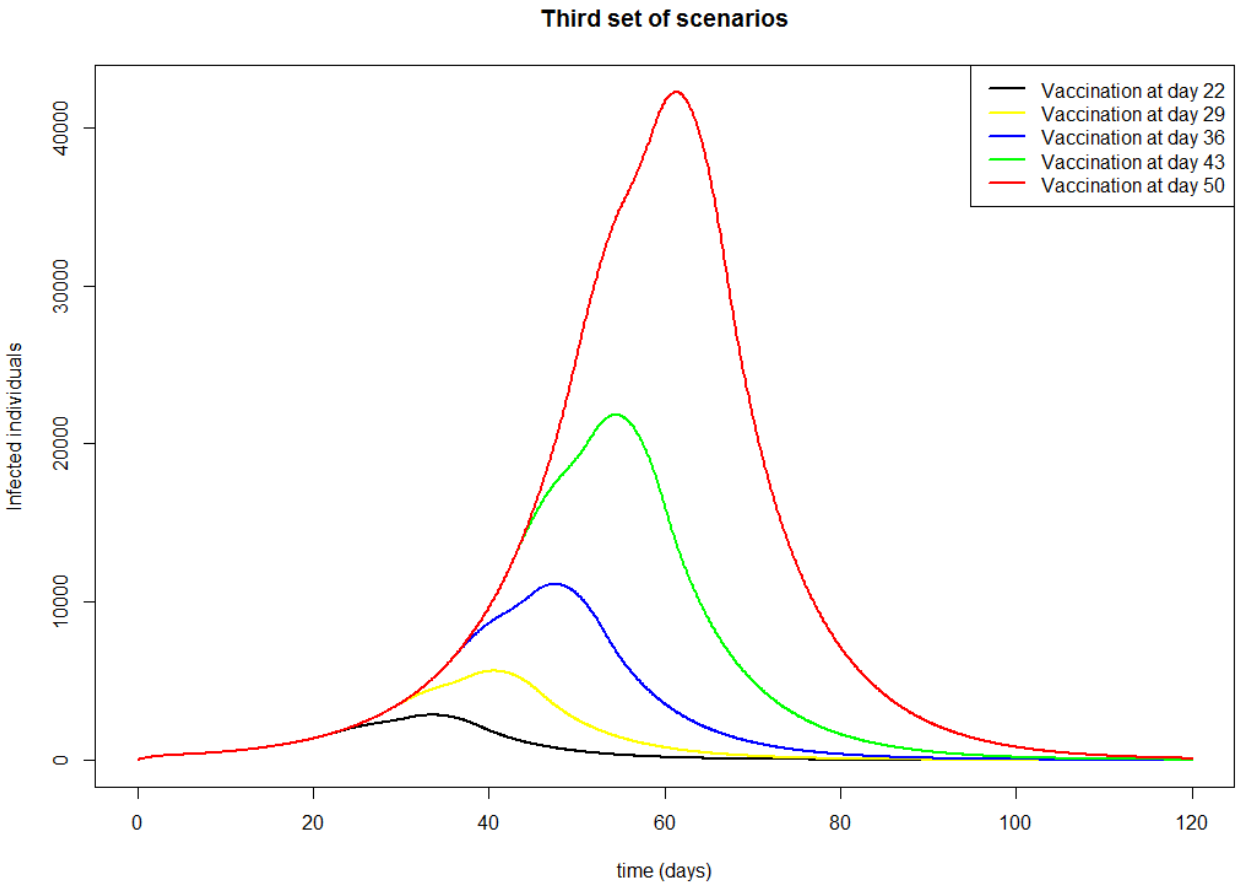


Figure 23: Cumulative number of infected individuals for the third set of scenarios

For building the fourth set of scenarios it has been considered that the overall vaccination rate is the same as in the third set of scenarios (5,900 per day/POD) as well as the vaccine's supply. In addition, limited logistical resources in terms of transportation and inventory capacity have been considered. Data relevant to the logistics network model may be seen in Annex C.

Vaccination's initiation day	Vaccination's termination day	Day when effective reproduction number drops below 1	Infected individuals
22	43	38	3,325
29	50	45	6,592
36	57	52	13,006
43	64	59	25,422
50	71	63	39,091

Table 19: Results of the fourth set of scenarios

Data from Tables 18 and 19 reveal the importance of available resources for controlling the outbreak. In particular, the cumulative number of infected individuals for the two last sets of scenarios is considerably greater than the number of infected individuals for the first two sets of scenarios (unconstrained sets). The more limited the response capacity becomes the more difficult it gets to control the outbreak. In addition, less response capacity also yields a more prolonged disease outbreak with obvious implications in social and economic activities (Figure 23 and 24). The way vaccine's stockpile is depleted may be seen in Figure 25. It is worth noting that a shortage in vaccine's supply takes place from period 9 to period 12.

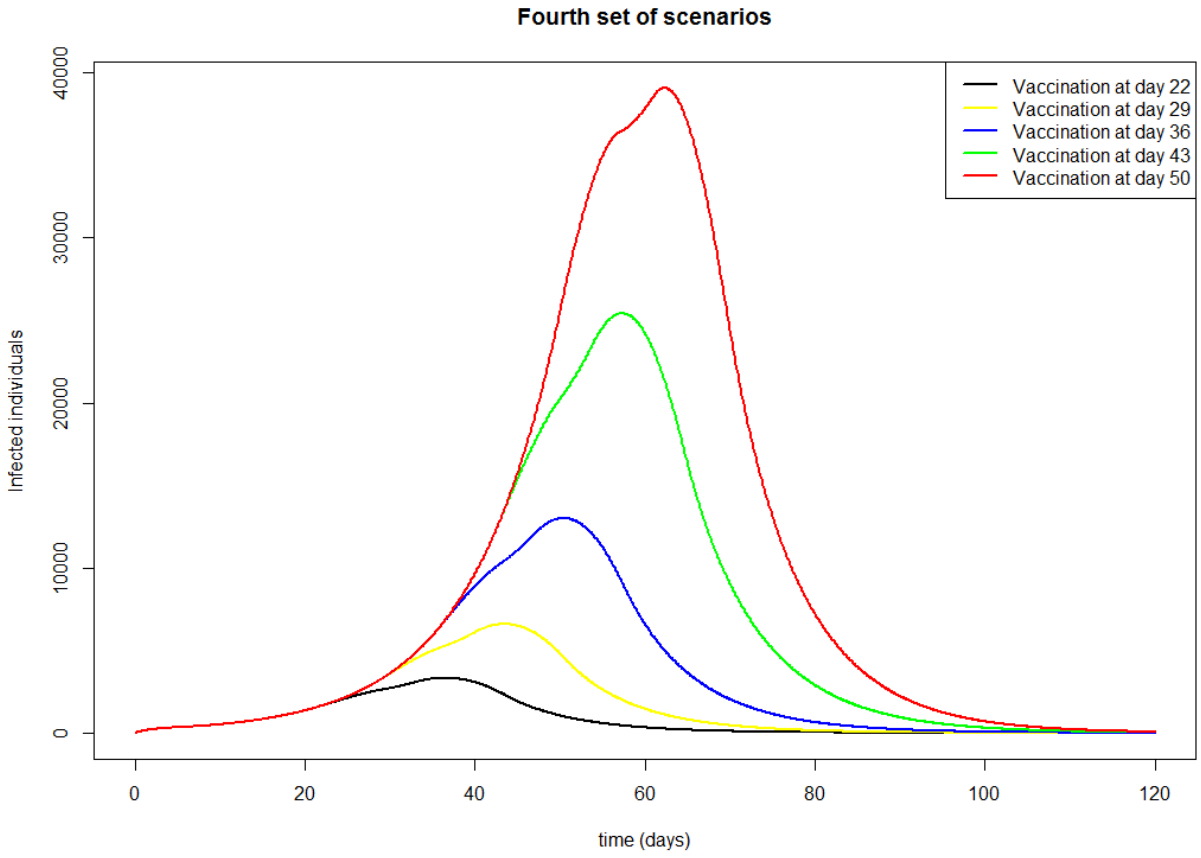


Figure 24: Cumulative number of infected individuals for the fourth set of scenarios

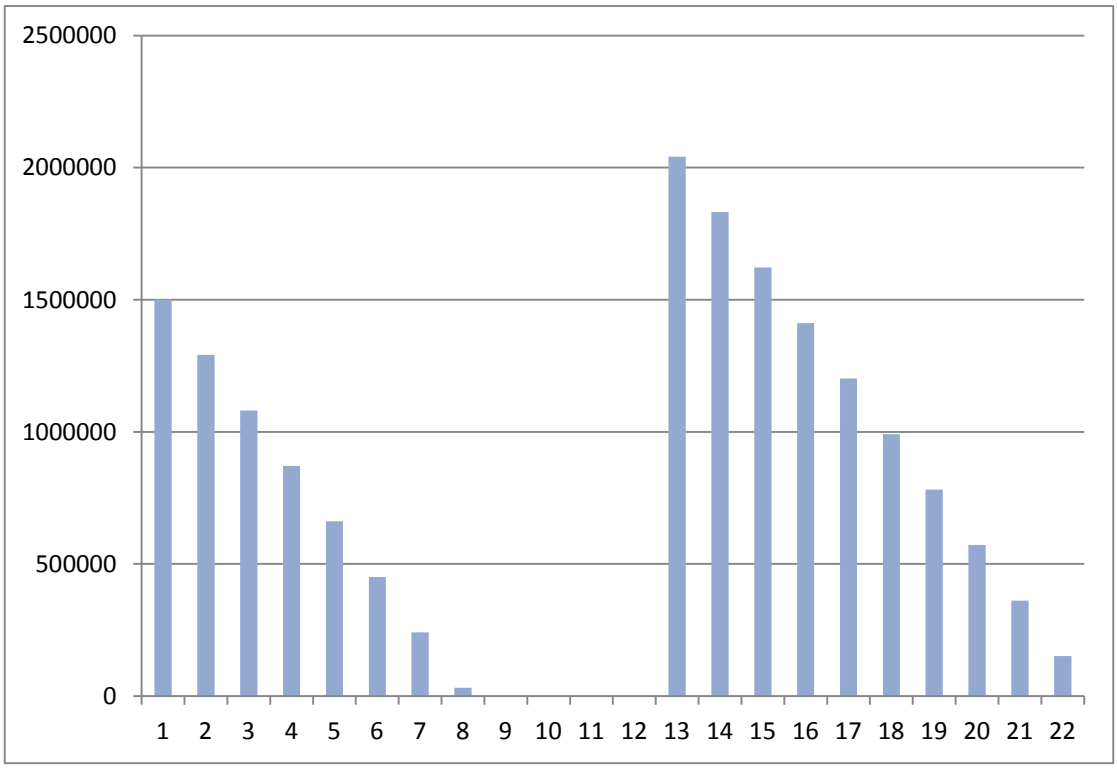


Figure 25: Vaccine's stockpile in the National Stockpile Centre for the fourth set of scenarios

3.6 Summary

Infectious disease outbreaks triggered either by natural causes or by deliberate human actions pose significant risks for modern societies. This chapter has dealt with the logistical implications for implementing a large-scale vaccination campaign in a large urban area for controlling a deliberate smallpox outbreak. A modelling approach has been developed consisting of two modules. The first module relates to disease's progression whereas the second one relates to optimally distributing a set of supplies (medical and ancillary) to affected sub-populations. For predicting the course of the outbreak a deterministic mathematical model parameterized to capture several biological properties of smallpox is used while simultaneously evaluating the effects of a reactive regional mass vaccination campaign. A linear programming model is developed for formulating the emergency supply chain problem where multiple commodities are distributed using a set of multiple transport modes within a number of time periods. Several logistical aspects are taken into consideration like predetermined levels of health care capacities (in terms of facilities available to care for those infected and relevant health-care personnel), limited number of vehicles for transportation/distribution activities, limited vaccine supply etc. For illustrating the proposed methodology a numerical experiment has been provided.

The results of the first two broad sets of scenarios reveal that the implementation of the vaccination campaign within 4 or 9 days requires the establishment and operation of a large amount of PODs. The same holds for the number of people that should be vaccinated within the certain timeframe so that the effective reproduction number drops below 1. It is worth noting that in both cases (vaccination within 4 and/or 9 days) any delay in vaccination's initiation day has a detrimental effect on the total number of infected individuals. On the other hand, the total number of individuals that should be vaccinated doesn't dramatically change for the different vaccination's initiation days. Most importantly, it seems that from day 36 onwards the immunization campaign might be counterproductive as its incremental benefits are outweighed by the pace of the outbreak. Therefore, from a policy perspective it seems that health officials have a very narrow time frame to make decisions regarding the scale and magnitude of the immunization campaign that should be implemented. With respect to the third and fourth sets of scenarios the results reveal the importance of available resources for controlling the outbreak. In particular, the cumulative number of infected individuals for the two last sets of scenarios is considerably greater than the number of infected individuals for the first two sets of scenarios (unconstrained sets). The more limited the response capacity becomes the more difficult it gets to control the outbreak. In addition, less response capacity also yields a more prolonged disease outbreak with obvious implications in social and economic activities.

Chapter 4: Controlling infectious disease outbreaks in complex humanitarian emergencies: the case of cholera

4.1 Introduction

Chapter 4 discusses the context and control prerequisites of infectious disease outbreaks (IDOs) in complex humanitarian emergencies (CHEs) and further explores the critical factors that affect the implementation of control interventions in these settings. Initially, the results of a systematic literature review regarding the factors that affect the control of IDOs in humanitarian emergencies for a pre-defined set of diseases are presented. In the sequel, an attempt is made for identifying critical success factors as well as the possible interrelationships among them for successfully implementing cholera vaccination campaigns in humanitarian emergencies. Several factors affecting the implementation of cholera vaccination campaigns are identified through systematically surveying the literature. Based on this survey and following experts' responses, relevant priorities are identified and the description and analysis of the interrelationships among these factors are given through the usage of the Decision Making Trial and Evaluation Laboratory (DEMATEL) method.

4.2 Challenges for controlling infectious disease outbreaks in complex humanitarian emergencies

Natural catastrophes (floods, famines, earthquakes, tsunamis) as well as man-made disasters (wars, civil conflicts) result in widespread disruption of socioeconomic activities and displacement of large parts of population. Outbreaks of communicable diseases are very common in these settings as affected populations are forced to live in dire conditions and public health systems are most of the times overwhelmed by the magnitude of the initial disaster. In particular, population displacement and overcrowding in conjunction with increased prevalence of malnutrition and degradation of sanitary conditions present the main drivers favoring disease outbreaks in CHEs (Connolly, Gayer et al. 2004). Diarrheal diseases (shigella dysentery, cholera), acute respiratory infections (pneumonia), measles, malaria,

meningitis, tuberculosis, viral haemorrhagic fevers, trypanosomiasis and leishmaniasis and HIV/AIDS are among the most prevalent diseases in CHEs (Connolly, Gayer et al. 2004). It is worth noting that natural or man-made disasters do not directly cause IDOs. Although sometimes they might increase the odds of their appearance due to exacerbation of certain disease risk factors, most of the times it is the collapse of public health systems and socioeconomic degradation that trigger IDOs in these settings.

In both grey and peer-reviewed literature there seems to be a differentiation between crises resulting from civil unrest and crises attributed to natural disasters. For instance, the state of emergency where civil unrest prevails is characterized as a complex emergency. According to the Inter-Agency Standing Committee (IASC) a complex emergency is defined as "*a humanitarian crisis in a country, region or society where there is total or considerable breakdown of authority resulting from internal or external conflict and which requires an international response that goes beyond the mandate or capacity of any single and/or ongoing UN country programme*" (Oxford Pocket Dictionary, 1992).

The differentiation between humanitarian emergencies attributed to wars or civil conflicts and to those resulting from natural disasters has its roots in many intrinsic aspects governing the different nature of emergency in each case as well as the different response required. For instance, humanitarian needs arising from civil unrest are different compared to those arising from natural catastrophes. In addition, the degree of societal endogeneity of causes and effects between complex emergencies and natural disasters is also different (Albala-Bertrand 2000). Finally, unlike wars and civil conflicts natural disasters present short term life cycle implications and necessitate a qualitatively different response (Salama, Spiegel et al. 2004).

On the other hand, the distinction between humanitarian emergencies resulting from conflicts and those resulting from natural disasters might be inaccurate in the sense that natural disasters are rarely truly 'natural'. Countries experiencing extensive violence and widespread damage are by definition more vulnerable to extreme climate conditions or geohazards. As a matter of fact, many geographical regions suffering from complex political emergencies have been subject to periodic natural hazards. For example, during the period 2000-2004, 140 'natural' disasters occurred in countries where civil unrest prevailed (Buchanan-Smith and Christoplos 2004). Therefore, different variety of hazards (natural, man-made or a combination thereof) coupled with different causes of vulnerabilities can lead to a complex emergency situation where a very large amount of people is affected.

Throughout this chapter the definition presented in (Chaignat and Monti 2007) is adopted for describing a more pragmatic perspective of the blur concept of complex emergencies. According to (Chaignat and Monti 2007), a complex emergency could be defined by the following terms:

- a large part of the population is affected, leading to potential massive movements of populations;
- coping capacities of the local and national authorities are overwhelmed by the magnitude of man-made or natural disasters; and
- numerous national and international actors may participate in the relief efforts.

In addition, the term complex humanitarian emergency (CHE) instead of complex emergency has been used for describing the state of emergency described above (resulting from both natural and man-made disasters).

The human toll of IDOs in CHEs can be enormous particularly when vulnerable groups are considered (children, immunocompromised individuals etc). Public health community has established certain indicators for describing the overall health impact of such emergencies on affected populations beyond the number of war-related or injury-related deaths. In particular, the Crude Mortality Rate (CMR) and under-5 mortality rate are the most commonly reported mortality indicators in CHEs. The threshold during the emergency phase for the CMR is 1 death per 10.000 people per day (Connolly, Gayer et al. 2004). Death rates of over 60-fold the baseline have been recorded in refugees and displaced people, with over three-quarters of these deaths caused by infectious diseases (Connolly, Gayer et al. 2004). Measles outbreaks can be devastating in CHEs and fatality rates as high as 20–30% have been recorded among children (Mallik, Mandal et al. 2011). Lack of clean water and degradation of sanitary conditions are responsible for huge cholera outbreaks in CHEs. An estimated 12,000 refugees died of cholera in the Goma refugee camp of the Democratic Republic of Congo in 1994 (Plotkin, Shin et al. 2011; Von Seidlein, Jiddawi et al. 2013). Thousands of people have also died by the cholera outbreak in Haiti and many more have been sickened (Adams 2013).

The control of IDOs in these settings encompasses a range of activities, from the establishment of proper surveillance mechanisms to coordination of a set of disparate key-players operating in the field. Past experience has shown that a prompt and coordinated response can substantially reduce the burden of communicable diseases in CHEs (Connolly, Gayer et al. 2004). In addition, during the acute phase of a CHE the provision of clean water and temporary sanitary facilities present mainstays of epidemic control (Waldor, Hotez et al. 2010). Generally, the first priority during the acute phase of an emergency situation with high mortality

rates is the establishment of effective life-saving interventions as soon as possible. Such interventions, although unsustainable, are fully justifiable in the short-term until mortality rates are brought below certain thresholds (World Health Organization 2005). The implementation of food and health education programs combined with immunization campaigns also remains critical. For example, the implementation of measles vaccination in conjunction with vitamin A supplementation for children up to ages 12 to 15 years is the first program priority in refugee camps (Salama, Assefa et al. 2001).

Unfortunately, effective control of IDOs in the generic context of CHEs may be a daunting task due to multitude constraints and barriers. Countries suffering from prolonged armed conflicts often have devastated public health infrastructures and a plethora of health priorities emerge. Establishing priorities to address communicable diseases in these settings is critical and control interventions may become subject of contention (World Health Organization 2013). In addition, lack of security may pose significant risks for humanitarian personnel and interventions strategies many times have to be postponed (Tong, Valverde et al. 2011). When issues of security have not been resolved, entire programs could be in jeopardy, particularly lengthy ones. For instance, the implementation of tuberculosis programs in CHEs is challenging as these programs require a prolonged period of treatment and their interruption might increase the odds of antibiotic resistance (Salama, Spiegel et al. 2004). In the case of vaccine-preventable diseases several issues might also arise. Vaccination campaigns are hard to implement in settings where insecurity prevails and human resources are scarce. Immunization campaigns are unsuccessful in cases where targeted populations are inaccessible and public health infrastructures have been compromised. In these circumstances the implementation of vaccination campaigns might be counter-productive as these campaigns are responsible for diverting scarce public health resources away from other interventions like surveillance, primary treatment and health education (Calain, Chaine et al. 2004).

Coordination and cooperation mechanisms may be hindered due to the presence of several disparate key-players in the field. In addition, overarching roles and responsibilities among key-players further complicate the situation, particularly in cases where a leading organization is missing. Conflicting opinions, poor cooperation among key-players and irrational use of resources are just a few among several issues arising (Clasen, Smith et al. 2006). The establishment of reliable surveillance mechanisms in CHEs is also difficult. Many times affected populations remain dispersed and inaccessible for a prolonged period of time and therefore, there is a lack of reliable and accessible population data. In humanitarian emergencies the true burden of infectious diseases is not captured either because surveillance systems are weak or because affected populations are inaccessible. Finally, emergency response

training in the developing world is poor and most of the healthcare workers involved in case management are either poorly trained or not trained at all (Oladele, Oyedeji et al. 2012).

From an operational perspective, the implementation of control actions in CHEs is really challenging for several reasons. Poor or destroyed infrastructure, lack of human resources and difficult logistics complicated by security and/or ethnic issues render the implementation of control actions difficult (Coninx 2007). Logistics operations may be easily disrupted due to the impacts of the initial disaster and, therefore, several managerial challenges could also arise. Medical supplies may be lacking, storage and transport facilities may be devastated and electricity supply might be disrupted in many places (Nicoll 2005). Mismanagement of supply systems is further exacerbated by unsolicited donations of medical supplies, medicines, and field hospitals brought into the affected country by other governments and NGOs (Valenciano, Coulombier et al. 2003). Past experience has shown that lack of security, limited vaccine supplies, extensive cold chain requirements and complex logistical aspects of multi-dose regimens may hinder the implementation of immunization campaigns in CHEs. For example, the WHO didn't authorize the implementation of cholera immunization programs in two cases; one being the cholera outbreak reported in Haiti, 2010 and the second being the outbreak of cholera in Iraq, 2007 (World Health Organization 2007; Date, Vicari et al. 2011).

Although the nature and impacts of IDOs in CHEs are relatively well documented (Connolly, Gayer et al. 2004; Salama, Spiegel et al. 2004; Coninx 2007; Gayer, Legros et al. 2007; Watson, Gayer et al. 2007; Bellos, Mulholland et al. 2010; Grais, Strebel et al. 2011; Bartels and VanRooyen 2012; Kimbrough, Saliba et al. 2012; Kouadio, Aljunid et al. 2012), several factors affecting the implementation of control actions have been poorly studied so far. In this section some evidence-based guidance regarding the factors that affect the control of IDOs in CHEs is presented. Based on a systematic review of relevant literature several factors affecting the implementation of outbreak control actions for specific diseases are studied, particularly from an operational perspective. The diseases under study are the following: meningitis, trypanosomiasis, leishmaniasis, viral hemorrhagic fevers, tuberculosis, acute respiratory infections, malaria, measles, and, finally, diarrheal diseases (shigella dysentery and cholera).

4.2.1 Methodology

For conducting the thematic analysis the Enhancing Transparency in Reporting the synthesis of Qualitative research (ENTREQ) statement was used (Tong, Flemming et al. 2012). In the sequel, the overall search strategy is presented.

4.2.1.1 Literature search

The literature review spans the period January 1994 to June 2014. The search was conducted during November 2013 and was subsequently updated during June 2014 targeting relevant peer-reviewed journal articles. The search included Scopus, PubMed and grey literature (several targeted websites of organizations like World Health Organization, Pan American Health Organization, Doctors without Borders, International Federation of Red Cross and Red Crescent Societies, etc). A flowchart of the overall strategy implemented is presented in Figure 26. A combination of Boolean operators (and, or) and key-words was used for searching specific information in titles and abstracts (for example, operator "ABS" in Scopus database). In addition, several refinement features of both databases (Scopus and PubMed) were extensively used (multiple refinements of results in accordance with the context of specific articles, related documents search etc). An overview of the search terms is presented in Table 20. In cases where the abstract of a certain study was not available, the full article was retrieved and further assessed for relevance. References of key articles were also examined for identifying additional citations. Prior to importing citations into the bibliographic manager several excluding criteria were applied (non-English language articles etc). All potentially relevant articles were retrieved in full text.

4.2.1.2 Eligibility criteria

The eligibility of the retrieved literature was evaluated based on a set of predefined exclusion and inclusion criteria (Table 21). Some exclusion criteria were used prior to introducing the literature in the bibliographic manager (language, subject area and document type restrictions). Initially, the abstracts of all research papers as well as the introductory sections of grey literature were assessed. Articles meeting one of the exclusion criteria were excluded and sorted by reason of exclusion (see Table 21). Afterwards, a full text review also took place and some additional articles were excluded from the study and reasons for exclusion were documented. Generally, several studies were excluded because of their epidemiological focus whereas aspects of impediments/barriers for implementing control actions were modestly reported. Some of the articles not fitting the inclusion criteria were set aside and consequently used in the introduction section of this chapter. All the articles and reports were included for analysis, irrespective of their scientific quality.

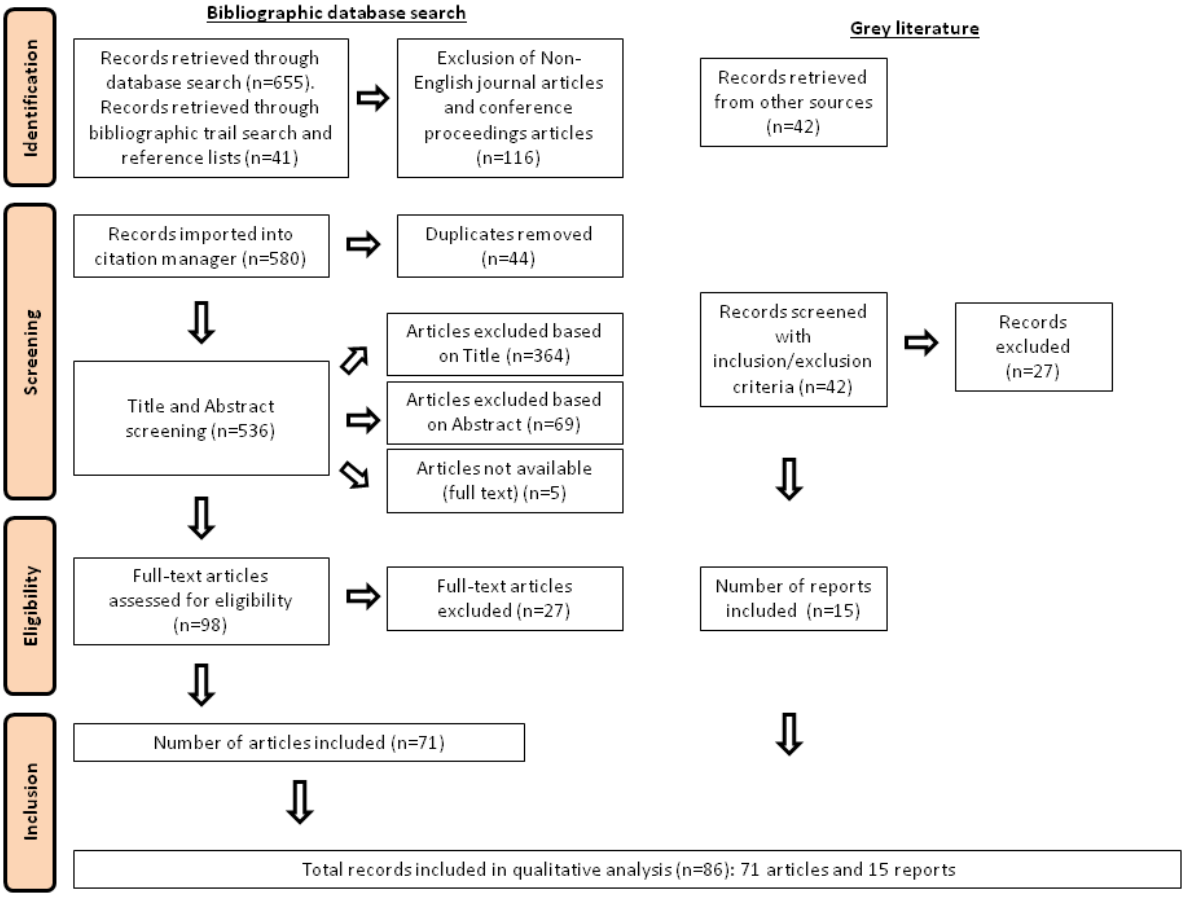


Figure 26: Flowchart of the overall search strategy

Search terms focus	Database	Grey literature
Generic context	(disaster OR humanitarian emergency OR complex emergency OR crisis OR conflict OR evacuee OR refugee OR displaced OR affected AND infectious OR contagious OR communicable OR disease OR epidemic OR outbreak) AND PUBYEAR > 1994	"humanitarian emergency", "complex emergency", "disaster", "crisis", "conflict", "evacuee", "refugee", "displaced" AND "infectious", "contagious", "communicable", "disease", "epidemic", "outbreak"
Disease-oriented	(disaster OR humanitarian emergency OR complex emergency OR crisis OR conflict OR evacuee OR refugee OR displaced OR affected AND "each disease[2]") and PUBYEAR > 1994	"humanitarian emergency", "complex emergency" "disaster", "crisis", "conflict", "evacuee", "refugee", "displaced" AND "each disease"

Table 20: Overview of search terms

[2] The diseases targeted are the following: meningitis, trypanosomiasis, leishmaniasis, viral hemorrhagic fevers, tuberculosis, acute respiratory infections, malaria, measles, diarrheal diseases, shigella dysentery, and cholera.

Selection criteria	Database search		Grey literature search
• Inclusion criteria	• During the initial database search	• Peer reviewed journal articles • Published after 1994 • English language articles	• English language reports • Published after 1994
• Exclusion criteria	• Prior to importation to bibliographic manager	• Conference proceedings articles • Non-English language articles	• Reports not addressing control/intervention challenges and prerequisites
	• During title screening process	• Articles addressing aspects of mortality rates in humanitarian emergencies • Articles modestly addressing infectious disease outbreaks in humanitarian emergencies • Articles related to general contingency plans (preparedness etc) and not to infectious disease outbreaks • Articles addressing disease outbreaks in non-compromised public health systems • Articles addressing bioterrorist events • Articles in which the agent triggering the outbreak is not in our disease list • Articles reporting on animal diseases	
	• During abstract screening process	• Articles reporting on diseases' incidence and mortality rates • Articles modestly addressing disease outbreaks in humanitarian settings	
	• During full article screening	• Articles not addressing issues of control/intervention challenges and prerequisites	

Table 21: Overview of selection criteria

4.2.1.3 Data extraction

All articles and reports meeting the inclusion criteria were entered into a qualitative analysis software (MAXQDA[11]) and data were analyzed in emerging themes. The author carried out the thematic content analysis. Afterwards, the cluster of the coded segments was revised by the supervisor and the author drafted a final set of themes and sub-themes.

4.2.2 Factors affecting the control of infectious disease outbreaks in complex humanitarian emergencies

In the sequel, several factors affecting the control of IDOs in CHEs are presented in detail.

4.2.2.1 Accessibility issues

Planning and implementation of health care programs in CHEs can be negatively affected by limited access of health care workers to affected communities. Lack of security, continuous population movements and destroyed infrastructure are just a few among the factors that might limit access of health care workers to affected communities.

Insecurity

Complicated logistics, limited access of vulnerable populations to health care and high humanitarian staff turnover are just a few of the implications of insecurity for the implementation of epidemic control actions in CHEs (Legros, Paquet et al. 1999; Hehenkamp and Hargreaves 2003; World Health Organization 2005; Martins, Heldal et al. 2006; World Health Organization 2006; Mauch, Weil et al. 2010). In addition, volatile security situations may severely hinder accessibility of health care workers to afflicted populations to perform control actions (World Health Organization 2005; Protopopoff, Van Herp et al. 2007; Howard, Shafi et al. 2010; World Health Organization 2012) or may entirely jeopardize control interventions (Kolaczinski, Graham et al. 2005; Global Task Force on cholera control 2006; World Health Organization 2006; Chaignat, Monti et al. 2008; Tong, Valverde et al. 2011; UNICEF 2012). Gathering reliable data in complex emergency settings is extremely problematic but the threat of violence further exacerbates the heavy task of public health officials to systematically collect data and establish proper surveillance systems (Valenciano, Coulombier et al. 2003; Pinto, Saeed et al. 2005; Chaignat and Monti 2007).

Mass immunization campaigns are particularly vulnerable to insecurity and result in very low vaccine coverage in settings where volatile security situations prevail (Centers for Disease Control and Prevention 2004; Gayer, Legros et al. 2007; World Health Organization 2013). Generally, lack of security presents formidable logistical constraints for the implementation of mas immunization campaigns in CHEs (Centers for Disease Control and Prevention 2004). Vaccination campaigns might be interrupted as protracted conflicts generate long-term inadequacies in cold chain and logistics (Gayer, Legros et al. 2007). Access of the population to organized vaccination services can be severely affected as insecurity affects traveling and communications (World Health Organization 2013). In light of these considerations some health officials argue that addressing the security situation in CHEs is a higher priority than implementing public-health interventions (World Health Organization 2013).

Issues of security are also critical when lengthy control interventions like tuberculosis control programs are to be implemented in CHEs. Evidence from the field suggests that such programs should not be implemented unless security issues have been resolved (Houston 1998; World Health Organization 2007; Seddiq, Enarson et al. 2014). In particular, armed conflicts are considered to be source of diagnostic delay in the case of tuberculosis as they prevent patients from seeking prompt care (Gele and Bjune 2010). Insecurity also threatens the continuity of lengthy control programs by hindering the supply of critical medical supplies and the follow up of the patients (Coninx 2007; Tong, Valverde et al. 2011). Past experience has shown that health care officials had to improvise new ways of overcoming security obstacles during the implementation of tuberculosis control programs like establishing run- away packs with fixed-dose combination drugs or providing treatment cards to help patients get treatment at a new treatment point (Biot, Chandramohan et al. 2003). Finally, major concerns about the risk of creating drug resistance has discouraged many agencies from actually implementing tuberculosis control programs in CHEs (Hehenkamp and Hargreaves 2003).

Population movements

Population movements are very frequent in settings where poor health and high risk of exposure due to insecurity prevail. Past experience has revealed that both planning and implementation of control interventions can be severely hindered due to population movements (World Health Organization 2006). For example, immunization campaigns in open settings or spontaneous internally displaced population settlements have been found to have very low coverage due to population movements (Calain, Chaine et al. 2004; Global Task Force on cholera

control 2006; World Health Organization 2006; Date, Vicari et al. 2011). On the other hand, high vaccine coverage was achieved in well-organized refugee camps even for immunization campaigns that required multi-dose regimens (Chaignat and Monti 2007; Chaignat, Monti et al. 2008; UNICEF 2012). Continuous population movements of internally displaced people make also extremely difficult for control mechanisms to identify target populations (Global Task Force on cholera control 2006; World Health Organization 2006; Chaignat, Monti et al. 2008). As a consequence, health officials often have to decentralize health care services to meet vaccine coverage targets and accelerate control of vaccine-preventable diseases in CHEs (Global Task Force on Cholera Control 2004). Finally, the implementation of lengthy treatment regimens like tuberculosis control programs is also very sensitive to population movements. Past experience has shown that such programs should be initiated provided that no major movements of the afflicted population are anticipated in the near future (Houston 1998; World Health Organization 2007).

Mass population movements may also trigger stability changes of the endemic equilibrium of certain diseases like, for example, malaria. In this case populations with malaria parasites might arrive in areas where there is normally little transmission or non-immune populations might arrive in areas where there is moderate or intense transmission. By this way different strains of malaria parasites may proliferate in regions outside their initial endemic range and could become resistant to certain anti-malarial drugs (World Health Organization 2005). Population movements also change the equilibrium of susceptible/immune individuals within refugee camps and IDOs might take place as a result of inadequate immunization of new arrivals (Kamugisha, Cairns et al. 2003). For overcoming this problem health officials and refugee camp managers often establish registration centers to track those individuals recently arrived or even proceed to their prompt immunization upon arrival (Polonsky, Ronsse et al. 2013).

Miscellaneous

Access to target populations could also be hindered by geographical or terrain obstacles, geohazards and cultural misbeliefs. Generally, the provision of medical care as well as the rapid mobilization of mass immunization campaigns in remote and geographically isolated territories is a daunting task (Centers for Disease Control and Prevention 2004; Kolaczinski, Graham et al. 2005; Tong, Valverde et al. 2011). Low vaccine coverage was attained in isolated regions as several logistical difficulties connected to geographical particularities arose (Global Task Force on cholera control 2006; Vijayaraghavan, Lievano et al. 2006; World Health Organization 2006). Geographical and terrain obstacles provide a unique backdrop against which lengthy control regimes are implemented, like, for instance, tuberculosis control programs.

Both geography and topography of a country can severely hinder the transportation of medical supplies from central points to remote areas, thus, jeopardizing the continuation of such programs (Mauch, Weil et al. 2010). Limiting of distances travelled by both patients and outreach workers facilitate the implementation of tuberculosis control programs in disaster settings (Rodger, Toole et al. 2002). Lessons learned suggest that tuberculosis control programs have been successfully implemented in well-organized refugee camps and geographically confined settings (Houston 1998).

Access to target populations following a natural disaster can be difficult due to destruction of existing infrastructure like roads and general transport networks (Global Task Force on cholera control 2006; Protopopoff, Van Herp et al. 2007; Chaignat, Monti et al. 2008; World Health Organization 2012). Particular climate conditions can also serve as an obstacle for accessing target populations in a specific region (World Health Organization 2006). People living in remote areas can be unreachable for months during the winter (Kolaczinski, Graham et al. 2005; Global Task Force on cholera control 2006). Strong religious misbeliefs may also hinder the accessibility of health care personnel to certain groups within a population (female population) (Kolaczinski, Graham et al. 2005). Sometimes affected populations perceive the implementation of control measures as a culturally inappropriate service and they are not motivated to take part (World Health Organization 2005). In cases where different ethnic groups reside in a particular region the employment of local community members from each group can facilitate the accessibility of health care workers to these groups (Rodger, Toole et al. 2002). For disease control actions implemented in the aftermath of natural disasters public health officials should take into account the fact that afflicted people try to return to their daily lives as soon as possible and, therefore, might be absent from a refugee camp during the day (finding a job or resuming work, rebuilding dwellings and participating in the reconstruction collective effort etc) (World Health Organization 2006). Finally, economic barriers to accessing health care have been reported in the literature, particularly in conflict-affected countries (World Health Organization 2005).

4.2.2.2 Human resources

Human resources are a critical element of IDO control mechanisms in humanitarian emergency settings (World Health Organization 1999; Global Task Force on Cholera Control 2004; World Health Organization 2007; Seddiq, Enarson et al. 2014). Health officials, logisticians, epidemiologists, laboratory technicians, community mobilizers and educators and field workers should be rapidly mobilized in the onset of an emergency situation to evaluate and coordinate activities regarding water and sanitation or to provide assistance and technical expertise to local health ministry

resources (Pinto, Saeed et al. 2005; World Health Organization 2005; French Red Cross 2010; International Federation of Red Cross and Red Crescent Societies 2011). Human resources are also a critical component of surveillance systems as collection, investigation, reporting, analysis and dissemination of information regarding diseases' occurrence relay on a network of people (World Health Organization 2012).

Availability of personnel

Past experience has shown that significant human resources are needed to carry out a mass vaccination campaign (Legros, Paquet et al. 1999; Global Task Force on cholera control 2006; World Health Organization 2006; Von Seidlein, Jiddawi et al. 2013; World Health Organization 2013). However, qualified public-health personnel (program managers, logisticians, public- health workers, drivers and translators) are consistently in short supply, particularly at the onset of an emergency (World Health Organization 2013). Generally, in low-income countries or countries affected by fragility and conflict lack of health personnel is a great obstacle to the effective delivery of health services (Mauch, Weil et al. 2010; Farmer, Almazor et al. 2011). Experience in planning and implementing mass immunization campaigns in CHEs reveals that shortages of skilled staff are the norm (World Health Organization 2005; Global Task Force on cholera control 2006; Martins, Heldal et al. 2006; Farmer, Almazor et al. 2011; UNICEF 2012). Such shortages of health-care personnel may result in last-minute changes in planning as well as in prolonged vaccination campaigns with significant cost increases (Dadgar, Ansari et al. 2003; Chaignat and Monti 2007; Mallik, Mandal et al. 2011). In addition, immunization campaigns implemented with insufficient human resources often result in low vaccine coverage (Vijayaraghavan, Lievano et al. 2006).

Shortages of human resources could be attributed to a multitude of reasons. For example, disaster-related loss of critical human resources is very common in CHEs (Global Task Force on Cholera Control 2004; World Health Organization 2006; Chaignat, Monti et al. 2008; Date, Vicari et al. 2011). Scarcity of personnel in CHEs also stems from the fact that multiple public health priorities emerge and have to be simultaneously addressed (World Health Organization 2006; Chaignat, Monti et al. 2008). Past experience has revealed that conflicting priorities of other programs implemented simultaneously resulted in lack of healthcare capacity to undertake cholera immunization campaigns. The scarcity of human resources was more apparent at management level where senior managers had the responsibility of numerous other health tasks and could not be dedicated to the immunization campaign (World Health Organization 2006). Finally, lack of adequately trained human resources is very common in countries suffering from prolonged war and

conflict as education systems are usually broken in these countries and people cannot attain adequate levels of education (Seddiq, Enarson et al. 2014).

Personnel training

Staff training has been a critical success factor for the implementation of outbreak control agendas in CHEs (Rowland and Nosten 2001; Rodger, Toole et al. 2002; Liddle, Elema et al. 2013). Emergency staff training is considered to be an essential element for preparedness, especially in high-risk areas (Global Task Force on Cholera Control 2004; World Health Organization 2005; World Health Organization 2007). Health care workers should have a good knowledge and practical experience in a broad range of subjects like, water and sanitation, food and nutrition, disease surveillance, immunization, communicable disease control, epidemic management, and maternal and child health care (Toole and Waldman 1997). In particular, health care workers must receive training prior to their deployment in the field (Clasen, Smith et al. 2006). Training programs can be carried out by health care workers who have previous experience of IDOs control. These workers should be mobilized to provide on-site training and supervision of less experienced personnel (Global Task Force on Cholera Control 2004).

Although emergency response training is key to epidemic control, in the developing world, most of the healthcare workers involved in case management are either poorly trained or not trained at all (Costanza Adinolfi, David S. Bassiouni et al. 2005; Oladele, Oyedeji et al. 2012). This lack of experience could be attributed to the fact that there are no formal training programs for field epidemiology in crises (Ratnayake 2011). In addition, front-line relief workers in CHEs are usually volunteers recruited by NGOs who sometimes lack specific training, knowledge and experience in emergency relief practices (Toole and Waldman 1997). Past experience has revealed that lack of staff expertise in humanitarian health systems may act as a barrier to implementing outbreak control campaigns in CHEs (Hehenkamp and Hargreaves 2003; Salama, Spiegel et al. 2004; Rolland, Checchi et al. 2006; World Health Organization 2006).

During the cholera epidemic in Haiti in 2010 extensive training programs were implemented focusing on cholera hygiene promotion activities and treatment practices (French Red Cross 2010; International Federation of Red Cross and Red Crescent Societies 2011; Tappero and Tauxe 2011). Master trainers were also assigned to various health departments in Haiti to train other health staff on cholera treatment practices (Farmer, Almazor et al. 2011). For vaccine-preventable diseases health care workers should be familiar with all the aspects of immunization campaigns like, for example, the purpose of such campaigns and the technical issues

pertinent to the specific vaccine(s) used, the importance of multi-dose regimens, the identification and follow-up of adverse events following immunization, the community social mobilization practices, the safe injection techniques etc (Dadgar, Ansari et al. 2003; World Health Organization 2005; Global Task Force on cholera control 2006; World Health Organization 2006). With respect to surveillance, health care workers must receive training relevant to the usage of surveillance tools, the management of cases of epidemic-prone diseases and the way data is collected and reported etc (Valenciano, Coulombier et al. 2003; Gayer, Legros et al. 2007; World Health Organization 2012). For vector-borne diseases like malaria, health care workers must be trained on diagnosis, case management, vector control and the rational use of anti-malarial drugs (World Health Organization 2005). For treating tuberculosis patients, health care workers should be trained on case-finding and supervising treatment of patients, monitoring and appropriate treatment (World Health Organization 2007; Seddiq, Enarson et al. 2014). Finally, laboratory technicians should also undergo a formal training program related to tuberculosis program operation, the quality control processes and record management etc (Rodger, Toole et al. 2002; World Health Organization 2007).

4.2.2.3 Communication mechanisms

Community participation and health education are critical for successfully planning and implementing IDOs control agendas in CHEs. However, both of them are often seen as being of low priority in disaster settings, and there is little published information reporting on issues of practical field experience of these areas of activity (World Health Organization 2005).

Mobilization campaigns

A key requirement to tackling IDOs in CHEs is public information on prevention measures through the implementation of social mobilization campaigns and health education programs (Global Task Force on Cholera Control 2004; Kouadio, Koffi et al. 2009; French Red Cross 2010; Date, Vicari et al. 2011; Farmer, Almazor et al. 2011; International Federation of Red Cross and Red Crescent Societies 2011; Mallik, Mandal et al. 2011). For instance, certain health education messages can help prevent diseases like sexually transmitted infections, HIV/AIDS and diarrheal diseases (Connolly, Gayer et al. 2004). Without communicating the benefits of control measures target population will not support the disease-specific interventions because it might have different priorities (World Health Organization 2005). According to past experience, insufficient social mobilization activities (limited

or started too late) resulted is less motivated individuals in terms of their participation in IDOs control activities (World Health Organization 2006).

Mobilization campaigns are based on carefully designed communication components that should address issues like the continuation of hygiene and diseases prevention behaviors, population perception of the risk of a specific disease, the possibility of the usage of a vaccine to provide immunity, improvements in health-seeking behavior and environment management to prevent degradation and vector reproduction etc (World Health Organization 2005; World Health Organization 2005; International Federation of Red Cross and Red Crescent Societies 2011; UNICEF 2012). Clear messages, therefore, should be designed and disseminated using several communication channels like posters, banners, leaflets, mobile phones, mass media broadcasts and community-level activities (Dadgar, Ansari et al. 2003; Valenciano, Coulombier et al. 2003; Centers for Disease Control and Prevention 2004; Global Task Force on Cholera Control 2004; Kolaczinski, Graham et al. 2005; World Health Organization 2006; Tappero and Tauxe 2011; World Health Organization 2013).

For achieving high coverage such campaigns should be produced in local languages and be visually attractive (World Health Organization 2006). Mobilization campaigns are more effective when culturally appropriate communication channels are used and issues of cultural beliefs, values and literacy level are fully respected (World Health Organization 2005). Social mobilization campaigns should ideally reach all groups of target population like representatives of the displaced or affected population, the host population, minority groups or marginalized populations, religious communities that resist public-health interventions, nomadic/migratory groups etc (World Health Organization 2005; World Health Organization 2013). Health education campaigns must also focus on the factors that influence the behavior of afflicted individuals towards certain hygiene practices. For example, norm, ability, and self-regulation factors are more important in explaining hand-washing behavior in an emergency situation than risk factors (Contzen and Mosler 2013). Health education campaigns should also focus on certain groups of the afflicted population. For instance, women should play a key role in cholera health education campaigns as they are the ones cleaning the house, preparing the meals and taking care of the children (World Health Organization 2006). For education activities to be effective special attention should also be paid to their timing (World Health Organization 2005).

Mobilization activities are crucial when immunization campaigns are implemented in CHEs (Legros, Paquet et al. 1999; World Health Organization 1999; Global Task Force

on cholera control 2006; World Health Organization 2006; Chaignat, Monti et al. 2008). Social mobilization activities provide all the necessary information the target population needs to know with respect to the risks and benefits of the vaccination campaign (Kouadio, Koffi et al. 2009; World Health Organization 2013). In addition, social mobilization messages are very important when multi-dose vaccination campaigns are implemented and target populations should be aware of the importance of taking the two doses to be protected against a specific disease (World Health Organization 2006).

Health education campaigns are very important in the case of tuberculosis control programs. Awareness of the importance of tuberculosis treatment and treatment adherence, encouragement and promotion of early presentation of tuberculosis suspects and reducing stigmatization are just a few of the goals of community education campaigns (World Health Organization 2007). Health education campaigns play also a key role in controlling vector-borne diseases like malaria. Distribution of educational leaflets and posters concerning net use can be very effective in the control of malaria (Spencer, Grant et al. 2004).

Community involvement

Social mobilization and health education activities should be closely linked to community involvement (Global Task Force on Cholera Control 2004; World Health Organization 2006). In particular, health agencies implementing outbreak prevention and control measures in emergency settings should work together with community and its organizational representatives to determine priority needs and to decide what interventions are needed to address these needs (World Health Organization 2005). According to past experience, strong community involvement was important in establishing effective surveillance systems and in mobilizing resources (World Health Organization 2005; Kouadio, Koffi et al. 2009). Community involvement can also ensure that communication activities and health education methods are socially and culturally appropriate (Connolly, Gayer et al. 2004; World Health Organization 2006).

Political and traditional leaders of the community should be invited to all major planning meetings with respect to planning and implementing health care programs within the community (World Health Organization 2005; World Health Organization 2006). Generally, affected community should be seen as a partner in, not the target of, control activities, and individuals who are well known and trusted by the community must be directly involved in planning and implementation of IDO control activities (World Health Organization 2005). For instance, the implementation of long-lasting treatments like tuberculosis control programs, require the acceptance,

trust and support of local community leaders (Rodger, Toole et al. 2002; Martins, Heldal et al. 2006; Coninx 2007; Liddle, Elema et al. 2013). Several influential individuals and groups (religious scholars etc) should be engaged by coordinating community-based activities and forging partnerships at the community level (Seddiq, Enarson et al. 2014). Leaders of the community could be given specific tasks to accomplish, like providing human resources, passing the word within their communities or even formally announcing IDO control events (World Health Organization 2013).

Community involvement is also crucial for the implementation of vaccination campaigns (Global Task Force on cholera control 2006; World Health Organization 2006). In fact, mass vaccination campaigns require strong community support particularly for the selection of the target groups (UNICEF 2012). Lessons learned include well informing the population to attain its acceptance and high coverage (World Health Organization 2012). Shortcomings in social mobilization activities and limited community involvement could jeopardize mass vaccination coverage (Chaignat, Monti et al. 2008).

4.2.2.4 Coordination and collaboration mechanisms

CHEs usually affect large geographical areas or even entire countries and a multitude of partners participate in relief efforts. Health interventions in these settings need to be implemented is a systematic way with high levels of coordination between governments, health care organizations and NGOs (Connolly, Gayer et al. 2004). Ministries of Health in affected countries are usually responsible for coordinating the overall humanitarian response. They have a strong coordination role for establishing effective partnerships with other health agencies, donors, and academic institutions, allocating resources for performing primary health actions and developing standards and indicators for monitoring and evaluation (Salama, Spiegel et al. 2004). With respect to IDOs control, coordination between partners and national authorities is usually ensured by the WHO, which also mobilizes international experts from various institutions belonging to its Global Outbreak Alert and Response Network (Gayer, Legros et al. 2007)**.** Prior to the implementation of an IDO control program one lead agency must be identified as taking responsibility for oversight of this program (Valenciano, Coulombier et al. 2003). It is also recommended that a memorandum of understanding must be developed between the program coordinator and the lead health agency (Ministry of Health, WHO etc)(World Health Organization 2007). National program leadership and stewardship are essential for quality and sustained disease control, particularly for diseases that require long course regimens and for

programs implemented in conflict areas (World Health Organization 2007; Mauch, Weil et al. 2010; Seddiq, Enarson et al. 2014).

Coordination is a key element of several aspects of IDOs control systems in CHEs. In particular, coordination is necessary for the establishment of proper surveillance mechanisms and early warning systems (Valenciano, Coulombier et al. 2003; Nicoll 2005; Pinto, Saeed et al. 2005; World Health Organization 2005; Chretien, Blazes et al. 2007; World Health Organization 2012; Polonsky, Luquero et al. 2013), the management of education, supply chain, treatment, and prevention channels (Farmer, Almazor et al. 2011), the establishment of good relationships between volunteers from NGOs and national health care workers in the field (Global Task Force on Cholera Control 2004), the implementation of collaborative disease activities targeting dual epidemics in emergency settings like, for instance, tuberculosis and HIV control programs (World Health Organization 2007) and, finally, the control of vectors (Protopopoff, Van Herp et al. 2007). Coordination is also critical for the implementation of immunization campaigns in CHEs. Such campaigns necessitate the involvement of several key-actors like local governments, international health organizations as well as NGOs and sound coordination mechanisms should be established among them (Salama, Spiegel et al. 2004; World Health Organization 2005; Kamadjeu, Assegid et al. 2011). Coordination mechanisms should be established not only in the case of immunization campaigns but also in cases where such campaigns are combined along with other preventive activities (World Health Organization 2006; Chaignat and Monti 2007; World Health Organization 2012).

During the initial phase of an emergency the provision of adequate shelter, water, food and basic health care are considered mainstays for preventing communicable diseases. Such interventions require strong coordination among agencies working at local, national and international levels. In addition, collaboration among agencies from different sectors like health, food and nutrition is also required (World Health Organization 2005; International Federation of Red Cross and Red Crescent Societies 2011; World Health Organization 2012). For guiding public health response and decision making officials need to know how a specific disease is being transmitted and which interventions are the most effective for its containment. Local authorities and operational partners, therefore, should collaborate with each other to conduct rapid field investigations and laboratory studies (Brown, Guerin et al. 2008; Tappero and Tauxe 2011).

Sound coordination mechanisms among the key players involved in CHEs can significantly increase population coverage and improve the efficiency of health interventions (Houston 1998; World Health Organization 2005; Global Task Force on

cholera control 2006; World Health Organization 2007; Tong, Valverde et al. 2011; Seddiq, Enarson et al. 2014). Coordination mechanisms assure that each disparate partner operating in the field knows exactly what other partners are currently planning or implementing and, therefore, complementarities are achieved (Seddiq, Enarson et al. 2014). Coordination committees should be formed in countries where outbreaks of specific diseases are recurrent. The aim of such committees is to strengthen collaboration mechanisms among all the parties involved and to assure the rapid and efficient execution of control activities (Global Task Force on Cholera Control 2004).

As CHEs usually involve large famine affected populations and/or internally displaced persons, no international agency has a mandate for overseeing critical aspects of humanitarian response like, for instance, the coordination of humanitarian agencies involved in relief efforts (Salama, Assefa et al. 2001). In these circumstances lack of coordination can have a very negative effect on various aspects of IDOs control. Past experience has shown that lack of coordination among the different agencies involved could hinder effective response or could lead to delays in the implementation of immunization campaigns (World Health Organization 2005; World Health Organization 2006). Lack of coordination also complicates the control of IDOs since disparate partners in field often implement overlapping health programs (Coninx 2007). A typical example is cholera, where emphasis should be placed on the coordination of all control measures like vaccination campaigns, health education activities and water and sanitation improvement projects (World Health Organization 2006).

4.2.2.5 Logistical features

The implementation of IDO control agendas in CHEs are based one heavy logistics (Rowland and Nosten 2001; Kolaczinski, Muhammad et al. 2004; Rolland, Checchi et al. 2006; Mallik, Mandal et al. 2011; Seddiq, Enarson et al. 2014). Prevention and control of IDOs in disaster settings necessitates the distribution of hygiene and sanitation supplies as well as first need articles in affected populations, particularly in the initial stage of the emergency. Among these supplies are water treatment unities, bladders, filters, equipment for pulverization, bucks, bowls, gloves, chlorine, syringes, detergent, soap, sanitary towels etc (Dadgar, Ansari et al. 2003; Global Task Force on Cholera Control 2004; World Health Organization 2005; Clasen, Smith et al. 2006; French Red Cross 2010; International Federation of Red Cross and Red Crescent Societies 2011).

Immunization campaigns in CHEs are considered logistics-intensive interventions for

several reasons. Procurement procedures, availability and distribution of vaccines, transport and storage of supplies, transport of field teams, cold chain facilities, waste management and reliable telecommunications are just a few of the logistical prerequisites of immunization campaigns in disaster settings (Centers for Disease Control and Prevention 2004; Global Task Force on cholera control 2006; UNICEF 2012; World Health Organization 2013). Several times cholera immunization campaigns have not been implemented in humanitarian settings due to shortages of crucial medical supplies (vaccines) and complex logistical and operational challenges of multi-dose regimens (Legros, Paquet et al. 1999; Lopez, Clemens et al. 2008; Date, Vicari et al. 2011; Tappero and Tauxe 2011; UNICEF 2012; Weil, Ivers et al. 2012). In the sequel several logistical prerequisite of IDO control interventions are analyzed in detail.

Waste management

Medical waste related to IDO control interventions includes needles, scalpels, laboratory samples, disposable materials stained with body fluids, and body tissue. Waste management is very important and should be planned prior to the implementation of IDO control actions (World Health Organization 2006). Such a waste should be burnt in an incinerator (World Health Organization 2005). During the implementation of vaccination campaigns a large amount of immunization and bio-medical waste is also generated. To ensure safe disposal of this waste appropriate medical waste management procedures should be followed (Connolly, Gayer et al. 2004; Mallik, Mandal et al. 2011). Used syringes, vaccine safety boxes and generic waste related to the preparation and use of the vaccine (cups, vials, boxes, etc.) should be collected and appropriately destroyed (Dadgar, Ansari et al. 2003; World Health Organization 2006).

Procurement

The procurement process involves activities like the identification of potential suppliers and relevant costs (cost of supplies, freight, insurance, customs duties or taxes etc) as well as the estimation of leading times (time from placing the order to the arrival of drugs/medical supplies) (Centers for Disease Control and Prevention 2004; World Health Organization 2007). A coordinated approach is essential if adequate supplies of good quality are to be purchased (World Health Organization 2005). During the cholera response in Haiti an estimated 25% of goods used were purchased locally (i.e. buckets, bars of soaps, sprayers for disinfections, disposable gloves) whereas the rest came from overseas (i.e. medical equipment and consumable) (International Federation of Red Cross and Red Crescent Societies 2011). Lessons learned clearly suggest that mismanagement of procurement

processes can negatively affect the implementation of disease control activities in humanitarian settings (Rolland, Checchi et al. 2006). Decisions related to vaccines' procurement are hard to make, particularly due to vaccines' limited life cycle and the possible obsolescence risks. Such risks can be managed through the establishment of reserved rather than pre-paid vaccines stockpiles. In this case the risk of unused purchased vaccine is minimized and at the same time the availability of vaccines' supply is assured (World Health Organization 2012).

Cold chain requirements

Medical supplies used during the containment effort of IDOs should be kept in either cold temperatures (usually at 2–8°C) or at temperatures ranging up to 25 or 30°C so that their potency and bioavailability are maintained (Arya and Agarwal 2012). For example, most rapid diagnostic tools for malaria should be stored and transported within the temperature range of 4–30 °C since they are sensitive to both moisture (humidity) and high temperatures (World Health Organization 2005). The implementation of mass immunization campaigns in CHEs also necessitates the establishment of a cold chain since most vaccines require refrigeration until the time of their administration (Legros, Paquet et al. 1999; Sharp, Burkle Jr et al. 2002; Centers for Disease Control and Prevention 2004; World Health Organization 2005; World Health Organization 2006; Mallik, Mandal et al. 2011; World Health Organization 2013). Prior to the implementation of a mass vaccination campaign an assessment should be made regarding the needs of cold chain facilities at all levels (World Health Organization 2006). Cold chain equipment like refrigerators, freezers, cold boxes, vaccine carriers, ice- packs, thermometers and temperature monitors are required to ensure that the vaccine cold chain has been properly maintained (World Health Organization 1999; World Health Organization 2005).

The establishment of a vaccine cold chain remains a logistics-intensive activity in CHEs not only because cold chain facilities are scarcely available in emergency settings but also due to the important volume of some vaccines. For example, the two pre-qualified by the WHO oral cholera vaccines require cold chain maintenance and present packed volumes larger than those of other Expanded Program on Immunization (EPI) vaccines. Past experience has shown that this important volume can complicate both the storage in, and the transport of the vaccines from the provincial center to the cities and thereafter to the vaccination sites (World Health Organization 2006; Date, Vicari et al. 2011). Improper storage and distribution activities in the cold chain might result in high vaccine waste (Global Task Force on cholera control 2006; World Health Organization 2006). In fact, the implementation of a mass vaccination campaign shouldn't be an option in the presence of an insufficient vaccine cold chain (Tappero and Tauxe 2011). Past experience has show

that public health officials had to find new and rather unorthodox ways of maintaining the vaccine cold chain (use of local sources of ice, use of local fisheries that had cold storage facilities etc) (Dadgar, Ansari et al. 2003; Calain, Chaine et al. 2004).

Laboratory logistics

Early detection of a suspected IDO relies on sound laboratory services. Managing the logistics in support of laboratory services encompasses a range of activities like specimen collection (recording, labeling/identification of specimens and packaging), transportation and storage as well as training of technicians for monitoring the quality of the examinations. It also entails the stockpiling of essential drugs, reagents, supplies and outbreak investigation kits (Houston 1998; Connolly, Gayer et al. 2004; Global Task Force on Cholera Control 2004; Pinto, Saeed et al. 2005; World Health Organization 2005; Gayer, Legros et al. 2007; World Health Organization 2012). All specimens should be placed in appropriate media and stored at recommended temperatures so that their bacterial or viral viability are preserved. A cold chain should also be established during their transportation where safety and cold boxes must be used so that optimum specimen management is achieved (World Health Organization 2005).

Stockpiling of supplies

Stockpiling of essential medical supplies is critical for assuring the availability of these supplies, particularly during the initial phase of an emergency where a great number of people is likely to seek medical treatment (World Health Organization 1999; Global Task Force on Cholera Control 2004; Nicoll 2005; World Health Organization 2005; World Health Organization 2005; Bracho, Varela et al. 2010; Farmer, Almazor et al. 2011; Tappero and Tauxe 2011). The implementation of immunization campaigns also relies on the establishment of adequate stockpiles of vaccines as well as supplementary supplies (auto- destruct syringes, safety boxes etc) (World Health Organization 1999; Global Task Force on cholera control 2006; Vijayaraghavan, Lievano et al. 2006; World Health Organization 2006). In view of changing political conditions and lack of security stockpiling of supplies may safeguard the continuity of health care interventions, particularly of lengthy ones like tuberculosis and malaria control programs (Rolland, Checchi et al. 2006; Coninx 2007; Liddle, Elema et al. 2013; Seddiq, Enarson et al. 2014). Stockpiling of supplies has also been used in emergencies as a buffer for managing delays during the procurement phase (International Federation of Red Cross and Red Crescent Societies 2011).

Vaccines are the most critical medical items that will be used in the forefront of any public health intervention. The cholera epidemic in Haiti has highlighted the importance of establishing an international vaccine stockpile to guarantee vaccine supplies and their rapid deployment (Waldor, Hotez et al. 2010; Date, Vicari et al. 2011; World Health Organization 2012; Von Seidlein, Jiddawi et al. 2013). In particular, the limited global cholera vaccine supply and Haiti's insufficient cold chain capabilities acted as barriers for the implementation of a mass immunization campaign in 2010 (Tappero and Tauxe 2011). Several studies indicate that a strategic deployment of 5 million doses of oral vaccine coupled with other health interventions in the 2010 epidemic in Haiti would have halved the number of cholera cases and deaths (Plotkin, Shin et al. 2011; Holmgren 2012). A global stockpile could assure the availability of vaccines, would reduce the projected high costs of mass immunization campaigns, would increase the demand and supply and would further motivate vaccine manufacturers to overcome their inability to produce large stocks without a firm demand (Date, Vicari et al. 2011; UNICEF 2012). Such a stockpile would be maintained on a rotating stock basis (World Health Organization 2012). A creation of a stockpile of at least 2 million doses of oral cholera vaccine (OCV) in epidemic settings was recommended at the 2011 WHO consultation on OCV stockpile and confirmed in a 2012 WHO consultation (UNICEF 2012). For establishing an OCV stockpile several issues had to be addressed like the size of the stockpile, the shelf-life of the vaccine, manufacturers' capabilities, production and inventory costs etc (World Health Organization 2012).

Vaccines' fieldability

The administration course of a vaccine and relevant logistical prerequisites (establishment of a cold chain, provision of buffer solution or clean water during its administration) should be paid special attention during the planning and implementation of vaccination campaigns in disaster settings (World Health Organization 2013). Several characteristics of the vaccine itself (shelf-life, required storage conditions, volume, number of doses administered, time to provide herd immunity) give rise to a series of questions that merit more detailed examination (Global Task Force on cholera control 2006). For example, planning and implementation of a multi-dose immunization campaign in settings characterized by shortages of human resources, erratic access to populations due to insecurity, limited cold-chain capacities, highly mobile populations and destroyed health system infrastructure require heavy logistics (Date, Vicari et al. 2011; World Health Organization 2013). Past experience has shown that a two dose vaccine presents major logistical and financial constraints to mount an effective vaccination campaign (World Health Organization 2012). In addition, vaccine's short shelf-life might also be a barrier, particularly for those vaccines that are administered in two doses (the

administration of the second dose should be carried out within short time frames in order loss of the stock be avoided) (Global Task Force on cholera control 2006). Generally, in resource-constrained settings certain vaccine's characteristics could pose logistical barriers to mount an efficient vaccination campaign, thus limiting the so-called vaccine's fieldability.

The use of OCVs in humanitarian emergencies (in either endemic or epidemic settings) and particularly the logistical prerequisites of their usage has been a controversial issue for years in public health literature. The currently available and internationally licensed two-dose OCVs require two doses to be administered within a short time frame (at least a 1-week), thus making their deployment in disaster settings a logistically difficult task (Holmgren 2012). Past experience has shown that the bulkiness of the vaccines and the requirement for buffer solution further complicated storage and shipment and, therefore, increased cold chain requirements for their deployment were needed (Legros, Paquet et al. 1999; Global Task Force on cholera control 2006; World Health Organization 2006; Chaignat, Monti et al. 2008; Lopez, Clemens et al. 2008; Date, Vicari et al. 2011). The rate of vaccine administration of OCVs is low compared with mass vaccination campaigns using injectable vaccines. This is a major problem for children and individuals under 2 years of age as the time needed to prepare the vaccine, especially the buffer solution, and the time needed to drink the vaccine, is significant (Legros, Paquet et al. 1999). Finally, the two-dose OCVs may complicate the keeping of logs in disaster settings as usually a specific vaccination card must be distributed during the first round of the campaign and any person coming to the second round without a vaccination card shouldn't be given the vaccine (Legros, Paquet et al. 1999).

4.2.2.6 Prioritization of actions

In CHEs several issues of health prioritization arise since resources to implement health interventions are usually scarce (health care personnel, frontline aid workers, medical supplies, infrastructures etc). For example, qualified public-health personnel are consistently in short supply, particularly at the onset of an emergency. Their engagement in lengthy immunization campaigns could adversely affect the relief effort and hamper other life-saving health interventions (World Health Organization 2013). During the implementation of vaccination campaigns target age groups may need to be reduced due to limited well-trained health care personnel, lack of security and limited vaccine supplies (Grais, Strebel et al. 2011).

Issues of prioritization of different vaccination campaigns in terms of urgency could also arise. Based on epidemiological risk assessments highly infectious diseases should be given priority in terms of timely delivery of the vaccine (World Health Organization 2013). For example, the fact that measles mass vaccination campaigns are considered health priority in CHEs (they are usually undertaken shortly after the onset of an emergency) means that other mass vaccination campaigns (for instance, cholera vaccination campaigns) should be delayed, particularly in the presence of limited human resources (Chaignat, Monti et al. 2008). Certain risk groups should also be given priority in CHEs as, for example, the vaccination of all displaced children against measles (Chaignat, Monti et al. 2008). Immunization campaigns in CHEs should be organized in such a way that their impact on other health activities is minimized, particularly in terms of human resources needed. In addition, they should be carried out during the weekends so that they don't interfere with the regular functioning of health services (Legros, Paquet et al. 1999).

Health officials opposing the implementation of immunization campaigns in CHEs have argued that such campaigns might divert attention from other more cost-effective interventions (Holmgren 2012). Generally, past experience has revealed that in CHEs the question of feasibility and relevance of health interventions, as well as the prioritization of health needs remain crucial and should be addressed prior to any decision for the initiation of an immunization campaign (Chaignat, Monti et al. 2008; Date, Vicari et al. 2011). In addition, the relative benefits of a mass vaccination campaign are difficult to be defined as their estimation requires the development of specific tools for risk assessment (Von Seidlein, Jiddawi et al. 2013).

4.2.2.7 Political aspects

CHEs are usually associated with highly charged, unstable political conditions where tensions between ruling government and parts of its population or between local authorities and humanitarian community, may exist (World Health Organization 2013). IDOs in these settings are often considered a sensitive event and could be complicated by political ramifications (World Health Organization 2012). Under these conditions, IDOs control actions could be politicized and become the subject of contention (World Health Organization 2013). Limited resources further exacerbate the already politically stretched conditions. For example, in the presence of limited vaccine supply the identification of an equitable and politically acceptable target population might be impossible (Date, Vicari et al. 2011). In addition, vaccination administered to only specific geographic areas may create tension among the affected population, necessitating justifications why certain groups are eligible for vaccination while others are not (World Health Organization 2013). On the other

hand, through the so-called vaccine diplomacy leading health care organizations and governments have successfully negotiated cease-fires in many conflict-affected regions worldwide. In particular, vaccine diplomacy relies on the establishment and use of sufficient vaccine supplies to advance a government's diplomatic aims of promoting peace and stability in certain conflicted-affected regions (Waldor, Hotez et al. 2010).

In CHEs government commitment for the implementation of control interventions is initially absent or completely lacking because of the very nature of such emergencies, particularly in the initial phase. Several priorities emerge and local governments are unable to commit resources to perform control interventions. In these circumstances, commitment from a lead agency may be a suitable replacement strategy (Coninx 2007). According to the WHO, political commitment is a critical element for successfully implementing tuberculosis control programs in CHEs (World Health Organization 2007). Tuberculosis control programs in these settings should enjoy commitment from the highest political level in order to achieve sustained implementation. Such a commitment should encompass a range of key players like local governments, leading health care organizations, NGO's and donors' community (Seddiq, Enarson et al. 2014). In Somalia an overall cure/treatment completed rate of 70% was achieved by a short course regimen where political commitment was a major contributor to this success (Rodger, Toole et al. 2002). Political commitment is also critical for the implementation of immunization campaigns in CHEs (Farmer, Almazor et al. 2011; World Health Organization 2012). Past experience has shown that vaccination campaigns were facilitated by the strong political commitment of both national and international partners (Chaignat, Monti et al. 2008).

4.2.2.8 Cultural aspects

Successful IDOs control depends on agencies understanding communities and communities understanding and using prevention and treatment measures. In this respect, cultural aspects and misbeliefs may act as a barrier for the implementation of IDOs control actions in CHEs. Health agencies may be unaware of the reasons why the target population fails to appreciate the merit benefits of control actions (World Health Organization 2005). These "understanding the community" aspects are critical for the successful implementation of control actions. Experience in planning and implementing mass immunization campaigns in low-income settings has revealed that cultural behaviors are key elements to be examined (Global Task Force on cholera control 2006; World Health Organization 2006). The same holds for

diseases necessitating lengthy treatment protocols like, for instance, tuberculosis (Hehenkamp and Hargreaves 2003).

With respect to malaria control, behavioral research has revealed that families often do not bring children with severe malaria for treatment because they believe that the cause of the disease is of spiritual nature and, therefore, it would be better the disease be treated by traditional healers within the community (World Health Organization 2005). Moreover, specific malaria control actions like, for example, the distribution of nets should be based on a clear understanding of the sleeping habits and practices of affected communities (World Health Organization 2005). Under these circumstances, social and behavioral research is crucial for designing effective interventions and might shed light on why a particular intervention fails to be accepted by the affected community (World Health Organization 2005).

For specific diseases the stigma attached to them can hinder the successful implementation of control interventions. A typical example remains cholera where the stigma attached to the disease deters people from actually reporting cases for fear of travel and trade sanctions, an obstacle that negatively affects surveillance (Chaignat and Monti 2007). Even worst, such a stigmatization means that many cholera sufferers might not seek prompt medical attention, at least not until their symptoms are severe (International Federation of Red Cross and Red Crescent Societies 2011). Stigma also prevents effective cadaver management as many funeral parlors refuse cadavers from patients who have died of cholera. Health care workers have encountered resistance to building treatment sites because local communities considered these facilities as a source of infection (Farmer, Almazor et al. 2011). For instance, during the initial stages of the response to cholera in Haiti, communities demonstrated a series of misconceptions over cholera's origin, spread and treatment mechanisms, leading to significant stigma towards sufferers. From an operational perspective, this meant that cholera treating points once established were violently attacked by neighboring communities who believed that by providing treatment to cholera patients relief organizations would be introducing cholera into their area (International Federation of Red Cross and Red Crescent Societies 2011).

Managing cadavers of people who have died of cholera poses many challenges, including honoring cultural practices related to dying and death, disinfecting cadavers, and identifying acceptable by the community burial sites (Farmer, Almazor et al. 2011). Funerals for people who have died of cholera can contribute to the spread of an epidemic and, therefore, certain hygiene measures should be taken. Health care workers designated at the funeral site can provide assistance and supervise the use of these hygienic measures (Global Task Force on Cholera Control

2004). Generally, the corpses of people who have died of cholera should be treated with disinfectants and hygiene solutions. Special attention should also be given to their transportation where corpse-carriers should wear gloves and corpses should be carefully wrapped. In addition, physical contact between close family members and the corpse should be prevented (Global Task Force on Cholera Control 2004).

4.2.2.9 Epidemiological and socio-demographic characteristics of affected populations

Prior to the implementation of IDOs control actions a thorough assessment relevant to epidemiological features of the affected population as well as its living conditions and health status should be carried out (World Health Organization 2005; Global Task Force on cholera control 2006). Target populations might vary by antigen, which means that some vaccines should be administered to wide age ranges and others to a smaller subset. By doing so, the exact quantity of vaccines required could also be determined (World Health Organization 2013). Populations experiencing cholera outbreaks often have limited background natural immunity to cholera and it should be assured that the vaccine used confers immunity to all age groups and all age groups are also targeted (Plotkin, Shin et al. 2011). Estimating the target age range eligible for vaccination is a difficult task. For this estimation health officials should be based on the expected age distribution of cases within the affected population (World Health Organization 2013). Obviously, when age distribution of cases is not known, as a precautionary measure it is better to overestimate, rather than underestimate the target population for vaccination (World Health Organization 2013).

Some particularities of specific diseases should be kept in mind. A typical example is measles where due to the increase of vaccination coverage worldwide, measles outbreaks have become less frequent and a noticeable shift of the age distribution of cases towards older age groups has gradually taken place (Grais, Strebel et al. 2011). Past experience has shown that measles outbreak could be characterized by an unusual age distribution where the median age of patients recorded in outbreaks was 23 years, with 75% of patients aged 15 years or older. The current recommendations for vaccinating all children aged 6 months to 15 years against measles seems not to take into account the aforementioned shift of age distribution, suggesting that a wider age group could be potentially benefitted from vaccination (Polonsky, Ronsse et al. 2013). Therefore, taking into account the year in which routine measles vaccination was introduced into a country provides valuable

information for determining the possible immunity profile of individuals within the affected population (Grais, Strebel et al. 2011).

4.2.2.10 Funds

Planning and implementation of communicable disease control interventions in CHEs require substantial financial resources (Global Task Force on Cholera Control 2004; World Health Organization 2005; Martins, Heldal et al. 2006; World Health Organization 2007; Farmer, Almazor et al. 2011; Tappero and Tauxe 2011; Tong, Valverde et al. 2011). Sustained financial resources are critical in the case of tuberculosis control programs where an uninterrupted supply of drugs should be maintained over a relatively long period of time (Rodger, Toole et al. 2002). Apart from drug supplies, tuberculosis control programs also require sufficient program funding to operate for at least twelve months (Houston 1998; World Health Organization 2007; Mauch, Weil et al. 2010). Stopping a successful program solely for lack of funds would be medically and ethically undesirable and, therefore, actions that assure sustained funding should be proactively taken (World Health Organization 2007). On the other hand, insufficient funding mechanisms or delayed funding decisions can negatively affect the implementation of control actions (World Health Organization 2005).

The implementation of immunization campaigns in CHEs also requires substantial and long term financial commitment from health agencies, governments and donors (Farmer, Almazor et al. 2011; Kamadjeu, Assegid et al. 2011). In fact, financing of any vaccination campaign should be assured prior to the decision to implement it (World Health Organization 2013). According to the World Health Organization, substantial financial resources are required for the establishment of an international vaccine stockpile which will guarantee vaccine supplies and their rapid deployment when necessary (World Health Organization 2012; World Health Organization 2012). Lessons learnt also indicate that substantial financial resources are necessary during the implementation of any cholera vaccination campaign in CHEs (World Health Organization 2006; Chaignat, Monti et al. 2008).

Funding received from donors can significantly help the implementation of IDO control actions, particularly in the initial stage of an emergency situation (Centers for Disease Control and Prevention 2004; Global Task Force on Cholera Control 2004; Seddiq, Enarson et al. 2014). Through rapid assessments of critical items needed, international relief community can mobilize donors' community to donate such items and subsequently distribute them to affected populations (International

Federation of Red Cross and Red Crescent Societies 2011). Finally, donations of critical medical supplies such as vaccines may form part of the strategy for timely access to vaccines in emergencies (World Health Organization 2013).

4.2.2.11 Information management

Timely and accurate data obtained from Health Information Systems (HIS) are essential for effectively responding to CHEs (Connolly, Gayer et al. 2004). Generally, three types of data are obtained through HIS (1) rapid health assessments (2) surveys, (gathering population-based health data) and (3) surveillance (Connolly, Gayer et al. 2004). Therefore, the main task of a HIS is to determine priority needs and assist in allocating available resources (Thieren 2005). Geographical information systems (GIS) are also used in CHEs. Such systems are used for investigating disease outbreaks, establishing HIS, integrating data and programs and monitor and evaluate health care interventions (Kaiser, Spiegel et al. 2003; Kolaczinski, Graham et al. 2005). However, obtaining accurate data in a timely manner in CHEs is a difficult task (Maxwell and Watkins 2003; Thieren 2005). Lack of political support and governmental authority is usually the norm in CHEs and negatively affect the establishment if HIS as no one seems to be in charge (McDonnell, Perry et al. 2007). Fragmented, incomplete or even contradictory statistics can be generated by poorly integrated HIS (Maxwell and Watkins 2003; Thieren 2005).

Surveillance mechanisms

The establishment of an early warning (EWARN) surveillance system in CHEs is of paramount importance for monitoring disease trends and detecting any possible outbreak (World Health Organization 2012). Well-established and reliable surveillance systems allowing for rigorous data collection, compilation and analysis may guide control interventions in CHEs. Surveillance data is necessary for determining the best timing for cholera vaccination as well as monitoring the outcome of the campaign (Chaignat and Monti 2007). A routine surveillance system not only predicts outbreaks but also helps epidemiologists to confirm an outbreak in settings where a sudden increase in cases of deaths from acute diarrheal syndrome is reported (Global Task Force on Cholera Control 2004). Surveillance systems may have a better predictive potential when combine information of seasonal outbreak risks prevalent to certain areas with GIS (Bruckner and Checchi 2011). In disaster settings, particularly in the acute phase where sophisticated data collection and analysis may be difficult, surveillance systems may rely on both formal and informal networks of informants (Waring and Brown 2005; Bruckner and Checchi 2011). Surveillance systems in these settings also necessitate sharing of information among

key-players involved like leading health agencies and local governments (Polonsky, Ronsse et al. 2013).

4.2.2.12 Cost aspects

Cost aspects of IDO control actions may relate to health staff salaries, training of health care personnel, transport of staff and supplies, stationery and other clinic needs, drugs and other medical supplies, social mobilization campaigns, general operational expenses etc (World Health Organization 2007; Chaignat, Monti et al. 2008). Cost aspects remain critical, however, as logistical and operational constraints could significantly increase the overall expenses of IDO control activities (Chaignat, Monti et al. 2008). In fact, past experience has shown that the usage of the same vaccine in different settings generates completely different costs. This difference in costs generated is largely attributable to several logistical and operational shortfalls prevalent in each setting (Chaignat and Monti 2007). For example, the volume and weight of vaccine can significantly increase the cost of its transportation and storage (World Health Organization 2006). Immunization campaigns with multi-dose regimens may also result in high vaccine wastage and, therefore, increased direct costs during the implementation of these campaigns (Global Task Force on cholera control 2006; World Health Organization 2006; Chaignat and Monti 2007). Vaccination campaigns implemented in countries where routine vaccination has been ceased or cold chain infrastructure is absent (due to protracted conflict) are accompanied by substantial increases in costs (Vijayaraghavan, Lievano et al. 2006). In addition, the cost of the vaccine itself is also a critical parameter (Legros, Paquet et al. 1999). Purchasing costs of the two available and pre-qualified cholera vaccines, for example, remain too high to be deployed in programs for the poor in either endemic or epidemic settings (Legros, Paquet et al. 1999; Lopez, Clemens et al. 2008; Plotkin, Shin et al. 2011). Limited usage of these vaccines also implies that production costs remain high and are not covered by the price of the vaccine (Global Task Force on cholera control 2006).

Cost-effectiveness of health care programs implemented in CHEs is also critical. For example, in tuberculosis control programs special attention should be paid to the trade-off between the extra costs of treating relapses and failures and the savings in future treatment costs (Biot, Chandramohan et al. 2003). Malaria control programs also present several challenges in terms of their cost- effectiveness. For instance, indoor residual spraying had been the mainstay of malaria control in many countries. In a chronic emergency situation, however, such a method could no longer be implemented due to high costs. Under conditions, the usage of insecticide-treated

nets could be a viable solution, particularly for chronic emergencies where funds from donors community substantially decrease over time (Rowland and Nosten 2001; Kolaczinski, Muhammad et al. 2004; World Health Organization 2005; Howard, Shafi et al. 2010). The same trade-offs exist for the usage of different diagnostic tools for malaria (rapid diagnostic tools vs microscopic diagnosis) (World Health Organization 2005).

4.2.2.13 Miscellaneous

Other aspects of IDO control in humanitarian settings that merit attention include:

- *Ethical considerations*: Due to the multitude of constraints prevalent in CHEs a series of ethical issues is raised related to both the humanitarian personnel providing health aid and to the populations receiving this aid (distributive justice, fair allocation of scarce resources, maximization of the utility of these resources, lack of optimum care etc) (Coninx 2007; Sheather and Shah 2011; Moodley, Hardie et al. 2013; World Health Organization 2013).
- *Prevalence of more than one disease*: A typical example is tuberculosis control programs where their implementation is further complicated by the concurrent epidemic of HIV/AIDS (Coninx 2007; World Health Organization 2007; Kimbrough, Saliba et al. 2012).
- *Volunteers*: In the absence of qualified health care personnel volunteers may have a key role to play in carrying out certain tasks. In particular, volunteers can be actively engaged in health care programs at the community level by carrying out supporting tasks like awareness-raising activities as well as mapping of priorities and needs of the affected populations (World Health Organization 2005; International Federation of Red Cross and Red Crescent Societies 2011).
- *Food and nutrition*: Malnutrition and food shortages are common features in CHEs. Malnourished people have compromised immunity system and are more susceptible to infectious diseases. Therefore, food shortages can have a negative effect on the nutritional status of affected populations, thus increasing the incidence of certain communicable diseases (like, for example, vitamin A deficiency and measles)(Houston 1998; World Health Organization 2005).
- *Sanitation:* Accesses to safe water and proper sanitation, as well as hygiene promotion are considered mainstays of IDO prevention and control in humanitarian emergency settings, particularly for diarrheal diseases (like cholera). Improvements in environmental management and sensitization on issues of water, latrine use, and hygiene are vital features of any water and

sanitation program in CHEs (Calain, Chaine et al. 2004; Connolly, Gayer et al. 2004; Global Task Force on Cholera Control 2004; Nicoll 2005; World Health Organization 2005; Doocy and Burnham 2006; Global Task Force on cholera control 2006; Chaignat, Monti et al. 2008; French Red Cross 2010; Farmer, Almazor et al. 2011; International Federation of Red Cross and Red Crescent Societies 2011; Tappero and Tauxe 2011; Kouadio, Aljunid et al. 2012).

- *Monitoring of health care programs:* The implementation of health care programs in CHEs can be compromised if close monitoring does not take place. This is particular true for diseases requiring lengthy control programs (like tuberculosis) where inadequate treatment protocols can do more harm than good (Biot, Chandramohan et al. 2003; World Health Organization 2007). The same holds for vector control programs ((Rowland and Nosten 2001; World Health Organization 2005) as well as immunization campaigns (Global Task Force on cholera control 2006; World Health Organization 2006; Date, Vicari et al. 2011; Mallik, Mandal et al. 2011).
- *Case management*: Active case management and case detection are critical for controlling IDOs. Certain case definitions must be developed for each disease and should be followed by all players (NGO's, governmental health organizations etc) so that consistency in reporting to the surveillance systems is assured (Hehenkamp and Hargreaves 2003; World Health Organization 2005; World Health Organization 2007; International Federation of Red Cross and Red Crescent Societies 2011; Tong, Valverde et al. 2011).
- *Vector control*: Certain diseases like malaria, dengue, and trypanosomiasis are spread by vectors (Connolly, Gayer et al. 2004). Vector control in this case may include the usage of insecticide-treated nets, indoor residual spraying for malaria, and traps for tsetse flies that transmit trypanosomiasis etc (Connolly, Gayer et al. 2004; Kolaczinski, Muhammad et al. 2004; Kolaczinski, Graham et al. 2005; World Health Organization 2005; Protopopoff, Van Herp et al. 2007).
- *Targeted therapies and adherence to treatment protocols*: IDOs control activities (protocols and drug treatment regimens) should be based on current WHO best practice guidelines if optimal cure targets are to be attained (Houston 1998; Rodger, Toole et al. 2002; World Health Organization 2007). For example, the use of fixed-dose combination drugs in tuberculosis control is highly recommendable in disaster settings as it reduces the risk of promoting resistance and ensures better cure rates (World Health Organization 2007). Close follow up of patients as well as compliance in settings where insecurity prevails are also an asset (Hehenkamp and Hargreaves 2003; World Health Organization 2005). Finally, patient adherence to treatment protocols is essential to ensure the cure of the patient as well as the prevention of drug resistance (Martins, Heldal et al.

2006; World Health Organization 2007; Liddle, Elema et al. 2013).

- *Resiliency and continuation of health care programs*: The implementation of IDOs control programs may be interrupted as a result of population movements, lack of funding, disruptions in logistics, shortages in health care personnel and changing security conditions. For tuberculosis control programs such interruptions confer an increased risk of relapse and might increase the odds of drug resistance (Biot, Chandramohan et al. 2003; Mauch, Weil et al. 2010). Therefore, the sustainability and resilience of IDOs control programs in humanitarian emergencies is critical and alternative plans should be put in place to deal with the inherent uncertainties of such emergencies (Hehenkamp and Hargreaves 2003; World Health Organization 2007; Liddle, Elema et al. 2013; Seddiq, Enarson et al. 2014).
- *Infrastructure*: In the aftermath of natural disasters or complex emergencies basic infrastructure and health facilities are usually damaged and disrupted (World Health Organization 2005; Global Task Force on cholera control 2006; Martins, Heldal et al. 2006; Vijayaraghavan, Lievano et al. 2006; Date, Vicari et al. 2011; Von Seidlein, Jiddawi et al. 2013). In these settings IDOs control measures are hard to be implemented (World Health Organization 2005; Mallik, Mandal et al. 2011). For overcoming such an obstacle and to ensure that population has access to treatment points temporary health care facilities must be established (independent treatment sites, vaccination stations etc) within the affected region (World Health Organization 1999; Global Task Force on Cholera Control 2004; World Health Organization 2005; French Red Cross 2010; Farmer, Almazor et al. 2011). Special attention should also be paid during the establishment of shelters (site planning) to ensure rational utilization of space, access to clean water, adequate solid waste management etc (Connolly, Gayer et al. 2004; Kouadio, Aljunid et al. 2012).

4.3 Implementation of cholera vaccination campaigns in complex humanitarian emergencies: A DEMATEL-based approach

Disruptions in water and sanitation infrastructure as well as overcrowding caused by large population displacements may create the ideal environment for the propagation of cholera strains (Date, Vicari et al. 2011). Cholera patients suffer from severe dehydration and electrolyte imbalance due to constant diarrhea. Past experience has shown that cholera outbreaks can be devastating and the disease, if left untreated, could lead to death in 50% of the cases (Kelvin 2011). For instance, an estimated 12,000 refugees died of cholera in the Goma refugee camp of the Democratic Republic of Congo in 1994 (Plotkin, Shin et al. 2011; Von Seidlein, Jiddawi et al. 2013). Thousands of people have also died by the cholera outbreak in Haiti and

many more have been sickened (Adams 2013).

Timely and proper case management of cholera patients, improvements in sanitary conditions and access to clean drinking-water and mobilization of communities have been reported as mainstays of preventing cholera outbreaks (World Health Organization 2010). Complementary to the aforementioned preventive strategies the World Health Organization also recommends the use of OCVs in both endemic and epidemic settings provided that a set of requirements can be met (Global Task Force on cholera control 2006). Past experience has shown that preemptive administration of OCVs (before the onset of the outbreak) could be feasible in emergency settings as long as target populations are stable (living inside organized camps) and security issues have been resolved (Connolly, Gayer et al. 2004; World Health Organization 2006; Desai and Clemens 2012). For instance, a vaccination campaign with a two-dose OCV targeting nearly 44,000 refugees living in stable camps was successfully implemented in Northern Uganda in 1997 (Legros, Paquet et al. 1999). Another successful cholera vaccination campaign was also implemented in Southern Darfur in 2004 where more than 40,000 internally displaced persons were administered a two-dose OCV (UNICEF 2012). Significant vaccine coverage was achieved in both cases.

On the other hand, reactive vaccination campaigns (after the onset of an outbreak) continue to be debated as the implementation of such campaigns remains still a difficult task in humanitarian emergencies (Desai and Clemens 2012). In addition, experience and guidelines for reactive use of OCVs after an outbreak has started are limited (Date, Vicari et al. 2011). Heavy logistics related to the deployment of the vaccine, limited health-care personnel, vaccine's shortages and civil unrest are reported as just a few among the problems public health officials are faced with when engaging into a mass vaccination campaign in these settings. For example, during the cholera outbreak in Haiti vaccination was not eventually implemented because of limited vaccine supply, heavy logistical and operational challenges of the multi-dose regimen, population movements and luck of security (Date, Vicari et al. 2011). For the same reasons the World Health Organization didn't authorize the implementation of a cholera vaccination campaign in Iraq (World Health Organization 2007).

During 2006 the World Health Organization issued some recommendations regarding the use of a prequalified oral cholera vaccine in CHEs. According to these recommendations the use of the specific vaccine is not recommended once a cholera outbreak has begun due to its 2-dose regimen and the time required to reach protective efficacy, high cost and the heavy logistics associated with its use. Prioritization of interventions is also critical as a cholera vaccination campaign could

divert attention from programs simultaneously implemented for addressing other public-health priorities. In the light of these considerations, WHO developed a three-step decision-making framework for assessing the potential use of OCVs in emergency settings (Figure 27). The framework consists of the following steps: a) assessment of the risk of cholera outbreak (epidemiology, level of sanitation and hygiene of affected populations etc), b) assessment of the capacity to contain a potential outbreak (surveillance systems, key-partners involved etc) and c) assessment of the feasibility of an OCV campaign (vaccines' availability, logistics, access issues etc) (Global Task Force on cholera control 2006).

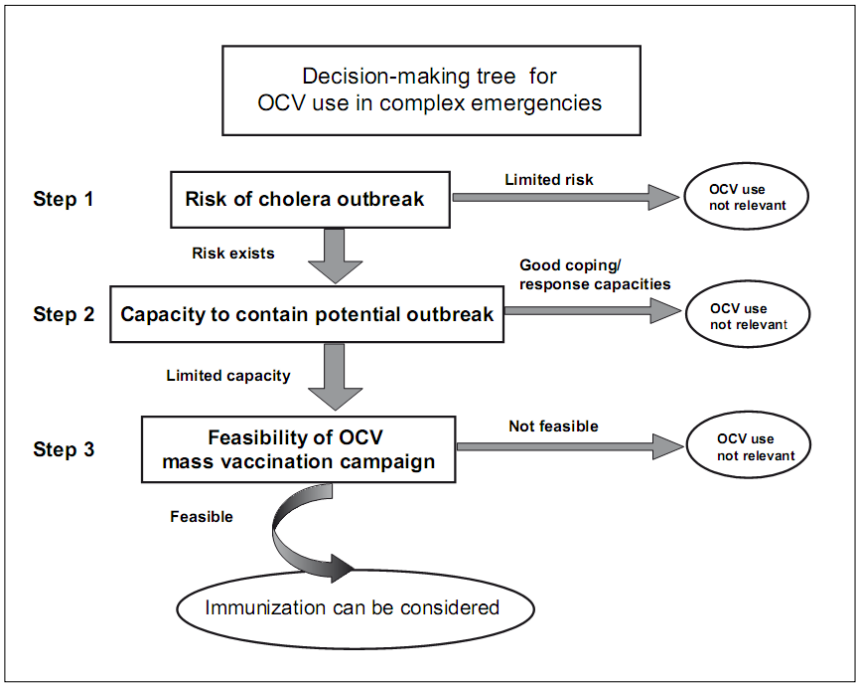


Figure 27: Decision-making framework for OCV use in CHE. Adapted from (Global Task Force on cholera control 2006)

Although several factors affecting the implementation of cholera vaccination campaigns have already been incorporated within the decision-making framework described above limited attention has been paid to their interrelationships, particularly causal relationships among them. Such interrelationships between the most important among these factors, in particular, may prove critical for the successful implementation of immunization campaigns. The present study attempts to address this concern. Based on a systematic survey of the literature and a thematic content analysis several critical factors affecting the implementation of cholera immunization campaigns in CHEs are identified. Following some experts' responses the description and analysis of the interrelationships among these factors are given through the usage of the Decision Making Trial and Evaluation Laboratory (DEMATEL) method. Several managerial implications are derived from the analysis.

4.3.1 Literature review and thematic content analysis

A systematic literature search was conducted followed by a thematic content analysis for identifying critical success factors for the implementation of cholera vaccination campaigns in CHEs. For carrying out the systematic review several features of the Enhancing Transparency in Reporting the synthesis of Qualitative research (ENTREQ) statement were used (Tong, Flemming et al. 2012).

4.3.1.1 Search strategy

The literature review spans the period January 1994 to June 2014. The search was conducted during November 2013 and was subsequently updated during June 2014 targeting relevant peer-reviewed journal articles. The search included Scopus, PubMed and grey literature (several targeted websites of organizations like the World Health Organization, the Pan American Health Organization, the Doctors without Borders, the International Federation of Red Cross and Red Crescent Societies, etc). In Figure 28 a flowchart of the overall search strategy is presented.

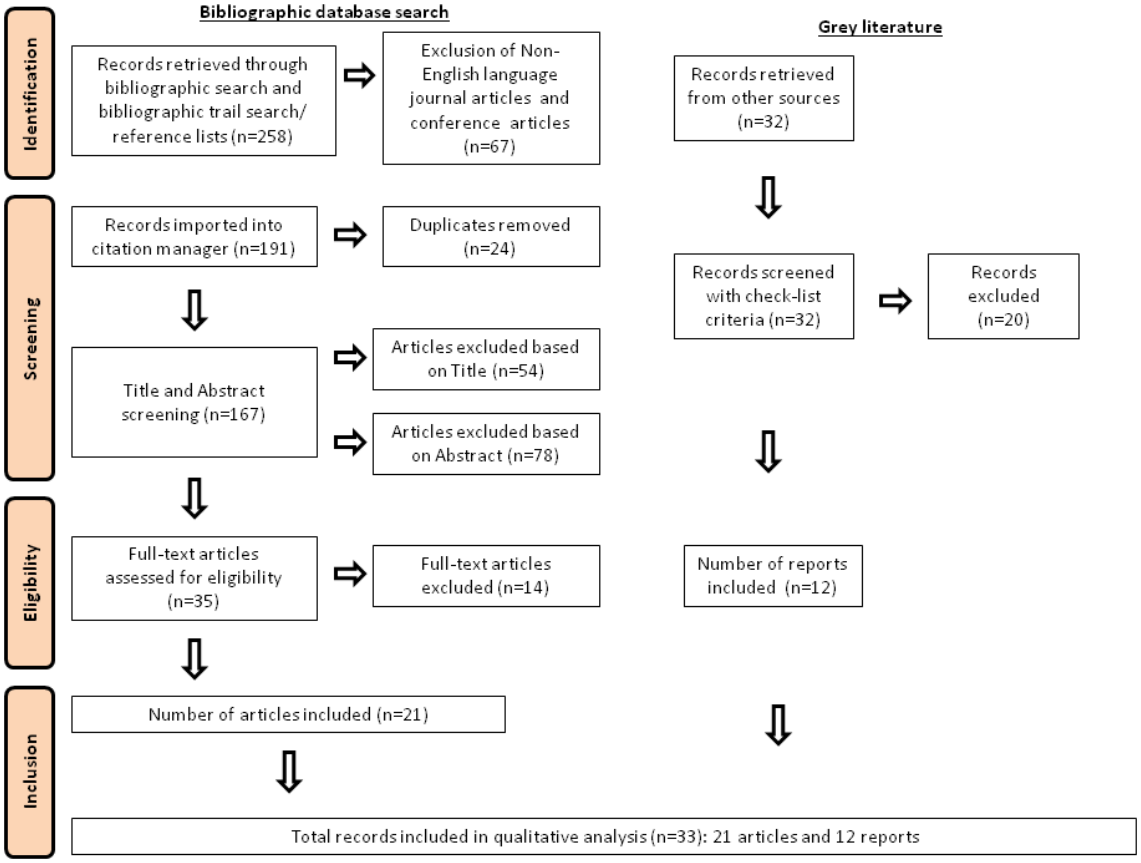


Figure 28: Overall search strategy

Several refinement features of Scopus and PubMed databases were extensively used (multiple refinements of results in accordance with the context of specific articles, related documents search etc). References of key articles were also examined for identifying additional citations.

4.3.1.2 Thematic content analysis for the identification of critical success factors

All the selected articles and reports were imported into a qualitative analysis software (MAXQDA[11]) and data were analyzed in emerging themes. During the coding process emerging themes were coded into pre-existing concepts, and new concepts were created when deemed necessary. The author carried out the thematic content analysis (line by line coding to search for concepts). Afterwards, the cluster of the coded segments was revised by the supervisor. A set of themes and sub-themes was then drafted, which was forwarded to a group of experts for evaluation. Based on feedback received from the group a final set of the most critical factors affecting the implementation of cholera vaccination campaigns in CHEs were identified (Table 22). These factors are presented in more detail in the sequel.

According to the literature surveyed, the implementation of vaccination campaigns during humanitarian crises could be jeopardized due to the lack of health-care personnel (World Health Organization 2006; Von Seidlein, Jiddawi et al. 2013; World Health Organization 2013). Generally, countries experiencing humanitarian crises suffer shortages of health-care personnel like physicians and nurses (Mauch, Weil et al. 2010). Emergency response training is key to epidemic control but, in the developing world, most of the healthcare workers involved in case management are either poorly trained or not trained at all (Costanza Adinolfi, David S. Bassiouni et al. 2005; Oladele, Oyedeji et al. 2012). This lack of experience could be attributed to the fact that there are no formal training programs for field epidemiology in crises (Ratnayake 2011).

Dimension	Factors	Source
Surveillance mechanisms (D1)	Establishment of surveillance mechanisms (F1)	Bruckner & Checchi (2011), Chaignat & Monti (2007), Chaignat et al. (2008), Connolly et al. (2004) Desai & Clemens (2012), Global Task Force on cholera control (2004, 2006), Tappero & Tauxe (2011), Valenciano et al. (2003), Waring & Brown (2005), World Health Organization (2012a, 2013)
Human resources (D2)	Availability of well-trained health-care personnel (F2)	Chaignat & Monti (2007), Chaignat et al. (2008), Costanza Adinolfi et al. (2005), Date et al. (2011), Global Task Force on cholera control (2006), Ratnayake (2011), Von Seidlein et al. (2013), World Health Organization (2006, 2013)
Logistics of supplies (D3)	Availability of vaccines and supplementary supplies (F3)	Chaignat & Monti (2007), Chaignat et al. (2008), Date et al. (2011), Farmer et al. (2011), Global Task Force on cholera control (2006), Plotkin et al. (2011), Tappero & Tauxe (2011), Von Seidlein et al. (2013), Waldor et al. (2010), Connolly et al. (2004), Holmgren (2012), Legros et al. (1999), Lopez et al. (2008), World Health Organization (2006, 2007, 2010, 2013, 2012b, 2012c), Weil et al. (2012)
Political considerations (D4)	Political context (F4)	Calain et al. (2004), Chaignat & Monti (2007), Chaignat et al. (2008), Date et al. (2011), World Health Organization (2013)
Communication mechanisms (D5)	Mobilization of target populations (F5)	Chaignat & Monti (2007) Chaignat et al. (2008) Date et al. (2011), Global Task Force on cholera control (2006), Legros et al. (1999), World Health Organization (2006, 2013)
Financial resources (D6)	Funding (F6)	Chaignat et al. (2008), World Health Organization (2006, 2012c, 2013), Chaignat & Monti (2007), Connolly et al. (2004), Lopez et al. (2008), Plotkin et al. (2011)
Coordination mechanisms (D7)	Coordination (F7)	Chaignat & Monti (2007), Farmer et al. (2011), Global Task Force on cholera control (2006), Pinto et al. (2005), Tappero & Tauxe (2011), World Health Organization (2006, 2012c), Salama et al. (2004)
Accessibility issues (D8)	Physical access to target populations (F8)	Chaignat & Monti (2007), Farmer et al. (2011), Global Task Force on cholera control (2006), Pinto et al. (2005), World Health Organization (2006, 2012b), Chaignat et al. (2008), Date et al. (2011)
	Insecurity (F9)	Chaignat & Monti (2007), Chaignat et al. (2008), Connolly et al. (2004), Date et al. (2011), Global Task Force on cholera control (2006), Pinto et al. (2005), Valenciano et al. (2003), World Health Organization (2006, 2007), Gayer et al. (2007)

Table 22: Critical factors for implementing cholera vaccination campaigns in CHE

The political context in which an emergency situation unfolds is also critical and has a great impact on any public health intervention implemented. Political tension among key-players involved (local authorities, international relief community, parts of population etc) may exist. Many times vaccination programs have been politicized and have become the subject of contention (World Health Organization 2013). Past experience has also shown that lack of coordination among the different agencies involved could lead to delays in the implementation of the vaccination campaign (World Health Organization 2006). Security issues may also arise hindering the accessibility of health-care workers to target populations (Connolly, Gayer et al. 2004; Chaignat and Monti 2007).

Several times vaccine interventions have not been implemented due to shortages of crucial medical supplies (vaccines) and complex logistical and operational challenges of multidose regimens (Date, Vicari et al. 2011). The cholera epidemic in Haiti has highlighted the importance of establishing an international vaccine stockpile to guarantee vaccine supplies and their rapid deployment (World Health Organization 2012). Several studies indicate that a strategic deployment of 5 million doses of oral vaccine coupled with other health interventions in the 2010 epidemic in Haiti would have halved the number of cholera cases and deaths (Plotkin, Shin et al. 2011; Holmgren 2012). Social mobilization activities are also important as target populations should be informed well in advance with respect to the role and procedure of the vaccination campaign. In addition, social mobilization activities should involve community and religious leaders of target populations in order culturally inappropriate activities be avoided (World Health Organization 2006; World Health Organization 2013). Vaccination campaigns should also be backed-up by surveillance systems. Timely and accurate information regarding disease's incidence and progression are critical (Waring and Brown 2005). Surveillance data are necessary for determining the best timing for vaccination as well as monitoring the outcome of the vaccination campaign (Chaignat and Monti 2007). Finally, lessons learnt from past experience indicate that substantial financial resources are also necessary for successfully implementing cholera vaccination campaigns in humanitarian emergencies (World Health Organization 2006; Chaignat, Monti et al. 2008).

4.3.2 The DEMATEL method

The Decision Making Trial and Evaluation Laboratory (DEMATEL) method was initially presented in 1973 (Fontela & Gabus, 1976). It is a structural modelling approach for visualizing the causal relationships among several distinct key-elements (expressed by criteria or factors) comprising a system. In particular, the factors or criteria under study may be classified into two broad categories: cause and effect category,

respectively. The method captures the relationships between the causes and effects of a set of criteria (or factors) governing a system and further visualizes their interrelationships. Through the usage of a numeral the strength of influence among several factors can be obtained and a $n \times n$ matrix can be formulated. Based on this initial data directed graphs and causal effect diagrams describing the contextual relations among the different factors or criteria of a system can be estimated and further depicted.

The DEMATEL method consists of the following steps:

Step 1: Calculation of the average matrix: Supposing that a panel consisting of R experts wishes to identify the interrelationships among n factors. By using pair-wise comparisons of the factors (dimensions), the degrees of perceptions from the experts regarding the level of impacts of particular dimensions are examined. Each expert r is asked to indicate the degree to which a factor i affects factor j by using a scale comprising 0, 1, 2, 3, and 4, representing 'No influence', 'Low influence', 'Medium influence', 'High influence', and 'Very high influence', respectively. Each expert is asked to indicate the direct effect he/she believes each element i exerts on every other element j, as indicated by x_{ij}^r. The scores provided by each respondent will provide an $n \times n$ non negative answer matrix $M^r = [x_{ij}^r]$, where r = 1,2,…,R the total number of the respondents. In this way a set of R matrices $M^1, M^2, \ldots, M^R$ is created where all the diagonal elements in each matrix equal zero. The $n \times n$ average matrix A for all expert opinions can be then computed by averaging the scores of the R experts using the following equation:

$$a_{ij} = \frac{1}{R} \sum_{r=1}^{R} x_{ij}^r \qquad (50)$$

The average matrix **A** is also called the original average matrix. Matrix **A** expresses the initial direct effects that a factor exerts on and receives from other factors and also shows the pair-wise comparison of their causal relationships.

Step 2: Calculation of the direct influence matrix: Step 2 consists of the normalization of the average matrix **A** and the creation of the normalized direct-relation matrix **N** by using the following equations:

$$N = \frac{A}{p}, \qquad (51)$$

$$p = \max_{ij}\left(\max_i \sum_{j=1}^{n} a_{ij}, \max_j \sum_{i=1}^{n} a_{ij}\right) \quad (52)$$

The sum of each row i of the matrix **A** expresses the total direct effects of factor i upon the other factors, thus the expression $\max_i \sum_{j=1}^{n} a_{ij}$ represents the most important total direct effects from the specific factor i to other factors. Similarly, the sum of each column j of the matrix **A** expresses the total direct effects of factor j received from other factors, thus the expression $\max_j \sum_{i=1}^{n} a_{ij}$ represents the most important total direct effects that a certain factor j has received from the other factors.

Step 3: Computation of the total relation matrix*:* The total relation matrix **T** can be obtained by using the normalized direct-relation matrix **N**, where **I** is the identity matrix as follows:

$$T = N(I - N)^{-1}. \quad (53)$$

Step 4: Generation of the causal diagram: Within the total relation matrix **T** the sum of rows and the sum of columns are denoted as vectors D and R, respectively, by using the equations (54)-(56):

$$T = [t_{ij}]_{n\times n}, i, j = 1, 2, \ldots n, \quad (54)$$

$$D = [\sum_{i=1}^{n} t_{ij}]_{1\times n} = [t_j]_{n\times 1}, \quad (55)$$

$$R = [\sum_{j=1}^{n} t_{ij}]_{1\times n} = [t_i]_{n\times 1} \quad (56)$$

Once the vectors D and R have been defined a causal and effect graph can be drawn. In this graph the horizontal axis vector (D+R) is made by adding vector D to R. Similarly, the vertical axis (D-R) can be formed by subtracting D from R. The logic behind both D and R vectors is the following: Vector D summarizes both direct and indirect effects given by factor i to the other factors. Similarly, vector R summarizes both direct and indirect effects given by factor i to the other factors. The ‘‘Influence’’ horizontal axis vector (D + R) shows how much importance the criterion has, and the ‘‘Relation’’ vertical axis (D-R) categorizes criteria into a cause group and an effect group. When (D - R) is positive, the criterion will be assigned to the cause group, and when negative, to the effect group. Thus, by mapping the data set of the (D + R, D - R), we can get the causal diagram. Based on the above statements, a factor belongs

either to the causal group, if (D - R) is positive, or to the effect group, when (D - R) is negative.

Step 5: Obtaining the inner dependence matrix: In the final step of the DEMATEL method the decision-maker should set a threshold value for the influence level. In particular, only the factors whose effect in matrix T is greater than the threshold value will be shown in the cognitive map. In this way an inner dependence matrix as well as a cognitive map is formulated. In this step, the threshold value θ has been chosen by the experts and the results of the literature review. Only factors with influence level in matrix T higher than the threshold value will be chosen to construct the map. If the threshold value is too low, the map will be too complicated, whereas, if the threshold value is too high, many factors will remain independent without showing the relationships with other factors.

4.3.3 Implementation of the DEMATEL method

Four respondents, two from each of two non-governmental organizations (NGOs), participated in the study. All respondents have long time experience in the implementation of outbreak response agendas and have been involved in at least one vaccination campaign in CHEs settings. Prior to retrieving the data, all respondents were informed about the DEMATEL methodology, the way it works and the results it creates. A video tutorial was also uploaded on YouTube for educational/informative purposes (particularly the way the direct relation matrix is generated). Additional information was provided to the respondents where necessary. All respondents were given a questionnaire in the form of a 9x9 matrix for generating the direct relation matrix. 4 valid questionnaires were retrieved.

Four matrices were initially generated based on the responses from the four respondents. R software was used for conducting the necessary DEMATEL computations (R Development Core Team 2008). By using Eq. (50) the average direct-influence matrix was generated. The normalized direct-relation matrix was then generated by using Eq. (51) and (52). The total-relation matrix was computed using Eq. (53), as seen in Table 23. Using Eq. (55) and Eq. (56) the final results of the analysis were derived (Table 24). In particular, Table 24 summarizes the direct and indirect effects of the nine factors affecting the implementation of cholera vaccination campaigns in CHEs.

	Establishment of surveillance mechanisms (F1)	**Availability of well-trained health-care personnel (F2)**	**Availability of vaccines and supplementary supplies (F3)**	**Political context (F4)**	**Mobilization of target populations (F5)**	**Funding (F6)**	**Coordination (F7)**	**Physical access to target populations (F8)**	**Insecurity (F9)**
Establishment of surveillance mechanisms (F1)	0,266	0,252	0,281	0,250	0,345	0,310	0,337	0,316	0,172
Availability of well-trained health-care personnel (F2)	**0,399**	0,212	0,273	0,228	0,376	0,305	0,334	0,337	0,192
Availability of vaccines and supplementary supplies (F3)	0,272	0,206	0,153	0,165	0,259	0,248	0,263	0,243	0,170
Political context (F4)	**0,448**	0,383	0,310	0,227	**0,421**	0,347	0,389	0,395	0,320
Mobilization of target populations (F5)	0,396	0,282	0,253	0,265	0,269	0,316	0,353	0,341	0,214
Funding (F6)	0,386	0,333	0,332	0,233	0,346	0,236	0,351	0,338	0,215
Coordination (F7)	**0,441**	0,334	0,331	0,280	**0,415**	0,372	0,285	0,367	0,242
Physical access to target populations (F8)	**0,427**	0,328	0,265	0,281	**0,425**	0,302	0,349	0,267	0,249
Insecurity (F9)	**0,517**	0,402	0,373	0,388	**0,495**	**0,422**	**0,460**	**0,480**	0,226

Table 23: The total-relation matrix

Factors	D	R	D+R	D-R
Establishment of surveillance mechanisms (F1)	2,529	3,552	6,081	-1,023
Availability of well-trained health-care personnel (F2)	2,656	2,732	5,388	-0,075
Availability of vaccines and supplementary supplies (F3)	1,980	2,572	4,552	-0,592
Political context (F4)	3,239	2,319	5,558	0,920
Mobilization of target populations (F5)	2,690	3,351	6,041	-0,661
Funding (F6)	2,772	2,857	5,628	-0,085
Coordination (F7)	3,066	3,121	6,187	-0,055
Physical access to target populations (F8)	2,893	3,083	5,976	-0,190
Insecurity (F9)	3,763	2,001	5,763	1,762

Table 24: Final results of the analysis

As mentioned earlier, the DEMATEL method assesses the importance of factors in terms of (D+R) values (the higher the value, the more important the factor is). Based on their degree of importance in the decision-making context the nine factors can be prioritized as seen in Table 25. More precisely, Coordination (F7), Establishment of surveillance mechanisms (F1) and Mobilization of target populations (F5) present the three most important factors with values of 6.187, 6.081 and 6.041, respectively. Other three important factors for implementing cholera vaccination campaigns in CHEs are the Physical access to target populations (F8), Insecurity (F9) and Funding (F6).

Order	D+R	Order	D-R
(F7)	6,187	(F9)	1,762
(F1)	6,081	(F4)	0,920
(F5)	6,041	(F7)	-0,055
(F8)	5,976	(F2)	-0,075
(F9)	5,763	(F6)	-0,085
(F6)	5,628	(F8)	-0,190
(F4)	5,558	(F3)	-0,592
(F2)	5,388	(F5)	-0,661
(F3)	4,552	(F1)	-1,023

Table 25: Prioritization of factors

The DEMATEL method also classifies the factors in accordance with the value of (D-R) vector, as seen in Figure 29. For instance, if the corresponding (D-R) value of a factor is positive then this factor is considered to be a net dispatcher. On the other hand, if the (D-R) value of a factor is negative then this factor is considered to be a net receiver. Based on the results of the DEMATEL method the two most influential factors are Insecurity (F9) and Political context (F4) with corresponding values of 1.762 and 0.920, respectively. Prior research and evidence from the field also suggest that health interventions in CHEs can be greatly affected by violence (World Health Organization 2013).

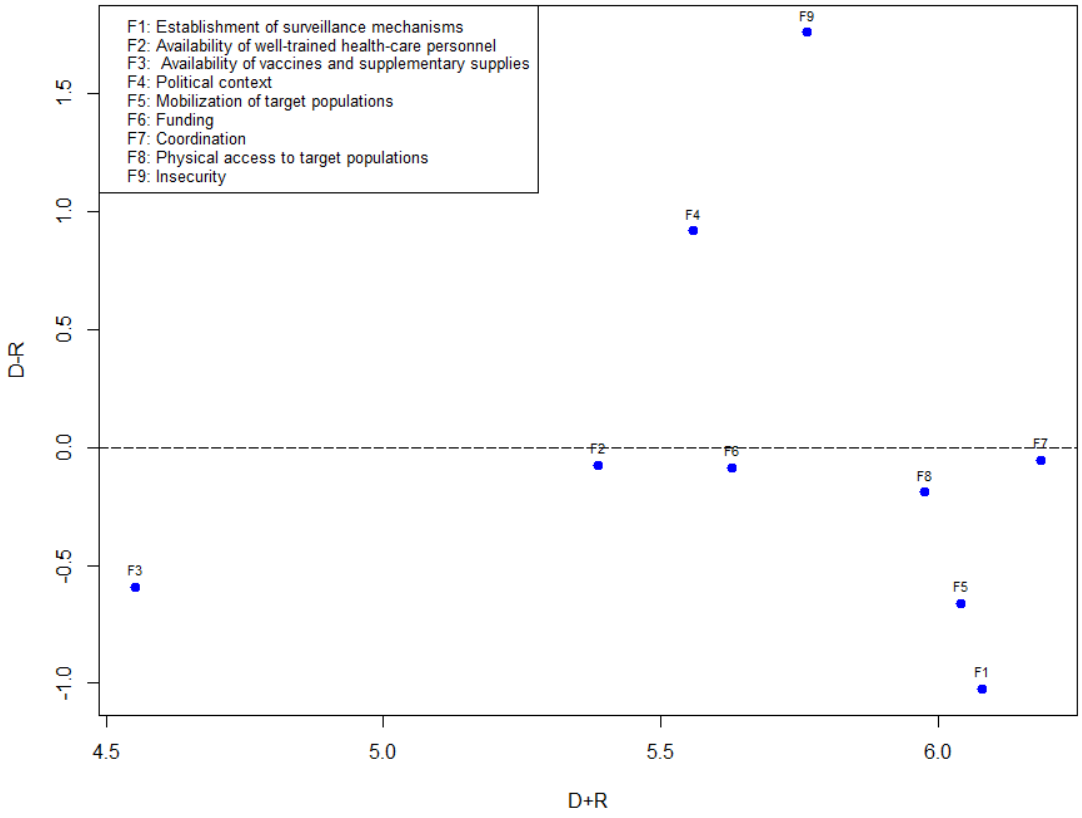


Figure 29: The causal diagram

For obtaining the casual relationships among the various factors (Figure 30) a threshold value θ for the influence level should be defined. For calculating the value θ the mean and standard deviation of the values of the total relation matrix T were initially obtained. In the sequence, one standard deviation to the mean was added, resulting in θ=0,397.

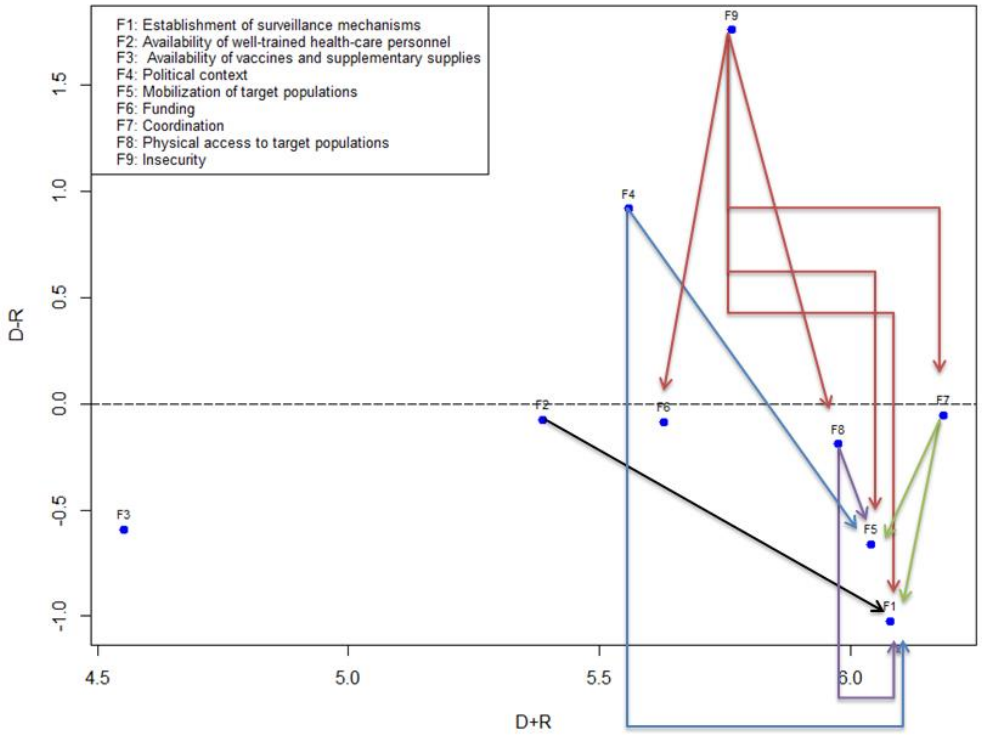


Figure 30: Cognition map of total relationships

A seen in Figure 30, Insecurity (F9) has a direct impact on Coordination (F7), Physical access to target populations (F8), Funding (F6), Mobilization of target populations (F5) and Establishment of surveillance mechanisms (F1). The Political context (F4) directly impacts on Mobilization of target populations (F5) and the Establishment of surveillance mechanisms (F1). The Availability of well-trained personnel has a direct impact on the Establishment of surveillance mechanisms (F1). Both Coordination (F7) and Physical access to target populations (F8) have a direct effect on Mobilization of target populations (F5) as well as on the Establishment of surveillance mechanisms (F1). From Figure 30 is also evident that Insecurity (F9), Political context (F4), Coordination (F7) and Physical access to target populations (F8) act as cross-functional drivers, affecting a plethora of other factors. On the other hand, the Establishment of surveillance mechanisms (F1) serves as the factor that receives a lot of influence from certain other factors. The Availability of vaccines and supplementary supplies (F3), finally, is not a significant net causal or effect factor. The reason why this factor has been isolated by the respondents is open to conjecture. The fact that the availability of vaccines must be assured prior to implementing any immunization campaign might serve as reasonable explanation. However, during the implementation phase a plethora of logistical issues might also arise, jeopardizing the availability of such supplies.

Several managerial implications could be derived from the results of the analysis. Although Insecurity (F9) and Political context (F4) are not considered priority factors with the highest value of importance, they however provide valuable insights for public health officials and decision-makers. They present the factors that directly affect all other factors and should be taken greatly into consideration. In particular, the main driving force for successfully implementing cholera vaccination campaigns in CHEs is the lack of security. Unless security is safeguarded, control interventions cannot be implemented. In addition, the political context in which a control intervention is implemented is also critical. Availability of health care personnel, sound coordination mechanisms among the key parties involved, stable political context, physical access to target populations and a secure environment serve as prerequisites for the establishment of robust surveillance systems in CHEs. The involvement of target populations through mobilization programs necessitates strong coordination mechanisms, a stable political context, resolved security issues and unrestricted access to target populations. It is worth mentioning that the findings of the analysis are in line with several reports published by leading health-care organizations where experience has shown the tremendous importance of security and the generic political context for successfully implementing vaccination campaigns in CHEs (Global Task Force on cholera control 2006; World Health Organization 2013).

4.4 Summary

In this chapter some evidence-based guidance regarding the factors that affect the control of IDOs in CHEs has been presented. Initially, based on a systematic review of relevant literature several factors affecting the implementation of outbreak control actions for specific diseases have been studied, particularly from an operational perspective. The diseases under study have been the following: meningitis, trypanosomiasis, leishmaniasis, viral hemorrhagic fevers, tuberculosis, acute respiratory infections, malaria, measles, and, finally, diarrheal diseases (shigella dysentery and cholera).

In the sequel, certain factors affecting the implementation of cholera vaccination campaigns in CHEs have been identified through a systematic bibliographical search and a thematic synthesis approach. Following a thorough bibliographic search and insights from experts a total of nine factors have been identified for successfully implementing cholera vaccination campaigns in CHEs. These factors are Establishment of surveillance mechanisms (F1), Availability of well-trained health-care personnel (F2), Availability of vaccines and supplementary supplies (F3), Political context (F4), Mobilization of target populations (F5), Funding (F6), Coordination (F7),

Physical access to target populations (F8), and, finally, Insecurity (F9). Through the usage of the DEMATEL method the prioritization of these factors on their degree of importance as well as the identification of their interrelationships have been presented. Coordination mechanisms, establishment of surveillance mechanisms and mobilization of target populations present the three most important success factors when cholera immunization campaigns are to be implemented in CHE settings. On the other hand, civil unrest and the generic political context in which an immunization campaign takes place present the most influential factors that public health officials and decision-makers should greatly take into consideration when cholera vaccination campaigns are to be implemented in CHEs.

Chapter 5: Discussion, limitations and suggestions for further research

5.1 Discussion

Comprehensive Emergency Management follows an all-hazards approach, generalizing policies and plans for all kinds of emergencies, but different optimal approaches for different specific incidents may be found. The decision-making process (response policy) during a disaster response differs drastically from conventional decision-making. The problem's environment is changing rapidly and there is very little time for making decisions. Disaster operations management shows great potential as a new direction for Operational Research/Management Science research. More specifically, epidemics will continue to appear and it is crucial to understand how they can be managed effectively and efficiently. The human history is full of public health incidents where pandemic outbreaks occurred causing a large number of deaths. In this thesis the dynamics of the spread of IDOs and their interactions with resource allocation decisions have been studied. In particular, logistical and resource allocation considerations of IDO control have been thoroughly studied for three distinct cases; the first being for epidemics attributed to natural causes, the second being for disease outbreaks due to deliberate bioterrorist actions and the third being for outbreaks in the aftermath of natural or man-made disasters. Influenza, smallpox and cholera have been chosen as the main infectious agents to be studied in each case, respectively.

In the case of influenza two deterministic mathematical models have been developed for facilitating in-context evaluation of alternative resource allocation policies (Chapter 2). Vaccination of the susceptible individuals has been the main control action taken into consideration. In the first case the problem has been tackled using the concept of deteriorating jobs, i.e. the model represents increasing loss rate as more susceptible individuals become infected, and increasing time and effort needed for the epidemic's containment. One resource (mobile medical team) is allocated to perform the control action (vaccination). A case study for a proposed application of the model in the case of the mass vaccination against A(H1N1)v influenza in the Attica region, Greece, from 11/2009 to 01/2010 has been presented. The second case considers the problem of allocating and scheduling limited multiple, identical or non-identical, resources employed in parallel, where several areas are

infected. A real-time synchronous heuristic algorithm has been proposed as the solution methodology. For illustrating the applicability of the modelling approach a numerical example has been presented.

In Chapter 3 the logistical implications for implementing a large-scale vaccination campaign in a large urban area for controlling a deliberate smallpox outbreak attack has been considered. A modelling approach has been developed consisting of two modules. The first module relates to disease's progression whereas the second one relates to optimally distributing a set of supplies (medical and ancillary) to affected sub-populations. For predicting the course of the outbreak a deterministic mathematical model parameterized to capture several biological properties of smallpox is used while simultaneously evaluating the effects of a reactive regional mass vaccination campaign. A linear programming model is developed for formulating the emergency supply chain problem where multiple commodities are distributed using a set of multi-modes within a number of time periods. Several logistical aspects are taken into consideration like predetermined levels of health care capacities (in terms of facilities available to care for those infected and relevant health-care personnel), limited number of vehicles for transportation/distribution activities, limited vaccine supply etc. For illustrating the applicability of the proposed methodology a numerical experiment is provided.

The research presented in Chapter 4 has been both exploratory and confirmatory and its purpose has been twofold. First, some evidence-based guidance regarding the factors that affect the control of IDOs in CHEs has been presented. Based on a systematic review of relevant literature several factors affecting the implementation of outbreak control actions for specific diseases have been studied, particularly from an operational perspective. The diseases under study have been the following: meningitis, trypanosomiasis, leishmaniasis, viral hemorrhagic fevers, tuberculosis, acute respiratory infections, malaria, measles, and, finally, diarrheal diseases (shigella dysentery and cholera). Second, based on the aforementioned bibliographic search and insights from experts a set of factors have been identified for successfully implementing cholera vaccination campaigns in CHEs. Through the usage of the DEMATEL method the prioritization of these factors on their degree of importance as well as the identification of their interrelationships have been presented.

5.1.2 Key-findings

A plethora of gaps and discrepancies in the literature regarding IDO control and logistics operations has been highlighted (Dasaklis, Pappis et al. 2012). From the analysis of the selected literature a series of insights can be derived with respect to

the issues of the outbreaks dealt with by the researchers, the logistical attributes taken into consideration as well as the methodologies applied. In the case of the nature of the outbreaks, most research approaches address topics of bioterrorist response logistics and natural outbreaks (influenza). As far as bioterrorist response logistics is concerned, it seems that the 2001 anthrax attack in the United States triggered a series of publications in this subject. Despite the fact that during an ongoing humanitarian crisis logistical activities must take place to ensure the maintenance of a high level of sanitary conditions and the provision of key medical supplies and vaccines, research approaches addressing IDO response operations in CHEs are limited. Finally, research approaches regarding epidemics control logistics in the case of mass gatherings were not located.

With respect to the Operational Research/Management Science literature interesting insights can be drawn. For instance, the research approaches developed so far in the case of epidemics control logistics network configuration are based on a series of assumptions and simplifications that have little correlation with real-world problems and especially problems arising "in the field". Most of the proposed methodologies combine differential equations for modelling the progression of the disease along with logistics network techniques for the transportation and/or distribution of medical supplies. Unfortunately, the epidemiological models used in this case do not take into account the biological characteristics of the disease under study. Additionally, most of the research approaches consider that the commodities transported and/or distributed are homogeneous or that medical supplies are bundled together. Practically, this is a simplification that contradicts with several guidelines proposed by health-care policy makers (Centers for Disease Control and Prevention 2007). These guidelines clearly state that essential medical supplies and especially vaccines should be transported by using specific vehicles under fully monitored conditions. Therefore, it is evident that issues of capacity and fleet management or breaks in the cold chain attributed to faulty equipment have been overlooked so far.

Another aspect of the IDO response supply chain configuration that has been paid little attention so far is the interrelationship between the agent triggering an outbreak and the configuration of the response supply chain. In fact, the logistics of response to a confirmed outbreak should rely heavily on the agent triggering an outbreak and, therefore, the configuration of the response supply chain may be different depending on the very nature of each agent. For instance, anthrax and smallpox could be both utilized as bioterrorist weapons but from an epidemiological point of view their control presents huge differences. As mentioned in (Whitworth 2006), anthrax, which is not contagious, can be treated with antibiotics dispensed to heads of households (who can then dispense the antibiotics to all the family

members). On the other hand, smallpox is contagious, is caused by a virus and can be only prevented by vaccination. In this case, each individual should be administered a fresh vaccine. Therefore, treatment centers would be more likely to handle a larger number of people in the case of a smallpox attack than in the case of an anthrax attack with obvious implications for facility location decisions. Response time frames are also different in each case, presenting different logistical challenges for the transportation and distribution of medical supplies. Generally, according to (Hupert, Cuomo et al. 2004) there are two conceptual approaches regarding mass prophylaxis in the case of IDO control: "push" and "pull." The "push" approach considers bringing medicine directly to affected individuals and households whereas the "pull" approach requires that individuals leave their homes or workplaces in order to travel to certain treatment centers to receive medication or to be administered a vaccine. Putting aside any strengths and weaknesses these two approaches may have, it is evident that the adoption of each approach calls for a different response supply chain configuration.

In the case of stockpiling of medical supplies most research approaches include in the problem formulation only the cost of actually purchasing the inventory. Other aspects of inventory cost as well as inventory management operations like maintenance, in-door handling, and activities of picking, packing and preparing for shipment are omitted. For example, in the case of control of influenza outbreaks antiviral drugs can be stockpiled in various forms (powder, pills etc) thus their management may necessitate additional handling operations during the containment effort. In addition, inventory replenishment policies during an ongoing epidemic outbreak are scarce. Unfortunately, the majority of the stockpiling approaches do not consider the fact that after a period of time inventories will be depleted and replenishing activities should take place. Finally, it seems that the possible trade-offs between centralized and decentralized policies of inventory management have been paid limited attention so far.

Research approaches addressing issues of triage management operations also rely on several assumptions that may contradict with real-world. The most surprising finding is that triage operations management approaches assume that there is an adequate supply of medical commodities and that the surge capacity of dispensing centers is, in most of the cases, infinite. Nevertheless, anthrax treatment requires a 60-day regimen of antibiotics and this treatment will likely be implemented in consecutive waves (Whitworth 2006). Therefore, replenishment policies of essential medical supplies should be taken into consideration. Apart from replenishment strategies, many approaches do not consider transporting people to the clinics to get vaccinated or to be administered medical treatment. Even further, it is assumed that the influx of patients to the treatment centers is constant and that the prevalence

and severity of disease are also constant over certain periods. In addition, issues of handling vaccines and other medical supplies are not taken into consideration. Service rates within dispensing centers are considered constant over time without taking into account fatigue of the personnel or even personnel illness. Issues of transshipment of medical supplies among dispensing centers are also not studied. Finally, possible bottlenecks attributed to post-vaccination complications for some people and, generally, severe adverse effects of vaccination are not modeled.

Other aspects of the IDO response supply chain poorly studied in the literature may refer to some cross-functional drivers like sourcing and information as well as to some aspects of coordination. Pricing and sourcing decisions in the case of essential medical supplies procured for the containment of an epidemic may result inconvenient and costly. Appropriate contractual agreements between manufacturers and public health institutions could alleviate any negative effects for the parties involved but they have not been studied at a large scale so far. Issues of information management in epidemics control supply chain have also been paid limited attention. Information management plays a vital role during the control of an IDO and the primary source of information remains the surveillance systems put in place. A prompt detection of a suspected disease outbreak has a great impact on the progression of the disease and triggers certain responses regarding the deployment of the available resources while providing strong insights towards real demand requirements. The flow of essential medical supplies, transportation activities and demand for medical personnel are some of the logistics-oriented features that depend on the available information regarding the disease's progression. At the same time the management of materials flow during the containment effort necessitates its own stream of information. Highly sophisticated systems in business supply chain and relevant technologies like RFID could also be adopted in the case of epidemics containment.

Additionally, successful control of an IDO requires strong co-ordination amongst the parties involved. For example, in (Butler, Cohen et al. 2002) aspects of coordination between public health and law enforcement agencies are studied but they do not relate to the established response supply chain. Moreover, synergies between private and public health organizations and governments should be explicitly studied and cooperation frameworks should be developed. For IDOs in the aftermath of natural or man-made disasters the control effort may be far more difficult as a result of the conflict generated among the different parties involved (humanitarian organizations, the army, national agencies, etc) or real-time problems like damaged or inadequate infrastructures.

Coordination and information management aspects may also have various implications for the adoption of several response supply chain strategies. For example, in (Brandeau, Hutton et al. 2007) several strategies are proposed that could lead to substantial increases in the responsiveness and efficiency of the epidemics response supply chain. As a matter of fact, strategies like lean, agile or leagile extensively adopted in the case of the business sector could also be adopted in the case of epidemics logistics provided that a series of prerequisites are met. Generally, the adoption of these strategies may be feasible but a thorough assessment is necessary for deciding the appropriate strategy to be adopted in each case (nature of the outbreak, disease type etc). In addition, the appropriate mixture of strategies (leagile) should be based on a clear understanding of the several building blocks of the IDO response supply chain like information, coordination, integration and alignment. For instance, in the case of the business sector information sharing and coordination are tied together (Chen 2003). This close relationship between them enables the business supply chains to adopt the appropriate strategy which ultimately leads them to match supply and demand. On the other hand, IDO response supply chains are overwhelmed with uncertainty and present low levels of coordination and information sharing among the parties engaged. Moreover, inherent uncertainties of the agent triggering the outbreak as well as the uncertainty of the supply chain itself to meet several needs render the adoption of these strategies a very difficult task.

Epidemics containment presents real challenges for logistics as specific determinants related to the agent triggering the outbreak as well as several particularities of the affected populations are hard to be defined. As a consequence, the real demand for medical supplies may be far different from the demand initially projected. A common example of the inherent uncertainty lurking behind the nature of the agent triggering an outbreak is influenza. In the case of influenza, not only we are unaware of the possible demand for vaccines and antiviral drugs during a future outbreak but we also lack the capability of determining exactly the efficacy of these supplies due to strain mutations. Unfortunately, a six-month period for producing the appropriate vaccine will be needed. Until then, antiviral drugs will be extensively used but still their level of efficacy against the influenza strain will remain uncertain (Siddiqui and Edmunds 2008). Generally, vaccine supply chain poses significant uncertainties, even in the case of seasonal influenza (Orenstein and Schaffner 2008).

Another source of complexity and uncertainty of epidemics logistics containment is the particularities of the affected sub-populations. Such particularities may span from different demographic characteristics across sub-populations to the attitude of each individual towards the epidemic. For example, different age-groups may necessitate different dosages of medical treatment or specific sub-populations

groups should be subject to a multi-dose regimen. Other issues of demand uncertainty may relate to each individual's choice to become vaccinated, the possible benefits from vaccination that may have been accrued from the participation in past vaccination campaigns or even how media cover issues of safety for a new vaccine. All the above have both direct and indirect effects on the demand for medical supplies.

As far as methodologies are concerned, economic analysis has been extensively utilized for decisions regarding stockpiling of medical supplies (especially in the case of future influenza outbreaks). Unlike the business sector, a small amount of papers addressing issues of inventory management in IDOs by using well established operations research techniques have been found. In the case of logistics network configuration the problems addressed are formulated using prescriptive models. The majority of these models are of deterministic nature and just a few of them incorporate stochastic parameters. Most of the models incorporate cost minimization as an objective while in the case of epidemics containment time is the crucial parameter. Techniques of decomposing and/or deconstructing of the initial problems into smaller ones have been limited and most approaches deal with small-scale problem. As a consequence, modelling and solving large-scale problems will necessitate the development of more efficient and effective heuristic algorithms. Furthermore, a large-scale epidemic emergency in the future might challenge the scalability of the existing modelling approaches. In the case of management of the triage operations and patient flow logistics, the majority of the developed models are descriptive. Logistical problems in the context of triage operations have been treated using simulation and queuing theory models. Finally, in the case of more integrated approaches both prescriptive and descriptive approaches have been developed where simulation models have been combined with mathematical and optimization models.

5.3 Limitations

The methodological approaches presented in this thesis, particularly the quantitative ones, have some limitations that worth noting. Most of these limitations are closely related to the inherent uncertainties surrounding any IDO and especially the dynamics of disease transmission. For example, the mean-field models used in the case of influenza and smallpox respectively and their deterministic nature comes with several simplifying assumptions related to diseases' transmission rates. In the case of influenza, for instance, social networks and contact processes that dictate disease transmission patterns or age-specific differences in the pathogenicity and transmissibility of the disease have not been considered. The same holds for

smallpox where age-specific heterogeneity and population movements have not been explicitly modeled. The transmissibility of smallpox, also, depends on social structures, the nature of close contacts as well as the spatiotemporal dynamics of the host population. Therefore, partitioning the host population by using social structures (households, offices, schools etc) and estimating relevant transmission rates would have been more appropriate for the calculation of the cumulative number of people affected by the smallpox outbreak. Apart from transmissibility, both diseases also present case fatality rates that are age-dependent. In addition, the influenza epidemic models used in this thesis are based on pharmaceutical interventions (vaccination) and other non-pharmaceutical interventions like isolation of infected individuals, social distancing or travel limitations have not been considered. Finally, levels of residual herd immunity within the host population for both diseases have not been considered.

Undoubtedly, the usage of an individual-based model in both cases (influenza and smallpox) would have yielded more accurate results as it would have captured more realistic disease patterns and contact structures among all individuals within the host 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. On the other hand, compartmental models are more computationally tractable and allow extensive sensitivity analysis (Kaplan et al., 2003). In addition, the differences between differential equations models and agent-based models in terms of several epidemiological outcomes (number of people infected, duration and peak of an outbreak etc) might be small compared to variability caused by stochastic events, parameter uncertainty and model boundary (Rahmandad and Sterman 2008). 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. Estimating the number of individuals that are immune to smallpox in Greece is also difficult since routine vaccination against smallpox ceased in Greece in 1980. Finally, it should be noted that the logistics/resource constraint modelling approaches presented in this thesis could be coupled with any epidemic transmission model (capturing more realistic disease patterns and population dynamics like age-specific groups, non-homogeneous mixing, mixing between regions, etc).

With respect to the resource allocation/logistics modelling approaches presented in this thesis some limitations should also be kept in mind. For example, logistical considerations for mounting the targeted vaccination campaigns in the case of influenza (for both single and multiple resources) could be incorporated within the currently developed resource allocation models. In this case limited number of vaccine supply, limited number of vaccinators and other vaccine administration

constraints could be taken into account. The logistics network configuration model presented in the case of the implementation of the targeted smallpox vaccination campaign should also incorporate some more detailed logistical features such as routing of the vehicles that perform the distribution of the smallpox vaccine and facility location considerations. Facility location in this context may refer to the number, size and geographical location of the various PODs by using certain demographical characteristics (population density etc), gradual opening up of PODs (in terms of quantity and capacity) etc.

Even though the structured systems evaluation approach presented in Chapter 4 provides valuable insights into several aspects of cholera immunization campaigns in CHEs, some limitations should also be kept in mind. For instance, the implementation of the DEMATEL method is based on responses of only four senior managers. Undoubtedly, a larger sample size would have yielded more trustworthy results or results that would have been robust enough to allow for generalization. In addition, some of the results should be interpreted with caution as the outcome of certain pair-wise comparisons might have been dictated by the respondents' own professional background. Three out of four respondents were physicians and their attitude towards certain factors might have been subjective due to their professional background. Another bias might relate to respondents' own field experience and particularly to the way respondents perceive risk and threats while providing humanitarian relief in conflict-affected settings. That having been said, issues of operational security might have been favored by the respondents, underscoring the importance of insecurity when cholera immunization campaigns are implemented in CHEs.

Some methodological limitations of the DEMATEL method itself are also worth noticing. In cases where a large number of factors should be compared and, therefore, large number of pair-wise comparisons should be made, the evaluation effort required for the generation of the direct relation matrix might be enormous, if not impossible. In this study a total of 25 factors were identified by using a systematic literature review and thematic content analysis approach (see Appendix I). However, when the respondents were asked to give their judgment they expressed concern about their ability to generate a matrix with as many as 625 pair-wise comparisons. To bypass this obstacle a clustering-based approach was adopted based on feedback received from the respondents where the initial 25 factors were merged into 9. This higher-level analysis performed, however, has come at a price since several interrelationships among the original set of factors have not been captured.

Another limitation of the DEMATEL method is that the results it generates are static and, therefore, dynamic aspects governing a system cannot be embedded in the analysis. In this study the thematic content analysis revealed that elements of certain factors might change over time, thus, changes in the interrelationships among the factors will take place. For instance, new cholera vaccines will be developed necessitating less qualified medical personnel for their administration (Clemens, Shin et al. 2011; Pastor, Pedraz et al. 2013). Such a change will certainly affect the importance of human resources and, subsequently, the interrelationships among the factors. Finally, in this study crisp numbers have been used for obtaining the rating of the scale for the pair wise comparisons instead of other metrics (e.g. fuzzy sets). Whether this point is a limitation is open to discussion, since the application of fuzzy DEMATEL scales, while making the application of the method more complex, has practically no effect on the causal relationships eventually obtained (Dytczak and Ginda 2013).

Apart from the DEMATEL method, the qualitative approach adopted in Chapter 4 (the scoping review and thematic synthesis of the factors that affect the control of IDOs in CHEs) has also some limitations. For example, the thematic content analysis, the extraction and coding of data as well as the overall emerging themes identified are conditioned to the author's subjectivity. In addition, like most scoping reviews, no appraisal of the quality of evidence in the primary research data has been conducted. However, during the eligibility phase only peer-reviewed articles were included in the analysis. Finally, during the search process conceptual saturation might not have been achieved since only articles in English have been included in the analysis.

5.4 Conclusions and suggestions for further research

As shown is this thesis, IDOs triggered either by natural causes or by deliberate human actions pose significant risks for modern societies. Effective control of an IDO calls for a rapid response and mobilization of huge amount of resources. Available resources such as essential medical supplies and well-trained personnel need to be deployed rapidly and to be managed in conjunction with available information and financial resources in order to contain the epidemic before it reaches uncontrollable or disastrous proportions. Therefore, the establishment and management of an emergency supply chain during the containment effort are of paramount importance. The findings of this thesis suggest that:

- IDOs are highly context-specific and, therefore, tailor-made approaches should be adopted in each case (based on the generic context in which an outbreak takes place, the agent that triggers the outbreak etc).
- IDO control literature is fragmented. In particular, two main streams of studies have been identified: one being the studies of epidemiological-oriented interest and the second being the Operational Research/Management Science-oriented studies.
- The importance of response operations management for controlling an IDO is of paramount importance and decision-makers/public health officials should pay special attention to the logistical prerequisites of IDO control.
- Clearly, more integration is needed that will bring together theory and practice. The main objective remains the validation in terms of applicability and effectiveness of several theoretical IDO response frameworks.
- IDOs usually have tremendous political ramifications and, therefore, political will is critical for tackling future outbreaks. This is particularly true for IDOs in humanitarian or low-income settings. The recent Ebola outbreak has highlighted the importance of political will and commitment for pooling resources to tackle the particular threat. Unless political commitment is assured, there is no reason to think that the world is on track to tackle future IDOs, particularly in resource-constrained settings.

Despite the fact that several logistical considerations have already been incorporated into IDO control approaches, the area of epidemics control supply chain still remains a promising research area. Following the insights provided in the discussion and particularly in the limitations section it is believed that there exist a lot of opportunities for future research. In particular, future research directions may include:

- **Use of operational research for the evaluation of different IDOs control strategies in CHEs**: in resource-constraint settings the use of operational research tools could be highly beneficial. Certain operational research tools could be used for the evaluation of different IDO control strategies, particularly in terms of their feasibility and effectiveness (from cost-effectiveness analysis to simulation and combinatorial optimization). In the case of cholera, for instance, operational research could be used for the evaluation and assessment of different control actions like hygiene promotion/sanitation improvement and vaccination. The benefits of the usage of pharmaceutical and non-pharmaceutical interventions in the case of cholera could also be assessed by using certain operational research tools. The same holds for other diseases like tuberculosis and measles. However, it should be noted that in CHEs data to perform such an analysis may be limited

or may be outdated due to disruption of government structures and services. Therefore, the possible benefits of operational research to guide control interventions in CHEs should be based on sound data collection and interpretation.

- **Multidisciplinary synergies**: the complex and multidisciplinary nature of IDO control calls for synergies among various players like epidemiologists, logisticians and health officials. Although some research efforts have been directed towards the development of multidisciplinary modelling approaches, there is a need for further development of more tailored IDO control strategies, at least from a theoretical perspective. A typical example may refer to the powerful disease progression methodologies developed by epidemiologists (mostly agent-based models), which could be combined with relevant operations management science approaches (multi-echelon, multi-commodity, multi-period, multi-vehicle approaches etc).
- **End-to-End approaches**: containing efficiently an IDO necessitates a holistic approach. More comprehensive and integrated approaches are needed embracing logistical operations from sourcing of medical supplies and supplementary commodities to finally dispensing them to affected populations. These approaches will enhance our understanding on how costs could be minimized throughout the entire emergency response chain while achieving a higher level of efficiency in terms of time response.
- **More realistic assumptions in epidemic response modelling approaches**: future Operational Research/Management Science literature should incorporate more realistic features regarding the nature of IDOs. For example, time is a critical parameter in IDO control and therefore future modelling approaches should be based more on containment time minimization. Generally, there is a gap between policy recommendations and modelling approaches and, therefore, researchers should follow standards and guidelines published by health-care organizations (best practices) when developing IDO response operations frameworks. Streamlining these assessments by taking into account more realistic assumptions would lead to more robust models allowing for substantial and prompt scaling up of interventions when necessary.
- **Inventory management and replenishment policies**: The availability of key medical supplies is essential, particularly in the case of vaccine-preventable diseases. A typical example may refer to the establishment of vaccine stockpiles which could be used for vaccination in CHEs when necessary (in either endemic or epidemic settings) and relevant logistic prerequisites to mount such campaigns (encompassing a range of key-players like pharmaceutical manufacturers, leading health organizations, governments and NGO's). In addition, during the containment effort it is more likely that

inventories of essential medical supplies will be depleted. Therefore, future research approaches should deal with the replenishment aspects of various medical supplies and how other non-pharmaceutical interventions could serve as a temporary solution in this case. Even further, decentralized versus centralized inventory management policies should also be examined.

- **Evaluation of models and large scale exercises**: Future research directions should evaluate and assess the applicability and effectiveness of the existing IDO response operations frameworks. Such assessments could validate the adaptability of the existing frameworks as well as the appropriateness of the methodologies applied. They could also provide useful insights towards the development of more robust methodological approaches.
- **Development of harmonized approaches**: In future research approaches pharmaceutical interventions should be combined with non-pharmaceutical ones. For example, closure of schools and travel restrictions could be combined with more detailed IDO response operations approaches (taking into account more logistical prerequisites). In addition, some qualitative aspects of IDO control like, for instance, disobedience to quarantine rules merit further investigation. Finally, the development of new drugs and more effective treatment protocols in the near future will be critical as these approaches are likely to affect the way health care is administered and, consequently, the resources needed to perform IDO control actions.
- **Stochasticity**: many parameters and variables of IDO response operations systems are of stochastic nature. Among them is the capacity of response systems, the amount of supplies available, the transportation and distribution times, triage processing times, etc. The development of more robust models could be achieved should future research models embed stochastic parameters.
- **Reverse logistics**: during the containment effort of an IDO huge amounts of medical waste are produced, particularly during the implementation of immunization campaigns. This kind of waste is hazardous and should be treated accordingly. Future research approaches should cater for the development of reverse logistics aspects of the IDO response operations frameworks.
- **Performance metrics:** Aspects of performance measurement in the existing IDO operations management approaches have been rarely studied. Therefore, research is needed for the development of specific performance indicators based on both epidemiological (best practices, standardization of treatments and response protocols etc) and logistical characteristics.
- **Cross-functional drivers**: Information's management in the generic context of IDO response operations have received limited attention so far. Information's management is critical for early planning in emergency situations. In the case

of IDO control two streams of information are critical: (a) information related to the overall emergency situation and the characteristics of the population affected by the emergency (the immune status of the refugee or displaced population, relevant mortality and morbidity rates etc) and (b) information related to the response operations and response capacities. Therefore, future research approaches are needed for the development of integrated information platforms that will bring together these two different streams of information while taking into account context-specific and disease-specific particularities.

- **Coordination issues**: The coordination of all the parties involved in IDO control operations (primary health-care agencies, international organizations, suppliers, national/local authorities and NGO's) presents a significant challenge. More research is needed in this area so we can better understand the role of each participant in the response chain. Cross functional, inter-agency collaboration and the role of practitioners should also be considered.

Several areas for further research of the approaches presented in this thesis also exist:

- With respect to the methodologies applied in the second chapter, the examination of the time horizon's impact to the models and the incorporation of different actions' rates that depend on time is a fruitful area for further research. Future studies can also incorporate a more realistic epidemic model including features such as subdivision of the population by risk group and disease stage, non-homogeneous mixing, different types of infectious contacts, non-constant population sizes, different rates of exit from different groups and stochastic parameters. Apart from the usage of a more detailed transmission model another fruitful area for further research is the utilization of the proposed methodology in combination with non-pharmaceutical intervention for controlling an influenza outbreak. In this case social distancing and travel limitations could be coupled with pharmaceutical interventions (like an immunization campaign). Finally, logistical constraints of actually delivering a targeted vaccination campaign like limited vaccine supply or daily administration constraints and their interaction with the disease process could also be examined.
- The logistics network configuration model presented in Chapter 3 (for the targeted smallpox vaccination campaign) could also incorporate some more detailed logistical features. For example, routing of the vehicles that perform the distribution of the smallpox vaccine, facility location considerations (regarding the size and geographical location of the various PODs) and inventory replenishing policies could be incorporated within the developed

logistics optimization model. A more detailed smallpox model could also be used. In particular, an agent-based model taking into account social structures, the nature of close contacts (different transmission rates) as well as the spatiotemporal dynamics of the host population could give more precise results. Finally, levels of residual herd immunity within the host population could also be considered.

- Future research directions should also consider larger sample size of responses in the case of the implementation of the DEMATEL method. In addition, broadening the type of experts participating in the research (public health officials, logisticians etc) could provide more insights regarding the nature and the degree of influence among the key factors retrieved from the literature. Finally, the DEMATEL method could be combined with other multi-criteria techniques (like the Analytic Hierarchy Process) for capturing both quantitative and qualitative aspects of IDO control in CHEs.

Appendixes

Appendix A: List of publications

Papers published in international journals

1. Rachaniotis, N.P., Dasaklis, T.K., Pappis, C.P., 2012. A deterministic resource scheduling model in epidemic control: A case study. European Journal of Operational Research 216, 225-231.
2. T.K. Dasaklis, N.P. Rachaniotis, C.P. Pappis, 2012, Epidemics' Control and Logistics Operations: A review, International Journal of Production Economics, special issue: Models for Compassionate Operations.

Papers submitted for publication in international journals

1. N.P. Rachaniotis, T.K. Dasaklis, C.P. Pappis, 2015. Controlling infectious disease outbreaks: A deterministic allocation-scheduling model with multiple discrete resources, submitted for publication, IIE Transactions on Healthcare Systems Engineering.
2. T.K. Dasaklis, N.P. Rachaniotis, C.P. Pappis, 2015. Emergency supply chain management for controlling a smallpox outbreak: the case for regional mass vaccination, submitted for publication, International Journal of Systems Science: Operations & Logistics, special issue: Modelling and Simulation in Healthcare Systems.
3. T.K. Dasaklis, C.P. Pappis, 2014. Critical success factors for implementing cholera vaccination campaigns in humanitarian emergencies: a DEMATEL-based approach, submitted for publication, IIE Transactions on Healthcare Systems Engineering.

Working papers (to be submitted for publication in international journals)

1. T.K. Dasaklis, C.P. Pappis, 2015. Factors driving operational success for controlling infectious disease outbreaks in complex humanitarian emergencies: A systematic review and thematic synthesis.

Papers published in proceedings of international conferences

1. T.K. Dasaklis and C.P. Pappis, 2014, Factors driving operational success for controlling infectious disease outbreaks in humanitarian emergencies: the

case of cholera, Eighteenth International Working Seminar on Production Economics, February 24-28, Innsbruck, Austria.

2. T.K. Dasaklis, N.P. Rachaniotis and C.P. Pappis, 2013, A multi-commodity, multi-period logistics network approach for controlling an epidemic's outbreak, 2013 International Symposium on Operational Research and Applications (ISORAP2013), May 08-10, Marrakech, Morocco.
3. C.P. Pappis and T.K. Dasaklis, 2013, Operations coordination for epidemics containment in complex emergency systems, 2013 International Symposium on Operational Research and Applications (ISORAP2013), May 08-10, Marrakech, Morocco.
4. C.P. Pappis, N.P. Rachaniotis and T.K. Dasaklis, 2009, A deterministic resource scheduling model in epidemic logistics, 4th Multidisciplinary International Scheduling Conference-MISTA, 10-12 August, Dublin, Ireland, 570-580.

Presentations in international conferences

1. T.K. Dasaklis and C.P. Pappis, 2013, Appraisal of critical success factors for controlling infectious disease outbreaks using the DEMATEL method, EURO XXVI Conference, 1-4 July, 2013, Rome, Italy.
2. T.K. Dasaklis, C.P. Pappis and N.P. Rachaniotis, 2012, Optimizing the emergency distribution network in the case of epidemic outbreaks response, EURO XXV Conference, 8-11 July, 2012, Vilnius, Lithuania.
3. N.P. Rachaniotis, T.K. Dasaklis and C.P. Pappis, 2010, A deterministic scheduling model in epidemic's control with multiple resources, OR for patient-centered healthcare delivery 2010 (ORAHS 2010), July 18-23, Genova, Italy.
4. T.K. Dasaklis, C.P. Pappis and N.P. Rachaniotis, 2010, Emergency Supply Chain Management in the Case of Epidemics Containment, ALIO-INFORMS Joint International Meeting, 6-9 June, Buenos Aires, Argentina.

Appendix B: R code for the SVEIR model

The following code has been written for simulating disease's transmission among the 13 Administrative Health Districts (AHDs). For illustrative purposes, only the R-code for two AHDs is presented here (when vaccination initiates at day 21).

……

```
# SVEIR MODEL-SCENARIO 1: East Macedonia and Thrace (AHD1)

# SVEIR <- function(t, x, parms)
# Use: calculates the derivatives for the SVEIR model
# Input:
#      t: time
#      x: vector of the current values of all variables
#      parms: vector of all parameter values
#      Output:
#     der: vector of derivatives

#     To use the lsoda function, the model function has to be a function of t (time),
#     x (the vector of the variables) and parms (the parameters of the model).

SVEIR <- function(t, x, parms){
with(as.list(c(parms,x)),{
betaV <- ifelse(t<21,betaV,0.2)  # adjust betaV based on value of t
f <- ifelse(t<21,f,0.002)  # adjust f based on value of t
dS <- - beta*betaE*E*(S/N) - beta*betaI*I*(S/N) -  f*S - m*S +delta*R + thita*V + r*N
dV <- - beta*betaE*betaV*E*(V/N) - beta*betaI*betaV*I*(V/N) - m*V - thita*V + f*S
dE <- + beta*betaE*E*(S/N) + beta*betaI*I*(S/N) + beta*betaE*betaV*E*(V/N) +
beta*betaI*betaV*I*(V/N) - (m + kapa + sigma)*E
dI <- + sigma*E - (m + alpha + gama)*I
dR <- kapa*E + gama*I - m*R - delta*R
   der <- c(dS, dV, dE, dI, dR)
   list(der)  # the output must be returned
  }) # end of 'with'
}  # end of function definition

# MAIN PROGRAM

#LOAD LIBRARIES
#load R library for ordinary differential equation solvers
library(deSolve)

# INITIALIZE PARAMETER SETTINGS
parms <- c(beta=0.514,
         betaE=0.25,
         betaI=1,
         betaV=0.0,
```

```
        sigma=0.5,
        gama=0.2,
        delta=1/365,
        m=0.000000046,
        r=0.0000052,
        kapa=1.857/10000,
        alpha=9.3/1000000,
        thita=1/365,
        f=0.00)    # set the parameters of the model
dt    <- seq(0,120,0.25)      # set the time points for evaluation

# Handling the different initiation periods of the outbreaks (in each AHD) by using
events

# CENTRAL MACEDONIA
eventdat1 <- data.frame(var = c("I"),time = c(10),
                value = c(1), method = c("add"))
eventdat1

# REST OF THE PREFECTURES
eventdat2 <- data.frame(var = c("I"),time = c(25),
                value = c(5), method = c("add"))
eventdat2

# Initial conditions
inits1 <- c(S=15000, V=0, E=0, I=0, R=0)

# Calculation of the total number of individuals in each sub-population
N <- sum(inits1)

# SIMULATION OF THE MODEL

# Use lsoda to numerically solve the differential equations.
AHD1 <- as.data.frame(lsoda(inits1, dt, SVEIR, parms=parms, events = list(data =
eventdat2)))

# Write the output of the simulation in external archives
library(xlsx)
write.xlsx(AHD1,
"C:/Users/oresths/Desktop/Output/Scenario_1_Day_21/East_Macedonia_Thrace.xls
x")

# Plotting the output
attach(AHD1) # this command allows to refer to the columns of the data frame
directly.

matplot(x = AHD1[,1], y = AHD1[,-1], type = "l", lwd = 2,
```

```
      lty = "solid", col = c("red", "blue", "black", "green", "darkgreen"),
      xlab = "time", ylab = "y", main = "East Macedonia and Thrace")

legend("bottomright", col = c("red", "blue", "black", "green", "darkgreen"),
     legend = c("S", "V", "E", "I", "R"), lwd = 2)


#########################################################################
```

Appendix C: GLPK (GNU Linear Programming Kit) code for the logistics network configuration model

The following code has been written for obtaining the optimal solution of the logistics network configuration model.

```
#########################################################################
set C;
set NSC;
set RSC;
set POD;
set K;

param T;
param S{n in NSC, c in C, t in 1..T};
param M{k in K, t in 1..T};
param V{k in K, c in C};
param v{c in C};
param LC_NSC{n in NSC, k in K};
param LC_RSC{r in RSC, k in K};
param UC_RSC{r in RSC, k in K};
param UC_POD{p in POD, k in K};
param SC_NSC{n in NSC};
param SC_RSC{r in RSC};
param SC_POD{p in POD};
param CONFIG{r in RSC, p in POD};
param MATCH{c in C, k in K}, binary;
param INII_NSC{n in NSC, c in C};
param INII_RSC{r in RSC, c in C};
param INII_POD{p in POD, c in C};
param D{p in POD, c in C, t in 1..T};

var U{p in POD, c in C, t in 1..T}, >=0;
var I_NSC{n in NSC, c in C, t in 1..T}, >=0;
var I_RSC{r in RSC, c in C, t in 1..T}, >=0;
var I_POD{p in POD, c in C, t in 1..T}, >=0;
var XNR{n in NSC, r in RSC, c in C, k in K, t in 1..T}, >=0;
var XRP{r in RSC, p in POD, c in C, k in K, t in 1..T}, >=0;

minimize UNSDEM: sum{p in POD, c in C, t in 1..T}(U[p, c, t]);

s.t. INVEN_NSCa{n in NSC, c in C}: I_NSC[n,c,1]=INII_NSC[n,c]+S[n,c,1]-sum{r in RSC, k
in K}(XNR[n,r,c,k,1]);
s.t. INVEN_NSCb{n in NSC, c in C, t in 2..T}: I_NSC[n,c,t]=I_NSC[n,c,t-1]+S[n,c,t]-sum{r
in RSC, k in K}(XNR[n,r,c,k,t]);
```

```
s.t. INVEN_RSCa{r in RSC, c in C}: I_RSC[r,c,1]=INII_RSC[r,c]+sum{n in NSC, k in
K}(XNR[n,r,c,k,1]) -sum{p in POD, k in K}(XRP[r, p, c, k, 1]);
s.t. INVEN_RSCb{r in RSC, c in C, t in 2..T}: I_RSC[r,c,t]=I_RSC[r,c,t-1]+sum{n in NSC, k
in K}(XNR[n,r,c,k,t]) -sum{p in POD, k in K}(XRP[r, p, c, k, t]);
s.t. INVEN_PODa{p in POD, c in C}: I_POD[p,c,1]-U[p,c,1]=INII_POD[p,c]-
D[p,c,1]+sum{r in RSC, k in K}(XRP[r, p, c, k, 1]);
s.t. INVEN_PODb{p in POD, c in C, t in 2..T}: I_POD[p,c,t]-U[p,c,t]=I_POD[p,c,t-1]-
U[p,c,t-1]-D[p,c,t]+sum{r in RSC, k in K}(XRP[r, p, c, k, t]);

s.t. SCAPNSC{n in NSC, t in 1..T}: sum{c in C} I_NSC[n,c,t] <= SC_NSC[n];
s.t. SCAPRSC{r in RSC, t in 1..T}: sum{c in C} I_RSC[r,c,t] <= SC_RSC[r];
s.t. SCAPPOD{p in POD, t in 1..T}: sum{c in C} I_POD[p,c,t] <= SC_POD[p];

s.t. VOLCAP{k in K, c in C, t in 1..T}: sum{n in NSC, r in RSC} v[c]*XNR[n,r,c,k,t] + sum{r
in RSC, p in POD} v[c]*XRP[r,p,c,k,t]<=MATCH[c,k]*V[k,c]*M[k,t];
s.t. LOADCAPNSC{n in NSC, k in K,t in 1..T}: sum{r in RSC,c in C}XNR[n,r,c,k,t]<=
LC_NSC[n,k];
s.t. LOADCAPRSC{r in RSC, k in K,t in 1..T}: sum{p in POD,c in C}XRP[r,p,c,k,t]<=
LC_RSC[r,k];

s.t. UNLOADRSC{r in RSC, k in K, t in 1..T}: sum{n in NSC,c in C}XNR[n,r,c,k,t]<=
UC_RSC[r,k];
s.t. UNLOADPOD{p in POD, k in K, t in 1..T}: sum{r in RSC,c in C}XRP[r,p,c,k,t]<=
UC_POD[p,k];

s.t. CONFIGRES{r in RSC, p in POD, c in C, k in K, t in 1..T}: if CONFIG[r,p] =0 then
XRP[r,p,c,k,t]=0;

solve;

table table1{i in NSC, j in RSC, c in C, k in K, t in 1..T} OUT "CSV"
"dispatchedNSCtoRSC.csv" :
i ~ NationalStockpileCentre, j ~ RegionalStockpileCentre, c ~ Commodities, k ~
vehicles, t ~ period, XNR[i,j,c,k,t] ~ DispathcedCommoditiesA;

table table2{i in RSC, j in POD, c in C, k in K, t in 1..T} OUT "CSV"
"dispatchedRSCtoPOD.csv" :
 i ~ RegionalStockpileCentre, j ~ PointsOfDispensing, c ~ Commodities, k ~ vehicles, t
~ period, XRP[i, j, c, k, t] ~ DispathcedCommoditiesB;

 table table3{i in POD, c in C, t in 1..T} OUT "CSV" "UnsDemandPOD.csv" :
 i ~ PointsOfDispensing, c ~ Commodities, t ~ period, U[i, c, t] ~ UnDemand;

table table4{i in RSC, c in C, t in 1..T} OUT "CSV" "InventoryRSC.csv" :
 i ~ RegionalStockpileCentre, c ~ Commodities, t ~ period, I_RSC[i, c, t] ~ InventRSC;

table table5{i in POD, c in C, t in 1..T} OUT "CSV" "InventoryPOD.csv" :
```

```
 i ~ PointsOfDispensing, c ~ Commodities, t ~ period, I_POD[i, c, t] ~ InventPOD;

table table6{i in NSC, c in C, t in 1..T} OUT "CSV" "InventoryNSC.csv" :
 i ~ ationalStockpileCentre, c ~ Commodities, t ~ period, I_NSC[i, c, t] ~ InventNSC;

data;

set C:= c1 c2 c3 c4;
set NSC:=N1;
set RSC:= N2 N3 N4 N5 N6 N7 N8;
set POD:= N9 N10 N11 N12 N13 N14 N15 N16 N17 N18 N19 N20 N21 N22 N23 N24
N25 N26 N27 N28 N29 N30 N31 N32 N33 N34 N35 N36 N37 N38 N39 N40 N41 N42
N43 N44 N45 N46 N47 N48 N49 N50 N51 N52 N53 N54 N55;
set K:= K1 K2 K3 K4 M1 M2 M3 M4 M5 M6 M7 M8 M9 M10;

param T:=25;


#########################################################################
```

Additional data for the model may be seen in the following table

Parameters	Value
Set of Commodities	• Vaccines • 3 other supplementary commodities (water, food, blankets)
Periods	25
Demand for vaccines	5,900/POD/period
Set of Vehicles	• 4 (for vaccines' distribution) • 10 (for supplementary commodities)
Points of Dispensing	47
Regional Stockpile Centers	7
National Stockpile Centers	1
Storage capacity of NSC	5.000.000 Units
Storage capacity of RSC	3.000.000 Units
Storage capacity of POD	600.000 Units
Vehicles capacity (for vaccines' distribution)	21.000 lt
Vehicles capacity (for distributing the other commodities)	90.000 lt
Loading capacity of NSC (the same for all commodities and periods)	1.000.000 Units
Loading capacity of RSC (the same for all commodities and periods)	750.000 Units
Unloading capacity of RSC (the same for all commodities and periods)	750.000 Units
Unloading capacity of POD (the same for	500.000 Units

all commodities and periods)	
Volume of commodities	Vaccines: 0.2 lt Water: 0.5 lt Food: 2 lt Blankets: 4 lt
Vaccine supply at the NSC	40% in the initiation of the vaccination campaign and 60% ten days after (for all scenarios)

Appendix D: R code for the smallpox model-Unconstrained

The following R-code simulates the course of the smallpox outbreak when vaccination initiates at day 43 and lasts for 9 days (calibrated in such a way that the Effective Reproduction Number at day 52 drops below one) for the unconstrained set of scenarios. All runs are seeded with 500 infectious individuals. The number of persons not eligible for vaccination (pregnant women and immunocompromised individuals) is 34.818 and has been estimated as follows:

- For estimating the number of pregnant women at any given time we use the guidelines provided by the CDC[3]. Based on data from the Hellenic Statistical Authority[4] and from the portal "Health map of Greece"[5] the number of pregnant women within Attica region at any given time is estimated to be 30.171.
- For estimating the number of immunocompromised individuals (mainly HIV-positive persons) data from the Hellenic Center for Disease Control and Prevention has been used[6]. According to estimations 4.647 men and women known to be HIV positive reside within Attica region.

……

```
# SMALLPOX MODEL-Unconstrained scenarios

# SEIR <- function(t, x, parms)
# Use: calculates the derivatives for the SEIR model
# Input:
#     t: time (not used here, because there is no explicit time dependence)
#     x: vector of the current values of all variables
#     parms: vector of all parameter values
# Output:
#     der: vector of derivatives

# To use the lsoda function, the model function has to be a function of t (time),
# x (the vector of the variables) and parms (the parameters of the model).

SEIR <- function(t, x, parms){

  with(as.list(c(parms,x)),{
    Inv <-   ifelse(t<43,Inv,274185)
```

[3] http://www.cdc.gov/reproductivehealth/emergency/PDFs/EstNoofPregWom_508.pdf
[4] http://www.statistics.gr/portal/page/portal/ESYE

[5] http://ygeiamap.gov.gr/

[6] http://www.keelpno.gr/Portals/0/%CE%91%CF%81%CF%87%CE%B5%CE%AF%CE%B1/HIV/2014/Epidimiologiko_2013_final.pdf

```
   dS2 <- - b*S2*I3
   dS3 <- - b*S3*I3-Inv*S3/(S3+I1+I2+I3)
   dI1 <-   b*S3*I3+b*S2*I3-r1*I1-Inv*I1/(S3+I1+I2+I3)
   dI2 <-   r1*I1-r2*I2
   dI3 <-   r2*I2-r3*I3
   dI4 <-   r3*I3-r4*I4
   dR  <-   r4*I4+Inv*S3/(S3+I1+I2+I3)+Inv*I1/(S3+I1+I2+I3)
   der <-   c(dS2, dS3, dI1, dI2, dI3, dI4,dR)
   list(der)  # the output must be returned
  }) # end of 'with'
}  # end of function definition

# MAIN PROGRAM

# LOAD LIBRARIES
#load R library for ordinary differential equation solvers
library(deSolve)

# INITIALIZE PARAMETER SETTINGS

parms <- c(b=1/3752973, r1=1/3, r2=1/8, r3=1/3, r4=1/12, Inv=0)    # set the
parameters of the model
dt    <- seq(0,53,0.001)      # set the time points for evaluation

# Initial conditions

inits <- c(S2=34818, S3=3717655, I1=500, I2=0, I3=0, I4=0,R=0)

# Calculation of the total number of individuals in each sub-population

N <- sum(inits)
N

# SIMULATION OF THE MODEL

# Use lsoda to solve the differential equations numerically.

out <- as.data.frame(lsoda(inits, dt, SEIR, parms=parms)) # this way our set 'parms'
will be used as default
#q<-cbind(out$S2+out$S3)
#r<-c((3/3827124)*(cbind(out$S2+out$S3)))
Effective_Rep_Number<-c((3/3752973)*(cbind(out$S2+out$S3)))

plot(Effective_Rep_Number)

o<-cbind(dt, Effective_Rep_Number)
# Calculate and print the Effective Reproduction Number on the screen
```

```
# WRITE THE OUTPUT OF THE SIMULATION IN EXTERNAL ARCHIVES

library(xlsx)
write.xlsx(o, "C:/Users/oresths/Desktop/Effective_Rep_Number.xlsx")

##########################################################################
```

Appendix E: Vaccine allocation for controlling the smallpox outbreak (constraint set of scenarios)

Day	Vaccination at day 22	Vaccination at day 29	Vaccination at day 36	Vaccination at day 43	Vaccination at day 50
22	277300				
23	277300				
24	277300				
25	277300				
26	277300				
27	114689				
28					
29		277300			
30		277300			
31	277300	277300			
32	277300	277300			
33	277300	277300			,
34	277300	114689			
35	277300				
36	277300		277300		
37	277300		277300		
38	277300	277300	277300		
39	33384	277300	277300		
40		277300	277300		
41		277300	114689		
42		277300			
43		277300		277300	
44		277300		277300	
45		277300	277300	277300	
46		33384	277300	277300	
47			277300	277300	
48			277300	114689	
49			277300		
50			277300		277300
51			277300		277300
52			277300	277300	277300
53			33384	277300	277300
54				277300	277300
55				277300	114689
56				277300	
57				277300	
58				277300	
59				277300	277300
60				33384	277300
61					277300
62					277300

63					277300
64					277300
65					277300
66					277300
67					33384

Appendix F: R code for the smallpox model-Constrained set of scenarios (limited vaccine supply)

The following R-code simulates the course of the smallpox outbreak when vaccination initiates at day 43 for the constrained set of scenarios (limited vaccine supply).

……

```
############################
# SMALLPOX MODEL
############################

# SEIR <- function(t, x, parms)
# Use: calculates the derivatives for the SEIR model
# Input:
#     t: time (not used here, because there is no explicit time dependence)
#     x: vector of the current values of all variables
#     parms: vector of all parameter values
# Output:
#     der: vector of derivatives

# To use the lsoda function, the model function has to be a function of t (time),
# x (the vector of the variables) and parms (the parameters of the model).

SEIR <- function(t, x, parms){

  with(as.list(c(parms,x)),{
    Inv <-   ifelse(t<43,Inv,277300)
    Inv <-   ifelse(t<48,Inv,114689)
    Inv <-   ifelse(t<49,Inv,0)
    Inv <-   ifelse(t<52,Inv,277300)
    Inv <-   ifelse(t<60,Inv,33384)
    Inv <-   ifelse(t<61,Inv,0)
    dS2 <- - b*S2*I3
    dS3 <- - b*S3*I3-Inv*S3/(S3+I1+I2+I3)
    dI1 <-   b*S3*I3+b*S2*I3-r1*I1-Inv*I1/(S3+I1+I2+I3)
    dI2 <-   r1*I1-r2*I2
    dI3 <-   r2*I2-r3*I3
    dI4 <-   r3*I3-r4*I4
    dR  <-   r4*I4+Inv*S3/(S3+I1+I2+I3)+Inv*I1/(S3+I1+I2+I3)
    der <-   c(dS2, dS3, dI1, dI2, dI3, dI4,dR)
    list(der)  # the output must be returned
  }) # end of 'with'
}  # end of function definition
```

Appendixes

```
############################
# MAIN PROGRAM
############################

### LOAD LIBRARIES
#load R library for ordinary differential equation solvers
library(deSolve)

### INITIALIZE PARAMETER SETTINGS

parms <- c(b=1/3752973, r1=1/3, r2=1/8, r3=1/3, r4=1/12, Inv=0)    # set the
parameters of the model
dt    <- seq(0,120,0.1)      # set the time points for evaluation

# Initial conditions

inits <- c(S2=34818, S3=3717655, I1=500, I2=0, I3=0, I4=0,R=0)

# Calculation of the total number of individuals in each sub-population

N <- sum(inits)
N
### SIMULATION OF THE MODEL

## Use lsoda to solve the differential equations numerically.

out <- as.data.frame(lsoda(inits, dt, SEIR, parms=parms)) # this way our set 'parms'
will be used as default
#q<-cbind(out$S2+out$S3)
#r<-c((3/3827124)*(cbind(out$S2+out$S3)))
Effective_Rep_Number<-c((3/3752973)*(cbind(out$S2+out$S3)))

plot(Effective_Rep_Number)

o<-cbind(dt, Effective_Rep_Number)
# Calculate and print the Effective Reproduction Number on the screen

# WRITE THE OUTPUT OF THE SIMULATION IN EXTERNAL ARCHIVES

library(xlsx)
write.xlsx(o, "C:/Users/oresths/Desktop/Effective_Rep_Number.xlsx")
#write.xlsx(out, "C:/Users/oresths/Desktop/out.xlsx")

#########################################################################
```

Appendix G: R code for the smallpox model-Constrained set of scenarios (limited vaccine supply and limited transportation capacities)

The following R-code simulates the course of the smallpox outbreak when vaccination initiates at day 43 for the constrained set of scenarios (limited vaccine supply, limited transportation capacities). Initially, the optimal solution of the logistics network model is derived (number of available vaccines per period). Based on these data the simulation of the smallpox model is performed.

……

```
############################
# SMALLPOX MODEL
############################

# SEIR <- function(t, x, parms)
# Use: calculates the derivatives for the SEIR model
# Input:
#     t: time (not used here, because there is no explicit time dependence)
#     x: vector of the current values of all variables
#     parms: vector of all parameter values
# Output:
#     der: vector of derivatives

# To use the lsoda function, the model function has to be a function of t (time),
# x (the vector of the variables) and parms (the parameters of the model).

SEIR <- function(t, x, parms){

 with(as.list(c(parms,x)),{
  Inv <-  ifelse(t<43,Inv,210000)
  Inv <-  ifelse(t<50,Inv,31189)
  Inv <-  ifelse(t<51,Inv,0)
  Inv <-  ifelse(t<54,Inv,210000)
  Inv <-  ifelse(t<64,Inv,151784)
  Inv <-  ifelse(t<65,Inv,0)
  dS2 <- - b*S2*I3
  dS3 <- - b*S3*I3-Inv*S3/(S3+I1+I2+I3)
  dI1 <-  b*S3*I3+b*S2*I3-r1*I1-Inv*I1/(S3+I1+I2+I3)
  dI2 <-  r1*I1-r2*I2
  dI3 <-  r2*I2-r3*I3
  dI4 <-  r3*I3-r4*I4
  dR  <-  r4*I4+Inv*S3/(S3+I1+I2+I3)+Inv*I1/(S3+I1+I2+I3)
  der <-  c(dS2, dS3, dI1, dI2, dI3, dI4,dR)
  list(der)  # the output must be returned
 }) # end of 'with'
```

```
}  # end of function definition

############################
# MAIN PROGRAM
############################

### LOAD LIBRARIES
#load R library for ordinary differential equation solvers
library(deSolve)

### INITIALIZE PARAMETER SETTINGS

parms <- c(b=1/3752973, r1=1/3, r2=1/8, r3=1/3, r4=1/12, Inv=0)    # set the
parameters of the model
dt    <- seq(0,120,0.1)      # set the time points for evaluation


# Initial conditions

inits <- c(S2=34818, S3=3717655, I1=500, I2=0, I3=0, I4=0,R=0)

# Calculation of the total number of individuals in each sub-population

N <- sum(inits)
N
### SIMULATION OF THE MODEL

## Use lsoda to solve the differential equations numerically.

out <- as.data.frame(lsoda(inits, dt, SEIR, parms=parms)) # this way our set 'parms'
will be used as default
#q<-cbind(out$S2+out$S3)
#r<-c((3/3827124)*(cbind(out$S2+out$S3)))
Effective_Rep_Number<-c((3/3752973)*(cbind(out$S2+out$S3)))

plot(Effective_Rep_Number)

o<-cbind(dt, Effective_Rep_Number)
# Calculate and print the Effective Reproduction Number on the screen

# WRITE THE OUTPUT OF THE SIMULATION IN EXTERNAL ARCHIVES

library(xlsx)
write.xlsx(o, "C:/Users/oresths/Desktop/Effective_Rep_Number.xlsx")
write.xlsx(out, "C:/Users/oresths/Desktop/out.xlsx")
#########################################################################
```

Appendix H: Items of the Enhancing transparency in reporting the synthesis of qualitative research (ENTREQ) statement used during the thematic synthesis.

No	Item	Guide and description	Check
1	Aim	State the research question the synthesis addresses.	√
2	Synthesis methodology	Identify the synthesis methodology or theoretical framework which underpins the synthesis, and describe the rationale for choice of methodology (e.g. meta-ethnography, thematic synthesis, critical interpretive synthesis, grounded theory synthesis, realist synthesis, meta-aggregation, meta-study, framework synthesis).	√
3	Approach to searching	Indicate whether the search was pre-planned (comprehensive search strategies to seek all available studies) or iterative (to seek all available concepts until they theoretical saturation is achieved).	√
4	Inclusion criteria	Specify the inclusion/exclusion criteria (e.g. in terms of population, language, year limits, type of publication, study type).	√
5	Data sources	Describe the information sources used (e.g. electronic databases (MEDLINE, EMBASE, CINAHL, psycINFO, Econlit), grey literature databases (digital thesis, policy reports), relevant organisational websites, experts, information specialists, generic web searches (Google Scholar) hand searching, reference lists) and when the searches conducted; provide the rationale for using the data sources.	√
6	Electronic Search strategy	Describe the literature search (e.g. provide electronic search strategies with population terms, clinical or health topic terms, experiential or social phenomena related terms, filters for qualitative research, and search limits).	√
7	Study screening methods	Describe the process of study screening and sifting (e.g. title, abstract and full text review, number of independent reviewers who screened studies).	√
8	Study characteristics	Present the characteristics of the included studies (e.g. year of publication, country, population, number of participants, data collection, methodology, analysis, research questions).	
9	Study selection results	Identify the number of studies screened and provide reasons for study exclusion (e,g, for comprehensive searching, provide numbers of studies screened and reasons for exclusion indicated in a figure/flowchart; for	√

		iterative searching describe reasons for study exclusion and inclusion based on modifications t the research question and/or contribution to theory development).	
10	Rationale for appraisal	Describe the rationale and approach used to appraise the included studies or selected findings (e.g. assessment of conduct (validity and robustness), assessment of reporting (transparency), assessment of content and utility of the findings).	
11	Appraisal items	State the tools, frameworks and criteria used to appraise the studies or selected findings (e.g. Existing tools: CASP, QARI, COREQ, Mays and Pope; reviewer developed tools; describe the domains assessed: research team, study design, data analysis and interpretations, reporting).	
12	Appraisal process	Indicate whether the appraisal was conducted independently by more than one reviewer and if consensus was required.	
13	Appraisal results	Present results of the quality assessment and indicate which articles, if any, were weighted/excluded based on the assessment and give the rationale.	
14	Data extraction	Indicate which sections of the primary studies were analysed and how were the data extracted from the primary studies? (e.g. all text under the headings " results /conclusions " were extracted electronically and entered into a computer software).	√
15	Software	State the computer software used, if any.	√
16	Number of reviewers	Identify who was involved in coding and analysis.	√
17	Coding	Describe the process for coding of data (e.g. line by line coding to search for concepts).	√
18	Study comparison	Describe how were comparisons made within and across studies (e.g. subsequent studies were coded into pre-existing concepts, and new concepts were created when deemed necessary).	√
19	Derivation of themes	Explain whether the process of deriving the themes or constructs was inductive or deductive.	√
20	Quotations	Provide quotations from the primary studies to illustrate themes/constructs, and identify whether the quotations were participant quotations of the authors' interpretation.	

21	Synthesis output	Present rich, compelling and useful results that go beyond a summary of the primary studies (e.g. new interpretation, models of evidence, conceptual models, analytical framework, development of a new theory or construct).	√

Appendix I: Full list of factors affecting the implementation of cholera vaccination campaigns in complex humanitarian emergencies

Dimension	Factors	Explanation	Source
Surveillance mechanisms	Establishment of surveilance mechanisms (F1)	Establishment of rapid, accurate and cost-effective public health surveillance systems for gathering data regarding disease's burden.	(Valenciano, Coulombier et al. 2003; Connolly, Gayer et al. 2004; Waring and Brown 2005; Global Task Force on cholera control 2006; Chaignat and Monti 2007; Chaignat, Monti et al. 2008; Bruckner and Checchi 2011; Desai and Clemens 2012; World Health Organization 2012; World Health Organization 2013)
	Laboratory logistics (F2)	Enhancing laboratory capacity for confirmation of suspected outbreaks.	(Valenciano, Coulombier et al. 2003; Connolly, Gayer et al. 2004; Global Task Force on cholera control 2006; Tappero and Tauxe 2011)
Human resources	Availability of health-care personnel (F3)	Shortages of health-care personnel are very common in humanitarian emergencies.	(Costanza Adinolfi, David S. Bassiouni et al. 2005; Global Task Force on cholera control 2006; Chaignat and Monti 2007; Chaignat, Monti et al. 2008; Date, Vicari et al. 2011; Von Seidlein, Jiddawi et al. 2013; World Health Organization 2013)
	Establishment of training programs for field workers (F4)	Training of emergency staff remains a significant issue as health workers have been found to be either inadequate or poorly mobilized during emergencies.	(Costanza Adinolfi, David S. Bassiouni et al. 2005; Global Task Force on cholera control 2006; Chaignat and Monti 2007; Chaignat, Monti et al. 2008; Ratnayake 2011)
Supplies	Availability of supplementary supplies (F5)	Complementary medical supplies as well as essential supplies (food and clean water)	(Chaignat, Monti et al. 2008; Von Seidlein, Jiddawi et al. 2013)

		should be delivered to affected populations.	
	Waste management (F6)	Waste related to the preparation and the use of the vaccine (cups, vials, boxes, etc.) should be collected and destroyed.	(Global Task Force on cholera control 2006; World Health Organization 2006)
	Vaccine supply (including the formation of an international stockpile of oral cholera vaccines) (F7)	The international community has long delayed putting in place a mechanism to ensure the availability of cholera vaccines when needed.	(Global Task Force on cholera control 2006; Chaignat and Monti 2007; World Health Organization 2007; Waldor, Hotez et al. 2010; Date, Vicari et al. 2011; Farmer, Almazor et al. 2011; Plotkin, Shin et al. 2011; Tappero and Tauxe 2011; Holmgren 2012; World Health Organization 2012; World Health Organization 2012; Von Seidlein, Jiddawi et al. 2013; World Health Organization 2013)
Vaccines' characteristics	Protective immunity (F8)	A major consideration is the time it takes a vaccine to provide protective immunity and the number of doses required.	(Connolly, Gayer et al. 2004; Date, Vicari et al. 2011; World Health Organization 2013)
	Cost (F9)	As financial resources are limited, the cost of the vaccine (production, delivery etc) plays a crucial role.	(Connolly, Gayer et al. 2004; World Health Organization 2006; Chaignat and Monti 2007; Chaignat, Monti et al. 2008; Lopez, Clemens et al. 2008; Plotkin, Shin et al. 2011; World Health Organization 2013)
	Logistical prerequisites (F10)	The type of vaccine involved, its weight, volume and the necessity for two doses to	(Legros, Paquet et al. 1999; Connolly, Gayer et al. 2004; Global Task Force on cholera control 2006; World Health

		be administered present logistical chalenges in acute humanitarian emergencies. The logistics of formulation of the vaccines define the so-called "vaccines' fieldability".	Organization 2006; Chaignat and Monti 2007; World Health Organization 2007; Chaignat, Monti et al. 2008; Lopez, Clemens et al. 2008; World Health Organization 2010; Date, Vicari et al. 2011; Holmgren 2012; World Health Organization 2013)
Contextual considerations	Political context (F11)	Tensions may exist between key-actors, making both the delivery and the acceptance of humanitarian assistance problematic. Vaccination interventions could be politicized and become the subject of contention.	(Calain, Chaine et al. 2004; World Health Organization 2013)
	Ethical considerations (F12)	Fair allocation of limited resources (health-care personnel, vaccines etc) is critical in emergencies.	(World Health Organization 2013)
	Insecurity (F13)	Safeguarding the security of both affected population and humanitarian agencies is of paramount importance.	(Valenciano, Coulombier et al. 2003; Connolly, Gayer et al. 2004; Pinto, Saeed et al. 2005; Global Task Force on cholera control 2006; World Health Organization 2006; Chaignat and Monti 2007; World Health Organization 2007; Chaignat, Monti et al. 2008; Date, Vicari et al. 2011)
	Existing vaccination and treatment delivery channels and relevant capacities (F14)	Existing vaccination and treatment delivery channels provide a base infrastructure for cholera vaccine administration.	(Farmer, Almazor et al. 2011; World Health Organization 2012; World Health Organization 2013)

	Populations mobility (F15)	Emergency affected populations present high mobility during humanitarian emergencies (continual population movements).	(Global Task Force on cholera control 2006; World Health Organization 2006; Chaignat and Monti 2007; Chaignat, Monti et al. 2008; Date, Vicari et al. 2011)
	Overall health status of the affected populations including levels of prior herd immunity (F16)	During emergencies there is a gradual degradation of the health status of affected populations. In addition, populations experiencing epidemic cholera often have limited background natural immunity to the disease.	(Connolly, Gayer et al. 2004; Plotkin, Shin et al. 2011)
	Prioritization of health-care actions (F17)	Prioritization of health needs in humanitarian emergencies remains crucial as several health priorities emerge (risk for other infectious disease outbreaks, case management, treatment of injuries).	(Legros, Paquet et al. 1999; World Health Organization 2006; Chaignat and Monti 2007; Chaignat, Monti et al. 2008; Date, Vicari et al. 2011; Holmgren 2012; World Health Organization 2013)
	Accessibility (F18)	Access to target populations is often limited by geographical factors (rural and remoted regions), destruction of roads, climatic conditions, poor infrastructure, inadequate transport services etc.	(Pinto, Saeed et al. 2005; Global Task Force on cholera control 2006; World Health Organization 2006; Chaignat and Monti 2007; Farmer, Almazor et al. 2011; World Health Organization 2012)
	Relevance of interventions (F19)	Cholera vaccination must be synergistic with other cholera prevention and control measures (access to water and proper	(Connolly, Gayer et al. 2004; Chaignat, Monti et al. 2008; Date, Vicari et al. 2011; World Health Organization 2013)

		sanitation etc)	
	Political commitment (F20)	Strong political commitment of both national and international partners facilitates immunization campaigns.	(Chaignat and Monti 2007; Chaignat, Monti et al. 2008; Date, Vicari et al. 2011)
Communication mechanisms	Mobilization of target populations through health education campaigns (F21)	Target population should be informed well in advance about the role and procedure of the vaccination campaign.	(Legros, Paquet et al. 1999; Global Task Force on cholera control 2006; World Health Organization 2006; Chaignat and Monti 2007; Chaignat, Monti et al. 2008; Date, Vicari et al. 2011; World Health Organization 2013)
	Community involvement (F22)	Involvement of the affected population is critical to ensure effective social mobilization and to avoid culturally-inappropriate activities.	(Global Task Force on cholera control 2006; World Health Organization 2006; Chaignat and Monti 2007; Chaignat, Monti et al. 2008)
Financial resources	Funds (including donations) (F23)	Financing of any vaccination program must be assured prior to the decision to implement it.	(Chaignat, Monti et al. 2008; World Health Organization 2012; World Health Organization 2013)
Collaboration and coordination mechanisms	Coordination (F24)	Planning and preparation of immunization campaigns call for coordination among several key-partners.	(Global Task Force on cholera control 2006; World Health Organization 2006; Chaignat and Monti 2007; Farmer, Almazor et al. 2011; World Health Organization 2012)
	Collaboration (F25)	The implementation of vaccination campaigns necessitate strong collaboration among health authorities	(Pinto, Saeed et al. 2005; Tappero and Tauxe 2011)

Appendix J: Experts' responses

Expert 1

	Establishment of surveillance mechanisms (F1)	Availability of well-trained health-care personnel (F2)	Availability of vaccines and supplementary supplies (F3)	Political context (F4)	Mobilization of target populations (F5)	Covering the cost of the campaign (F6)	Coordination (F7)	Physical access to target populations (F8)	Insecurity (F9)
Establishment of surveillance mechanisms (F1)	0	2	4	4	4	4	4	4	1
Availability of well-trained health-care personnel (F2)	4	0	3	2	4	3	3	4	2
Availability of vaccines and supplementary supplies (F3)	3	2	0	0	2	3	3	3	3
Political context (F4)	3	4	2	0	2	2	3	3	4
Mobilization of target populations (F5)	4	2	2	4	0	4	4	4	2
Covering the cost of the campaign (F6)	3	4	4	2	2	0	3	3	3
Coordination (F7)	4	3	3	3	4	4	0	3	4
Physical access to target populations (F8)	4	3	1	4	4	2	3	0	3
Insecurity (F9)	3	2	3	4	3	3	3	4	0

Expert 2

	Establishment of surveillance mechanisms (F1)	Availability of well-trained health-care personnel (F2)	Availability of vaccines and supplementary supplies (F3)	Political context (F4)	Mobilization of target populations (F5)	Covering the cost of the campaign (F6)	Coordination (F7)	Physical access to target populations (F8)	Insecurity (F9)
Establishment of surveillance mechanisms (F1)	0	2	4	4	4	4	4	4	1
Availability of well-trained health-care personnel (F2)	4	0	3	2	4	3	3	4	2
Availability of vaccines and supplementary supplies (F3)	3	2	0		2	3	3	3	3
Political context (F4)	3	4	2	0	2	2	3	3	4
Mobilization of target populations (F5)	4	2	2	4	0	4	4	4	2
Covering the cost of the campaign (F6)	3	4	4	2	2	0	3	3	3
Coordination (F7)	4	3	3	3	4	4	0	3	3
Physical access to target populations (F8)	4	3	1	4	4	2	3	0	4
Insecurity (F9)	3	2	3	4	3	3	3	4	0

Expert 3

	Establishment of surveillance mechanisms (F1)	Availability of well-trained health-care personnel (F2)	Availability of vaccines and supplementary supplies (F3)	Political context (F4)	Mobilization of target populations (F5)	Covering the cost of the campaign (F6)	Coordination (F7)	Physical access to target populations (F8)	Insecurity (F9)
Establishment of surveillance mechanisms (F1)	0	0	1	0	1	2	2	0	0
Availability of well-trained health-care personnel (F2)	3	0	1	0	2	2	2	1	0
Availability of vaccines and supplementary supplies (F3)	0	1	0	0	2	2	2	0	0
Political context (F4)	3	3	3	0	4	2	2	3	4
Mobilization of target populations (F5)	2	1	0	0	0	1	1	0	2
Covering the cost of the campaign (F6)	3	3	4	0	2	0	3	2	0
Coordination (F7)	3	2	3	0	3	3	0	2	0
Physical access to target populations (F8)	3	3	2	0	4	1	2	0	1
Insecurity (F9)	4	3	3	3	4	2	3	4	0

Expert 4

	Establishment of surveillance mechanisms (F1)	Availability of well-trained health-care personnel (F2)	Availability of vaccines and supplementary supplies (F3)	Political context (F4)	Mobilization of target populations (F5)	Covering the cost of the campaign (F6)	Coordination (F7)	Physical access to target populations (F8)	Insecurity (F9)
Establishment of surveillance mechanisms (F1)	0	1	1	3	3	2	2	3	4
Availability of well-trained health-care personnel (F2)	3	0	1	3	3	2	2	3	4
Availability of vaccines and supplementary supplies (F3)	0	1	0	3	3	2	2	3	4
Political context (F4)	4	3	1	0	3	2	2	3	4
Mobilization of target populations (F5)	0	2	1	3	0	2	2	3	4
Covering the cost of the campaign (F6)	2	2	2	2	3	0	2	3	4
Coordination (F7)	2	2	2	2	3	2	0	3	4
Physical access to target populations (F8)	2	2	2	2	3	2	2	0	4
Insecurity (F9)	1	3	3	3	3	3	3	3	0

Appendix K: R code for the implementation of the DEMATEL method

The following R-code was used for implementing the DEMATEL method.

……

```
################################
#R-code for the DEMATEL method#
################################

#Step 1: Calculation of the average matrix
#Reading experts' responses from external files

Response_1 <-
as.matrix(read.table("C:/Users/oresths/Desktop/Import_DEMATEL/response_1.txt",head=
F))
Response_2 <-
as.matrix(read.table("C:/Users/oresths/Desktop/Import_DEMATEL/response_2.txt",head=
F))
Response_3 <-
as.matrix(read.table("C:/Users/oresths/Desktop/Import_DEMATEL/response_3.txt",head=
F))
Response_4 <-
as.matrix(read.table("C:/Users/oresths/Desktop/Import_DEMATEL/response_4.txt",head=
F))
A <-as.matrix((Response_1+Response_2+Response_3+Response_4)/4)

#Step 2 and 3: Calculation of the direct influence matrix/total relation matrix

N <- A/26.25

T<-N%*%(solve(diag(9)-N))
D<-c(apply(T,1,sum))
R<-c(apply(T,2,sum))

#Step 4: Generation of the causal diagram

X<-D+R
Y<-D-R
H<-cbind(D,R,X,Y)

#Writing the output in external files

library(xlsx)

write.xlsx(H, "C:/Users/oresths/Desktop/DEMATEL/H.xlsx")
write.xlsx(T, "C:/Users/oresths/Desktop/DEMATEL/T.xlsx")
```

```
#Defining the vector of the factors
Factors <- c("F1","F2","F3","F4","F5","F6","F7","F8","F9")

#Plotting the causal diagram

plot(X, Y,
    xlab= "D+R",
    ylab= "D-R",
    col= "blue", pch = 19, cex = 1, lty = "solid", lwd = 2)

text(X, Y, labels=Factors, cex= 0.7, pos=3)
legend("topleft", c("F1: Establishment of surveillance mechanisms",
                    "F2: Availability of well-trained health-care personnel",
                    "F3:  Availability of vaccines and supplementary supplies",
                    "F4: Political context",
                    "F5: Mobilization of target populations",
                    "F6: Funding",
                    "F7: Coordination",
                    "F8: Physical access to target populations",
                    "F9: Insecurity"),
      cex=.8, col=c("black", "black"))
abline(h=0,lty=5)
```

References

Aaby, K., J. W. Herrmann, et al. (2006). "Montgomery county's public health service uses operations research to plan emergency mass dispensing and vaccination clinics." Interfaces **36**(6): 569-579.

Adams, P. (2013). "Cholera in Haiti takes a turn for the worse." The Lancet **381**(9874): 1264.

Adida, E., P. C. C. DeLaurentis, et al. (2011). "Hospital stockpiling for disaster planning." IIE Transactions (Institute of Industrial Engineers) **43**(5): 348-362.

Adu, F. D., A. A. Adedeji, et al. (1996). "Live viral vaccine potency: An index for assessing the cold chain system." Public Health **110**(6): 325-330.

Afshar, A. and A. Haghani (2012). "Modeling integrated supply chain logistics in real-time large-scale disaster relief operations." Socio-Economic Planning Sciences **46**(4): 327-338.

Ajelli, M., B. Gonçalves, et al. (2010). "Comparing large-scale computational approaches to epidemic modeling: Agent-based versus structured metapopulation models." BMC Infectious Diseases **10**.

Ajelli, M. and S. Merler (2008). "The impact of the unstructured contacts component in influenza pandemic modeling." PLoS ONE **3**(1).

Ak, A., J. L. Heier Stamm, et al. (2012). Improving the Pan American Health Organization's Vaccine Supply Chain. To appear in: Humanitarian Logistics and Supply Chains: Case Studies and Research Issues, D. Goldsman, P. Goldsman, and S. Kumar (editors), Taylor and Francis. Article in press (accepted 2010). .

Albala-Bertrand, J. M. (2000). "Complex emergencies versus natural disasters: An analytical comparison of causes and effects." Oxford Development Studies **28**(2): 187-204.

Aldis, G. K. and M. G. Roberts (2005). "An integral equation model for the control of a smallpox outbreak." Mathematical Biosciences **195**(1): 1-22.

Alexander, M. E., S. M. Moghadas, et al. (2008). "A delay differential model for pandemic influenza with antiviral treatment." Bulletin of Mathematical Biology **70**(2): 382-397.

Alidaee, B. and N. K. Womer (1999). "Scheduling with time dependent processing times: review and extensions." Journal of the Operational Research Society **50**(7): 711-720.

Altay, N. and W. G. Green Iii (2006). "OR/MS research in disaster operations management." European Journal of Operational Research **175**(1): 475-493.

Anderson, R. and R. May (1992). Infectious diseases of humans: dynamics and control, Oxford University Press, USA.

Arinaminpathy, N. and A. McLean (2008). "Antiviral treatment for the control of pandemic influenza: some logistical constraints." Journal of the Royal Society Interface **5**(22): 545.

Arinaminpathy, N. and A. R. McLean (2009). "Logistics of control for an influenza pandemic." Epidemics **1**(2): 83-88.

Arinaminpathy, N., J. Savulescu, et al. (2009). "Effective use of a limited antiviral stockpile for pandemic influenza." Journal of Bioethical Inquiry **6**(2): 171-179.

Arino, J., F. Brauer, et al. (2008). "A model for influenza with vaccination and antiviral treatment." Journal of Theoretical Biology **253**(1): 118-130.

Arita, I., M. Nakane, et al. (2004). "Role of a sentinel surveillance system in the context of global surveillance of infectious diseases." Lancet Infectious Diseases **4**(3): 171-177.

Arora, H., T. S. Raghu, et al. (2010). "Resource allocation for demand surge mitigation during disaster response." Decision Support Systems **50**(1): 304-315.

References

Artenstein, A. W. (2008). "New generation smallpox vaccines: A review of preclinical and clinical data." Reviews in Medical Virology **18**(4): 217-231.

Arya, S. C. and N. Agarwal (2012). "Prevention and control of infections after natural disasters." Expert Review of Anti-Infective Therapy **10**(5): 529-530.

Bachman, A., T. C. E. Cheng, et al. (2002). "Scheduling start time dependent jobs to minimize the total weighted completion time." Journal of the Operational Research Society **53**(6): 688-693.

Bachman, A., A. Janiak, et al. (2002). "Minimizing the total weighted completion time of deteriorating jobs." Information Processing Letters **81**(2): 81-84.

Balcan, D., H. Hu, et al. (2009). "Seasonal transmission potential and activity peaks of the new influenza A(H1N1): A Monte Carlo likelihood analysis based on human mobility." BMC Medicine **7**: 45.

Balicer, R. D., M. Huerta, et al. (2005). "Cost-benefit of stockpiling drugs for influenza pandemic." Emerging Infectious Diseases **11**(8): 1280-1282.

Barbera, J., A. Macintyre, et al. (2001). "Large-scale quarantine following biological terrorism in the United States - Scientific examination, logistic and legal limits, and possible consequences." Jama-Journal of the American Medical Association **286**(21): 2711-2717.

Bartels, S. A. and M. J. VanRooyen (2012). "Medical complications associated with earthquakes." The Lancet **379**(9817): 748-757.

Bellos, A., K. Mulholland, et al. (2010). "The burden of acute respiratory infections in crisis-affected populations: A systematic review." Conflict and Health **4**(1).

Benedictow, O. J. (1987). "Morbidity in historical plague epidemics (Tuscany and France)." Population Studies **41**(3): 401-431.

Berman, O. and A. Gavious (2007). "Location of terror response facilities: A game between state and terrorist." European Journal of Operational Research **177**(2): 1113-1133.

Biot, M., D. Chandramohan, et al. (2003). "Tuberculosis treatment in complex emergencies: Are risks outweighing benefits?" Tropical Medicine and International Health **8**(3): 211-218.

Blecken, A., C. Danne, et al. (2010). Optimal stock relocation under uncertainty in post-disaster humanitarian operations. 43rd Annual Hawaii International Conference on System Sciences, HICSS-43, Koloa, Kauai, HI.

Blower, S. and H. Dowlatabadi (1994). "Sensitivity and uncertainty analysis of complex models of disease transmission: an HIV model, as an example." International Statistical Review/Revue Internationale de Statistique: 229-243.

Boëlle, P. Y., S. Ansart, et al. (2011). "Transmission parameters of the A/H1N1 (2009) influenza virus pandemic: A review." Influenza and other Respiratory Viruses **5**(5): 306-316.

Boni, M. F., B. H. Manh, et al. (2009). "Modelling the progression of pandemic influenza A (H1N1) in Vietnam and the opportunities for reassortment with other influenza viruses." BMC Medicine **7**: 43.

Bozzette, S. A., R. Boer, et al. (2003). "A model for a smallpox-vaccination policy." New England Journal of Medicine **348**(5): 416-425.

Bracho, G., E. Varela, et al. (2010). "Large-scale application of highly-diluted bacteria for Leptospirosis epidemic control." Homeopathy **99**(3): 156-166.

Brandeau, M. (2005). Allocating resources to control infectious diseases. Operations Research and Health Care, Springer. **Volume 70:** 443-464.

Brandeau, M. L., D. W. Hutton, et al. (2007). "Planning the bioterrorism response supply chain: learn and live." American journal of disaster medicine **2**(5): 231-247.

References

Brandeau, M. L., G. S. Zaric, et al. (2008). "An ounce of prevention is worth a pound of cure: improving communication to reduce mortality during bioterrorism responses." American journal of disaster medicine **3**(2): 65-78.

Brandeau, M. L., G. S. Zaric, et al. (2003). "Resource allocation for control of infectious diseases in multiple independent populations: Beyond cost-effectiveness analysis." Journal of Health Economics **22**(4): 575-598.

Bravata, D. M., K. M. McDonald, et al. (2004). "Systematic review: Surveillance systems for early detection of bioterrorism-related diseases." Annals of internal medicine **140**(11): 910-922.

Bretthauer, K. and B. Shetty (1995). "The nonlinear resource allocation problem." Operations Research **43**(4): 670-683.

Brown, V., P. J. Guerin, et al. (2008). "Research in complex humanitarian emergencies: The Médecins Sans Frontières/Epicentre experience." PLoS Medicine **5**(4): 0553-0556.

Bruckner, C. and F. Checchi (2011). "Detection of infectious disease outbreaks in twenty-two fragile states, 2000-2010: A systematic review." Conflict and Health **5**(1).

Buchanan-Smith, M. and I. Christoplos (2004). "Natural disasters amid complex political emergencies." Humanitarian Exchange **27**: 36-38.

Buehler, J., R. Berkelman, et al. (2003). "Syndromic surveillance and bioterrorism-related epidemics." Emerging Infectious Diseases **9**(10): 1197-1204.

Burke, D. S., J. M. Epstein, et al. (2006). "Individual-based Computational Modeling of Smallpox Epidemic Control Strategies." Academic Emergency Medicine **13**(11): 1142-1149.

Butler, J. C., M. L. Cohen, et al. (2002). "Collaboration between public health and law enforcement: New paradigms and partnerships for bioterrorism planning and response." Emerging Infectious Diseases **8**(10): 1152-1156.

Calain, P., J.-P. Chaine, et al. (2004). "Can oral cholera vaccination play a role in controlling a cholera outbreak?" Vaccine **22**(19): 2444-2451.

Carr, S. and S. Roberts (2010). Planning for infectious disease outbreaks: A geographic disease spread, clinic location, and resource allocation simulation, Baltimore, MD.

Carrasco, L. R., V. J. Lee, et al. (2011). "Strategies for antiviral stockpiling for future influenza pandemics: A global epidemic-economic perspective." Journal of the Royal Society Interface **8**(62): 1307-1313.

Carrat, F., J. Luong, et al. (2006). "A 'small-world-like' model for comparing interventions aimed at preventing and controlling influenza pandemics." BMC Medicine **4**.

Centers for disease control and prevention (2002). Smallpox Response Plan and Guidelines (Version 3.0). Annex 3. Guidelines for Large Scale Smallpox Vaccination Clinics. Logistical Considerations and Guidance for State and Local Planning for Emergency, Large-Scale, Voluntary Administration of Smallpox Vaccine in Response to a Smallpox Outbreak. Retrieved January 15, 2014 from www.bt.cdc.gov/agent/smallpox/response-plan/files/annex-3.pdf

Centers for Disease Control and Prevention (2004). "Emergency measles control activities - Darfur, Sudan, 2004." Morbidity and Mortality Weekly Report **53**(38): 897-899.

Centers for Disease Control and Prevention (2007). Guidelines for Smallpox Vaccine Packing & Shipping. Retrieved October 5, 2011 from http://emergency.cdc.gov/agent/smallpox/vaccination/pdf/packing-shipping.pdf.

Chaignat, C. L. and V. Monti (2007). "Use of oral cholera vaccine in complex emergencies: What next? Summary report of an expert meeting and recommendations of WHO." Journal of Health, Population and Nutrition **25**(2): 244-261.

Chaignat, C. L., V. Monti, et al. (2008). "Cholera in disasters: Do vaccines prompt new hopes?" Expert Review of Vaccines **7**(4): 431-435.

Chen, F. (2003). Information Sharing and Supply Chain Coordination. **11:** 341-421.

References

Cheng, T. C. E., Q. Ding, et al. (2003). "Scheduling Jobs with Piecewise Linear Decreasing Processing Times." Naval Research Logistics **50**(6): 531-554.

Cheng, T. C. E., Q. Ding, et al. (2004). "A concise survey of scheduling with time-dependent processing times." European Journal of Operational Research **152**(1): 1-13.

Chick, S. E., H. Mamani, et al. (2008). "Supply chain coordination and influenza vaccination." Operations Research **56**(6): 1493-1506.

Chowell, G., C. E. Ammon, et al. (2006). "Transmission dynamics of the great influenza pandemic of 1918 in Geneva, Switzerland: Assessing the effects of hypothetical interventions." Journal of Theoretical Biology **241**(2): 193-204.

Chowell, G., C. Viboud, et al. (2009). "Adaptive vaccination strategies to mitigate pandemic influenza: Mexico as a case study." PLoS ONE **4**(12).

Chretien, J. P., D. L. Blazes, et al. (2007). "The importance of militaries from developing countries in global infectious disease surveillance." World hospitals and health services : the official journal of the International Hospital Federation **43**(4): 32-37.

Cinti, S., C. Chenoweth, et al. (2005). "Preparing for pandemic influenza: Should hospitals stockpile oseltamivir?" Infection Control and Hospital Epidemiology **26**(11): 852-854.

Ciofi degli Atti, M. L., S. Merler, et al. (2008). "Mitigation measures for pandemic influenza in Italy: An individual based model considering different scenarios." PLoS ONE **3**(3).

Clasen, T., L. Smith, et al. (2006). "The drinking water response to the Indian Ocean tsunami, including the role of household water treatment." Disaster Prevention and Management **15**(1): 190-201.

Clemens, J., S. Shin, et al. (2011). "New-generation vaccines against cholera." Nature Reviews Gastroenterology and Hepatology **8**(12): 701-710.

Coburn, B. J., B. G. Wagner, et al. (2009). "Modeling influenza epidemics and pandemics: Insights into the future of swine flu (H1N1)." BMC Medicine **7**.

Colizza, V., A. Barrat, et al. (2007). "Modeling the worldwide spread of pandemic influenza: Baseline case and containment interventions." Plos Medicine **4**(1): 0095-0110.

Collin, N. and X. de Radiguès (2009). "Vaccine production capacity for seasonal and pandemic (H1N1) 2009 influenza." Vaccine **27**(38): 5184-5186.

Coninx, R. (2007). "Tuberculosis in complex emergencies." Bulletin of the World Health Organization **85**(8): 637-640.

Conn, R., F. Welch, et al. (2008). "Management of vaccine inventories as a critical health resource." IEEE Engineering in Medicine and Biology Magazine **27**(6): 61-65.

Connolly, M. A., M. Gayer, et al. (2004). "Communicable diseases in complex emergencies: Impact and challenges." Lancet **364**(9449): 1974-1983.

Contzen, N. and H. J. Mosler (2013). "Impact of different promotional channels on handwashing behaviour in an emergency context: Haiti post-earthquake public health promotions and cholera response." Journal of Public Health (Germany): 1-15.

Cooper, B. S., R. J. Pitman, et al. (2006). "Delaying the international spread of pandemic influenza." PLoS Medicine **3**(6): 0845-0855.

Costanza Adinolfi, David S. Bassiouni, et al. (2005). "Humanitarian response review. An independent report commissioned by the United Nations Emergency Relief Coordinator & Under-Secretary-General for Humanitarian Affairs, Office for the Coordination of Humanitarian Affairs (OCHA). Retrieved March 14, 2013 from http://www.unicef.org/emerg/files/ocha_hrr.pdf."

Craft, D. L., L. M. Wein, et al. (2005). "Analyzing bioterror response logistics: The case of anthrax." Management Science **51**(5): 679-694.

Cruz-Aponte, M., E. C. McKiernan, et al. (2011). "Mitigating effects of vaccination on influenza outbreaks given constraints in stockpile size and daily administration capacity." BMC Infectious Diseases **11**.

References

Dadgar, N., A. Ansari, et al. (2003). "Implementation of a mass measles campaign in Central Afghanistan, December 2001 to May 2002." Journal of Infectious Diseases **187**(SUPPL. 1): S186-S190.

Daley, D. and J. Gani (1999). Epidemic modelling: an introduction, Cambridge University Press.

Das, T. K., A. Savachkin, et al. (2008). "A large-scale simulation model of pandemic influenza outbreaks for development of dynamic mitigation strategies." IIE Transactions (Institute of Industrial Engineers) **40**(9): 893-905.

Dasaklis, T. K., C. P. Pappis, et al. (2012). "Epidemics control and logistics operations: A review." International Journal of Production Economics **139**(2): 398-410.

Date, K. A., A. Vicari, et al. (2011). "Considerations for oral cholera vaccine use during outbreak after earthquake in Haiti, 2010-2011." Emerging Infectious Diseases **17**(11): 2105-2112.

Dato, V., M. M. Wagner, et al. (2004). "How outbreaks of infectious disease are detected: A review of surveillance systems and outbreaks." Public Health Reports **119**(5): 464-471.

De Laurentis, P. C., E. Adida, et al. (2008). A game theoretical approach for hospital stockpile in preparation for pandemics. IIE Annual Conference and Expo 2008, Vancouver, BC.

DeLaurentis, P. C. C., E. Adida, et al. (2009). Hospital stockpiling for influenza pandemics with pre-determined response levels. 2009 IEEE/INFORMS International Conference on Service Operations, Logistics and Informatics, SOLI 2009, Chicago, IL.

Department of Health (2005). Smallpox Mass Vaccination. An operational planning Framework. Department of Health, Scottish Government. Retrieved June 11, 2013 from http://www.scotland.gov.uk/Publications/2005/09/20160232/02428.

Desai, S. N. and J. D. Clemens (2012). "An overview of cholera vaccines and their public health implications." Current Opinion in Pediatrics **24**(1): 85-91.

Dhankhar, P., E. J. Dasbach, et al. (2009). "Economics of stockpiling for an influenza pandemic." The Lancet Infectious Diseases **9**(8): 459-460.

Dhankhar, P., J. D. Grabenstein, et al. (2010). "Cost-effectiveness of stockpiling 23-valent pneumococcal polysaccharide vaccine to prevent secondary pneumococcal infections among a high-risk population in the united states during an influenza pandemic." Clinical Therapeutics **32**(8): 1501-1516.

Dietz, V. J., D. J. Gubler, et al. (1990). "Epidemic dengue 1 in Brazil, 1986: Evaluation of a clinically based dengue surveillance system." American Journal of Epidemiology **131**(4): 693-701.

Dimitrov, N. B., S. Goll, et al. (2011). "Optimizing tactics for use of the U.S. antiviral strategic national stockpile for pandemic influenza." PLoS ONE **6**(1).

Dimitrov, N. B. and L. A. Meyers (2010). "Mathematical approaches to infectious disease prediction and control. J. J. Hasenbein, ed. INFORMS TutORials in Operations Research, Vol. 7. INFORMS, Hanover, MD, pp. 1--25.".

Doocy, S. and G. Burnham (2006). "Point-of-use water treatment and diarrhoea reduction in the emergency context: An effectiveness trial in Liberia." Tropical Medicine and International Health **11**(10): 1542-1552.

Duintjer Tebbens, R. J., M. A. Pallansch, et al. (2010). "Optimal vaccine stockpile design for an eradicated disease: Application to polio." Vaccine **28**(26): 4312-4327.

Dytczak, M. and G. Ginda (2013). "Is explicit processing offuzzy direct influence evaluations in DEMATEL indispensable?" Expert Systems with Applications **40**(12): 5027-5032.

Egan, J. R., I. M. Hall, et al. (2011). "Stamping out fires! Controlling smallpox with targeted mass vaccination." Medical Decision Making **31**(1): 69-78.

Eichner, M. (2003). "Case isolation and contact tracing can prevent the spread of smallpox." American Journal of Epidemiology **158**(2): 118-128.

References

Eichner, M. and K. Dietz (2003). "Transmission potential of smallpox: Estimates based on detailed data from an outbreak." American Journal of Epidemiology **158**(2): 110-117.

Eidelson, B. M. and I. Lustick (2004). "VIR-POX: An agent-based analysis of smallpox preparedness and response policy." JASSS **7**(3).

Ekici, A., P. Keskinocak, et al. (2008). Pandemic influenza response. Winter Simulation Conference, 2008. WSC 2008. .

Epstein, J. M., D. M. Goedecke, et al. (2007). "Controlling pandemic flu: The value of international air travel restrictions." PLoS ONE **2**(5).

Esbitt, D. (2003). "The strategic National Stockpile: Roles and responsibilities of health care professionals for receiving the stockpile assets." Disaster Management and Response **1**(3): 68-70.

Eubank, S., H. Guclu, et al. (2004). "Modelling disease outbreaks in realistic urban social networks." Nature **429**(6988): 180-184.

European Centre for Disease Prevention and Control (2009). Surveillance and studies in a pandemic in Europe-Technical Report. Retrieved May 17, 2010, from http://www.ecdc.europa.eu/en/publications/Publications/0906_TER_Surveillance_and_Studies_in_a_Pandemic_in_Europe.pdf.

Farmer, P., C. P. Almazor, et al. (2011). "Meeting Cholera's Challenge to Haiti and the World: A Joint Statement on Cholera Prevention and Care." PLoS Negl Trop Dis **5**(5): e1145.

Feldstein, M. S. (1963). "Economic analysis, operational research, and the national health service." Oxford Economic Papers **15**(3): 19-31.

Ferguson, N., M. Keeling, et al. (2003). "Planning for smallpox outbreaks." Nature **425**(6959): 681-685.

Ferguson, N. M., D. A. T. Cummings, et al. (2005). "Strategies for containing an emerging influenza pandemic in Southeast Asia." Nature **437**(7056): 209-214.

Ferguson, N. M., D. A. T. Cummings, et al. (2006). "Strategies for mitigating an influenza pandemic." Nature **442**(7101): 448-452.

Ferguson, N. M., M. J. Keeling, et al. (2003). "Planning for smallpox outbreaks." Nature **425**(6959): 681-685.

Fiedrich, F., F. Gehbauer, et al. (2000). "Optimized resource allocation for emergency response after earthquake disasters." Safety Science **35**(1-3): 41-57.

Finin, P., A. Kosaraju, et al. (2013). "The role of vaccination, antiorthopoxvirus drug, and social cooperativity in a mathematical model of smallpox control." Biosecurity and Bioterrorism **11**(1): 59-72.

Flahault, A., E. Vergu, et al. (2006). "Strategies for containing a global influenza pandemic." Vaccine **24**(44-46): 6751-6755.

French Red Cross (2010). French Red Cross Response to the Cholera Epidemic in Haiti. Retrieved March 18, 2013 from http://reliefweb.int/sites/reliefweb.int/files/resources/061AEBF2C2291D8C852577E4006BB434-Full_Report.pdf.

Fusco, F. M., S. Schilling, et al. (2012). "Infection control management of patients with suspected highly infectious diseases in emergency departments: Data from a survey in 41 facilities in 14 European countries." BMC Infectious Diseases **12**.

Gani, R. and S. Leach (2001). "Transmission potential of smallpox in contemporary populations." Nature **414**(6865): 748-751.

Gayer, M., D. Legros, et al. (2007). "Conflict and emerging infectious diseases." Emerging Infectious Diseases **13**(11): 1625-1631.

Gele, A. and G. Bjune (2010). "Armed conflicts have an impact on the spread of tuberculosis: the case of the Somali Regional State of Ethiopia." Conflict and Health **4**(1): 1-6.

References

Germann, T. C., K. Kadau, et al. (2006). "Mitigation strategies for pandemic influenza in the United States." Proceedings of the National Academy of Sciences of the United States of America **103**(15): 5935-5940.

Giovachino, M., T. Calhoun, et al. (2005). "Optimizing a District of Columbia Strategic National Stockpile dispensing center." Journal of public health management and practice **11**(4): 282-290.

Glasser, J., D. Taneri, et al. (2010). "Evaluation of targeted influenza vaccination strategies via population modeling." PLoS ONE **5**(9): 1-8.

Glasser, J. W., S. O. Foster, et al. (2008). "Evaluating public health responses to reintroduced smallpox via dynamic, socially structured, and spatially distributed metapopulation models." Clinical Infectious Diseases **46**(SUPPL. 3): S182-S194.

Global Task Force on Cholera Control (2004). Cholera outbreak: assessing the outbreak response and improving preparedness. Retrieved November 12, 2013 from http://whqlibdoc.who.int/hq/2004/WHO_CDS_CPE_ZFk_2004.4_eng.pdf.

Global Task Force on cholera control (2006). Oral cholera vaccine use in complex emergencies: what next? Retrieved November 14, 2013 from http://www.who.int/cholera/publications/cholera_vaccines_emergencies_2005.pdf.

Gould, E. A. and S. Higgs (2009). "Impact of climate change and other factors on emerging arbovirus diseases." Transactions of the Royal Society of Tropical Medicine and Hygiene **103**(2): 109-121.

Grais, R. F., P. Strebel, et al. (2011). "Measles vaccination in humanitarian emergencies: A review of recent practice." Conflict and Health **5**(1).

Hadler, J. L. (2005). "Public health strategies for distribution of influenza vaccine during an influenza pandemic." The Yale journal of biology and medicine **78**(5): 277-286.

Hall, I. M., J. R. Egan, et al. (2007). "Comparison of smallpox outbreak control strategies using a spatial metapopulation model." Epidemiology and Infection **135**(7): 1133-1144.

Halloran, M. E., N. M. Ferguson, et al. (2008). "Modeling targeted layered containment of an influenza pandemic in the United States." Proceedings of the National Academy of Sciences of the United States of America **105**(12): 4639-4644.

Halloran, M. E., I. M. Longini Jr, et al. (2002). "Containing bioterrorist smallpox." Science **298**(5597): 1428-1432.

Hansen, E. and T. Day (2011). "Optimal control of epidemics with limited resources." Journal of Mathematical Biology **62**(3): 423-451.

Harrington Jr, J. E. and E. B. Hsu (2010). "Stockpiling anti-viral drugs for a pandemic: The role of Manufacturer Reserve Programs." Journal of Health Economics.

Hashikura, M. and J. Kizu (2009). "Stockpile of personal protective equipment in hospital settings: Preparedness for influenza pandemics." American Journal of Infection Control **37**(9): 703-707.

Hehenkamp, A. and S. Hargreaves (2003). "Tuberculosis treatment in complex emergencies: South Sudan." Lancet **362 Suppl**: s30-31.

Henderson, D. A. (1999). "Biological terrorism - The looming threat of bioterrorism." Science **283**(5406): 1279-1282.

Henderson, D. A., T. V. Inglesby, et al. (1999). "Smallpox as a biological weapon: Medical and public health management." Journal of the American Medical Association **281**(22): 2127-2137.

Herrmann, J. W., S. Lu, et al. (2009). Delivery volume improvement for planning medication distribution. IEEE International Conference on Systems, Man and Cybernetics, 2009. SMC 2009. .

Hessel, L. (2009). "Pandemic influenza vaccines: Meeting the supply, distribution and deployment challenges." Influenza and other Respiratory Viruses **3**(4): 165-170.

References

Hethcote, H. (2000). "The Mathematics of Infectious Diseases." SIAM review **42**(4): 599-653.

Hollingsworth, T. D., D. Klinkenberg, et al. (2011). "Mitigation strategies for pandemic influenza a: Balancing conflicting policy objectives." PLoS Computational Biology **7**(2).

Holmgren, J. (2012). "A case for control of cholera in Africa by vaccination." The Lancet Infectious Diseases **12**(11): 818-819.

House, T., I. Hall, et al. (2009). "Contingency planning for a deliberate release of smallpox in Great Britain - the role of geographical scale and contact structure." BMC Infectious Diseases **10**.

Houston, S. (1998). "Tuberculosis in refugees and displaced persons." International Journal of Tuberculosis and Lung Disease **2**(9 SUPPL. 1): S94-S97.

Howard, N., A. Shafi, et al. (2010). "Malaria control under the Taliban regime: Insecticide-treated net purchasing, coverage, and usage among men and women in eastern Afghanistan." Malaria Journal **9**(1).

Hu, J. and L. Zhao (2011). "Emergency logistics strategy in response to anthrax attacks based on system dynamics." International Journal of Mathematics in Operational Research **3**(5): 490-509.

Hu, J. and L. Zhao (2012). "Emergency logistics network based on integrated supply chain response to public health emergency." ICIC Express Letters **6**(1): 113-118.

Huang, R., S. Kim, et al. (2010). "Facility location for large-scale emergencies." Annals of Operations Research: 1-16.

Hui, Q. (2010). Optimal control of bio-attack induced infectious disease dynamics: The case of anthrax. International Conference on Automation Science and Engineering, CASE 2010, Toronto, ON.

Hull, H. F., R. Danila, et al. (2003). "Smallpox and bioterrorism: Public-health responses." Journal of Laboratory and Clinical Medicine **142**(4): 221-228.

Hupert, N., J. Cuomo, et al. (2004). Community-Based Mass Prophylaxis: A Planning Guide for Public Health Preparedness. Prepared by Weill Medical College of Cornell University, Department of Public Health under Contract No. 290-02-0013-3. AHRQ Pub No. 04-0044. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved June 08, 2010 from http://archive.ahrq.gov/downloads/pub/biotertools/cbmprophyl.pdf

Hupert, N., A. I. Mushlin, et al. (2002). "Modeling the Public Health Response to Bioterrorism: Using Discrete Event Simulation to Design Antibiotic Distribution Centers." Med Decis Making **22**(suppl_1): s17-25.

Ibaraki, T. and N. Katoh (1988). Resource allocation problems: algorithmic approaches, The MIT Press

International Federation of Red Cross and Red Crescent Societies (2011). Haiti: Cholera outbreak – response and preparedness. 6-month summary update. Retrieved April 14, 2013 from http://www.ifrc.org/docs/appeals/10/MDR49007eu6.pdf.

Ippolito, G., V. Puro, et al. (2006). "Hospital preparedness to bioterrorism and other infectious disease emergencies." Cellular and Molecular Life Sciences **63**(19-20): 2213-2222.

Janiak, A. and M. Y. Kovalyov (2006). "Job sequencing with exponential functions of processing times." Informatica **17**(1): 13-24.

Janiak, A. and M. Y. Kovalyov (2006). "Scheduling in a contaminated area: A model and polynomial algorithms." European Journal of Operational Research **173**(1): 125-132.

Janiak, A. and M. Y. Kovalyov (2008). "Scheduling jobs in a contaminated area: A model and heuristic algorithms." Journal of the Operational Research Society **59**(7): 977-987.

Janiak, A. and T. Krysiak (2005). Multiprocessor Scheduling Problem with Stepwise Model of Job Value Change. Operations Research Proceedings 2004, Springer.

References

Janiak, A. and T. Krysiak (2007). "Single processor scheduling with job values depending on their completion times." Journal of Scheduling **10**(2): 129-138.

Jansson, A., M. Arneborn, et al. (2005). "Sensitivity of the Swedish statutory surveillance system for communicable diseases 1998-2002, assessed by the capture-recapture method." Epidemiology and Infection **133**(3): 401-407.

Jennings, L. C., A. S. Monto, et al. (2008). "Stockpiling prepandemic influenza vaccines: a new cornerstone of pandemic preparedness plans." The Lancet Infectious Diseases **8**(10): 650-658.

Jia, H., F. Ordóñez, et al. (2007). "A modeling framework for facility location of medical services for large-scale emergencies." IIE Transactions (Institute of Industrial Engineers) **39**(1): 41-55.

Jia, H., F. Ordóñez, et al. (2007). "Solution approaches for facility location of medical supplies for large-scale emergencies." Computers and Industrial Engineering **52**(2): 257-276.

Jingjing, X., Z. Lindu, et al. (2009). Collaborative Research between Epidemic Diffusion Network and Emergency Rescue Network in Anti-bioterrorism System. International Joint Conference on Computational Sciences and Optimization, CSO 2009. .

John Hopkins Bloomberg School of Public Health and the International Federation of Red Cross and Red Crescent Societies (2008). The Johns Hopkins and Red Cross Red Crescent. Public health guide for emergencies. Second edition. Retrieved July 17, 2010, from http://www.jhsph.edu/bin/s/c/Forward.pdf.

Kaiser, R., P. B. Spiegel, et al. (2003). "The application of geographic information systems and global positioning systems in humanitarian emergencies: Lessons learned, programme implications and future research." Disasters **27**(2): 127-140.

Kamadjeu, R., K. Assegid, et al. (2011). "Measles control and elimination in Somalia: The good, the bad, and the ugly." Journal of Infectious Diseases **204**(SUPPL. 1): S312-S317.

Kamugisha, C., K. L. Cairns, et al. (2003). "An outbreak of measles in Tanzanian refugee camps." Journal of Infectious Diseases **187**(SUPPL. 1): S58-S62.

Kaplan, E. H., D. L. Craft, et al. (2002). "Emergency response to a smallpox attack: The case for mass vaccination." Proceedings of the National Academy of Sciences of the United States of America **99**(16): 10935-10940.

Kaplan, E. H., D. L. Craft, et al. (2003). "Analyzing bioterror response logistics: The case of smallpox." Mathematical Biosciences **185**(1): 33-72.

Ke, Y. and L. Zhao (2008). Optimization of emergency logistics delivery model based on anti-bioterrorism. International Conference on Industrial Engineering and Engineering Management, IEEM 2008, Singapore.

Kelvin, A. A. (2011). "Cholera outbreak in the republic of congo, the Democratic Republic of Congo, and cholera worldwide." Journal of Infection in Developing Countries **5**(10): 688-691.

Kennedy, R. B., I. Ovsyannikova, et al. (2009). "Smallpox vaccines for biodefense." Vaccine **27**(SUPPL. 4): D73-D79.

Kerrod, E., A. M. Geddes, et al. (2005). "Surveillance and control measures during smallpox outbreaks." Emerging Infectious Diseases **11**(2): 291-297.

Kim-Farley, R. J., J. T. Celentano, et al. (2003). "Standardized emergency management system and response to a smallpox emergency." Prehospital and disaster medicine : the official journal of the National Association of EMS Physicians and the World Association for Emergency and Disaster Medicine in association with the Acute Care Foundation **18**(4): 313-320.

Kimbrough, W., V. Saliba, et al. (2012). "The burden of tuberculosis in crisis-affected populations: A systematic review." The Lancet Infectious Diseases **12**(12): 950-965.

References

Klein, K. R., J. G. Atas, et al. (2004). "Testing emergency medical personnel response to patients with suspected infectious disease." Prehospital and disaster medicine : the official journal of the National Association of EMS Physicians and the World Association for Emergency and Disaster Medicine in association with the Acute Care Foundation **19**(3): 256-265.

Kolaczinski, J., K. Graham, et al. (2005). "Malaria control in Afghanistan: Progress and challenges." Lancet **365**(9469): 1506-1512.

Kolaczinski, J. H., N. Muhammad, et al. (2004). "Subsidized sales of insecticide-treated nets in Afghan refugee camps demonstrate the feasibility of a transition from humanitarian aid towards sustainability." Malaria Journal **3**.

Kouadio, I. K., S. Aljunid, et al. (2012). "Infectious diseases following natural disasters: Prevention and control measures." Expert Review of Anti-Infective Therapy **10**(1): 95-104.

Kouadio, I. K., A. K. Koffi, et al. (2009). "Outbreak of measles and rubella in refugee transit camps." Epidemiology and Infection **137**(11): 1593-1601.

Kovacs, G. and K. Spens (2007). "Humanitarian logistics in disaster relief operations." International Journal of Physical Distribution & Logistics Management **37**(2): 99-114.

Koyuncu, M. and R. Erol (2010). "Optimal resource allocation model to mitigate the impact of pandemic influenza: A case study for Turkey." Journal of Medical Systems **34**(1): 61-70.

Krause, G., D. Altmann, et al. (2007). "SurvNet electronic surveillance system for infectious disease outbreaks, Germany." Emerging Infectious Diseases **13**(10): 1548-1555.

Kress, M. (2005). "The effect of social mixing controls on the spread of smallpox - A two-level model." Health Care Management Science **8**(4): 277-289.

Kretzschmar, M., S. Van Den Hof, et al. (2004). "Ring Vaccination and Smallpox Control." Emerging Infectious Diseases **10**(5): 832-841.

Krumkamp, R., M. Kretzschmar, et al. (2011). "Health service resource needs for pandemic influenza in developing countries: A linked transmission dynamics, interventions and resource demand model." Epidemiology and Infection **139**(1): 59-67.

Lee, B. Y., S. T. Brown, et al. (2010). "A computer simulation of vaccine prioritization, allocation, and rationing during the 2009 H1N1 influenza pandemic." Vaccine **28**(31): 4875-4879.

Lee, E. K., S. Maheshwary, et al. (2006). "Decision support system for mass dispensing of medications for infectious disease outbreaks and bioterrorist attacks." Annals of Operations Research **148**(1): 25-53.

Lee, S., G. Chowell, et al. (2010). "Optimal control for pandemic influenza: The role of limited antiviral treatment and isolation." Journal of Theoretical Biology **265**(2): 136-150.

Lee, S., M. Golinski, et al. (2012). "Modeling Optimal Age-Specific Vaccination Strategies Against Pandemic Influenza." Bulletin of Mathematical Biology **74**(4): 958-980.

Lee, V. J., H. P. Kai, et al. (2006). "Economics of neuraminidase inhibitor stockpiling for pandemic influenza, Singapore." Emerging Infectious Diseases **12**(1): 95-102.

Lee, V. J., D. C. Lye, et al. (2009). "Combination strategies for pandemic influenza response - a systematic review of mathematical modeling studies." BMC Medicine **7**.

Lee, Y. M. (2008). Analyzing dispensing plan for emergency medical supplies in the event of bioterrorism. Proceedings of the 40th Conference on Winter Simulation. Miami, Florida, Winter Simulation Conference**:** 2600-2608.

Legrand, J., C. Viboud, et al. (2004). "Modelling responses to a smallpox epidemic taking into account uncertainty." Epidemiology and Infection **132**(1): 19-25.

Legros, D., C. Paquet, et al. (1999). "Mass vaccination with a two-dose oral cholera vaccine in a refugee camp." Bulletin of the World Health Organization **77**(10): 837-842.

References

Li, Z. and C. Jie (2010). A Network Equilibrium Model for Emergency Logistics Response under Disaster Spreading. International Conference on Logistics Engineering and Intelligent Transportation Systems (LEITS 2010).

Liddle, K. F., R. Elema, et al. (2013). "TB treatment in a chronic complex emergency: Treatment outcomes and experiences in Somalia." Transactions of the Royal Society of Tropical Medicine and Hygiene **107**(11): 690-698.

Lipsitch, M., T. Cohen, et al. (2003). "Transmission dynamics and control of severe acute respiratory syndrome." Science **300**(5627): 1966-1970.

Liu, M. and J. iang (2013). "Dynamic optimization model for allocating medical resources in epidemic controlling." Journal of Industrial Engineering and Management **6**(1 LISS 2012): 73-88.

Liu, M. and L. Zhao (2011). "Analysis for epidemic diffusion and emergency demand in an anti-bioterrorism system." International Journal of Mathematical Modelling and Numerical Optimisation **2**(1).

Liu, M., L. Zhao, et al. (2011). "Mixed-collaborative distribution mode for emergency resources in an anti-bioterrorism system." International Journal of Mathematics in Operational Research **3**(2): 148-169.

Liu, Y. (2007). "Mathematical models of vaccine inventory design for a breakout of epidemic disease." PAMM **7**(1): 2150013-2150014.

Lober, W. B., B. T. Karras, et al. (2002). "Roundtable on bioterrorism detection: Information system-based surveillance." Journal of the American Medical Informatics Association **9**(2): 105-115.

Lombardo, J., H. Burkom, et al. (2003). "A Systems Overview of the Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCE II)." Journal of Urban Health **80**(2 SUPPL. 1).

Longini Jr, I. M., M. Elizabeth Halloran, et al. (2007). "Containing a large bioterrorist smallpox attack: a computer simulation approach." International Journal of Infectious Diseases **11**(2): 98-108.

Lopez, A. L., J. D. Clemens, et al. (2008). "Cholera vaccines for the developing world." Human Vaccines **4**(2): 165-169.

Lugnér, A. K. and M. J. Postma (2009). "Investment decisions in influenza pandemic contingency planning: Cost-effectiveness of stockpiling antiviral drugs." European Journal of Public Health **19**(5): 516-520.

M'ikanatha, N., R. Lynfield, et al. (2007). Infectious disease surveillance, Wiley-Blackwell.

Mallik, S., P. K. Mandal, et al. (2011). "Mass measles vaccination campaign in Aila cyclone-affected areas of west Bengal, India: An in-depth analysis and experiences." Iranian Journal of Medical Sciences **36**(4): 300-305.

Mamani, H., S. E. Chick, et al. (2013). "A game-theoretic model of international influenza vaccination coordination." Management Science **59**(7): 1650-1670.

Manley, D. K. and D. M. Bravata (2009). "A decision framework for coordinating bioterrorism planning: lessons from the BioNet program." American journal of disaster medicine **4**(1): 49-57.

Maon, F., A. Lindgreen, et al. (2009). "Developing supply chains in disaster relief operations through cross-sector socially oriented collaborations: A theoretical model." Supply Chain Management **14**(2): 149-164.

Martins, N., E. Heldal, et al. (2006). "Tuberculosis control in conflict-affected East Timor, 1996-2004." International Journal of Tuberculosis and Lung Disease **10**(9): 975-981.

Matrajt, L., M. E. Halloran, et al. (2013). "Optimal Vaccine Allocation for the Early Mitigation of Pandemic Influenza." PLoS Computational Biology **9**(3).

Matrajt, L. and I. M. Longini Jr (2010). "Optimizing vaccine allocation at different points in time during an epidemic." PLoS ONE **5**(11).

References

Mauch, V., D. Weil, et al. (2010). "Structure and management of tuberculosis control programs in fragile states—Afghanistan, DR Congo, Haiti, Somalia." Health Policy **96**(2): 118-127.

Maxwell, D. and B. Watkins (2003). "Humanitarian information systems and emergencies in the Greater Horn of Africa: Logical components and logical linkages." Disasters **27**(1): 72-90.

Mbah, M. L. N. and C. A. Gilligan (2011). "Resource allocation for epidemic control in metapopulations." PLoS ONE **6**(9).

McDonnell, S. M., H. N. Perry, et al. (2007). "Information for disasters, information disasters, and disastrous information." Prehospital and disaster medicine : the official journal of the National Association of EMS Physicians and the World Association for Emergency and Disaster Medicine in association with the Acute Care Foundation **22**(5): 406-413.

McMichael, A. J. (2003). "Global climate change: will it affect vector-borne infectious diseases?" Internal Medicine Journal **33**(12): 554-U552.

Meltzer, M. I., I. Damon, et al. (2001). "Modeling potential responses to smallpox as a bioterrorist weapon." Emerging Infectious Diseases **7**(6): 959-969.

Meyers, L., A. Galvani, et al. (2009). "Optimizing allocation for a delayed influenza vaccination campaign." PLoS Currents(DEC).

Miller, G., S. Randolph, et al. (2006). "Responding to bioterrorist smallpox in San Antonio." Interfaces **36**(6): 580-590.

Mizumoto, K., K. Ejima, et al. (2013). "Vaccination and clinical severity: Is the effectiveness of contact tracing and case isolation Hampered by past vaccination?" International Journal of Environmental Research and Public Health **10**(3): 816-829.

Mjelde, K. (1978). "Discrete resource allocation by a branch and bound method." Journal of the Operational Research Society **29**(10): 1021-1023.

Moodley, K., K. Hardie, et al. (2013). "Ethical considerations for vaccination programmes in acute humanitarian emergencies." Considérations éthiques des programmes de vaccination dans les situations d'urgence humanitaire graves **91**(4): 290-297.

Murali, P., F. Ordóñez, et al. (2012). "Facility location under demand uncertainty: Response to a large-scale bio-terror attack." Socio-Economic Planning Sciences **46**(1): 78-87.

Mylius, S. D., T. J. Hagenaars, et al. (2008). "Optimal allocation of pandemic influenza vaccine depends on age, risk and timing." Vaccine **26**(29-30): 3742-3749.

Nicoll, A. (2005). "Preventing and controlling disease outbreaks in a complex emergency situation: discussion of the tsunami aftermath." Euro surveillance : bulletin européen sur les maladies transmissibles = European communicable disease bulletin. **10**(3).

Nishiura, H., S. O. Brockmann, et al. (2008). "Extracting key information from historical data to quantify the transmission dynamics of smallpox." Theoretical Biology and Medical Modelling **5**.

Nishiura, H. and G. Chowell (2009). The Effective Reproduction Number as a Prelude to Statistical Estimation of Time-Dependent Epidemic Trends. Mathematical and Statistical Estimation Approaches in Epidemiology. G. Chowell, J. Hyman, L. A. Bettencourt and C. Castillo-Chavez, Springer Netherlands**:** 103-121.

Nishiura, H. and I. M. Tang (2004). "Modeling for a smallpox-vaccination policy against possible bioterrorism in Japan: The impact of long-lasting vaccinal immunity." Journal of Epidemiology **14**(2): 41-50.

O'Toole, T., M. Mair, et al. (2002). "Shining light on "dark winter"." Clinical Infectious Diseases **34**(7): 972-983.

References

Ohkusa, Y., K. Taniguchi, et al. (2005). "Prediction of smallpox outbreak and evaluation of control-measure policy in Japan, using a mathematical model." Journal of Infection and Chemotherapy **11**(2): 71-80.

Oladele, D. A., K. S. Oyedeji, et al. (2012). "An assessment of the emergency response among health workers involved in the 2010 cholera outbreak in northern Nigeria." Journal of Infection and Public Health **5**(5): 346-353.

Oloruntoba, R. and R. Gray (2006). "Humanitarian aid: An agile supply chain?" Supply Chain Management **11**(2): 115-120.

Ompad, D. C., S. Galea, et al. (2006). "Distribution of influenza vaccine to high-risk groups." Epidemiologic Reviews **28**(1): 54-70.

Orenstein, W. A. and W. Schaffner (2008). "Lessons Learned: Role of Influenza Vaccine Production, Distribution, Supply, and Demand-What It Means for the Provider." American Journal of Medicine **121**(7 SUPPL. 2).

Pappis, C. P. and N. P. Rachaniotis (2010). "Scheduling a single fire fighting resource with deteriorating fire suppression times and set-up times." Operational Research **10**(1): 27-42.

Pappis, C. P. and N. P. Rachaniotis (2010). "Scheduling in a multi-processor environment with deteriorating job processing times and decreasing values: The case of forest fires." J. of Heuristics **16**(4): 617-632.

Pastor, M., J. L. Pedraz, et al. (2013). "The state-of-the-art of approved and under-development cholera vaccines." Vaccine **31**(38): 4069-4078.

Patvivatsiri, L., E. J. Montes Jr, et al. (2007). Modeling bioterrorism preparedness with simulation in rural healthcare system. Winter Simulation Conference, WSC 2007 Washington, DC.

Pavlin, J. A., F. Mostashari, et al. (2003). "Innovative Surveillance Methods for Rapid Detection of Disease Outbreaks and Bioterrorism: Results of an Interagency Workshop on Health Indicator Surveillance." American Journal of Public Health **93**(8): 1230-1235.

Pietz, F., B. Benecke, et al. (2009). "Modeling and optimizing the public-health infrastructure for emergency response." Interfaces **39**(5): 476-490.

Pinto, A., M. Saeed, et al. (2005). "Setting up an early warning system for epidemic-prone diseases in Darfur: A participative approach." Disasters **29**(4): 310-322.

Platt, R., C. Bocchino, et al. (2003). "Syndromic Surveillance Using Minimum Transfer of Identifiable Data: The Example of the National Bioterrorism Syndromic Surveillance Demonstration Program." Journal of Urban Health **80**(2 SUPPL. 1).

Plotkin, S., S. Shin, et al. (2011). "Oral vaccines against cholera." Clinical Infectious Diseases **52**(11): 1343-1349.

Polonsky, J., F. Luquero, et al. (2013). "Public health surveillance after the 2010 Haiti earthquake: The experience of Médecins Sans Frontières." PLoS Currents(JAN): 1-19.

Polonsky, J. A., A. Ronsse, et al. (2013). "High levels of mortality, malnutrition, and measles, among recently-displaced Somali refugees in Dagahaley camp, Dadaab refugee camp complex, Kenya, 2011." Conflict and Health **7**(1).

Porco, T. C., K. Holbrook, et al. (2004). "Logistics of community smallpox control through contact tracing and ring vaccination: A stochastic network model." BMC Public Health **4**.

Protopopoff, N., M. Van Herp, et al. (2007). "Vector control in a malaria epidemic occurring within a complex emergency situation in Burundi: A case study." Malaria Journal **6**.

R Development Core Team (2008). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org.

References

Rachaniotis, N. P., T. K. Dasaklis, et al. (2012). "A deterministic resource scheduling model in epidemic control: A case study." European Journal of Operational Research **216**(1): 225-231.

Rachaniotis, N. P. and C. P. Pappis (2006). "Scheduling fire-fighting tasks using the concept of "deteriorating jobs"." Canadian Journal of Forest Research **36**(3): 652-658.

Radonovich, L. J., P. D. Magalian, et al. (2009). "Stockpiling supplies for the next influenza pandemic." Emerging Infectious Diseases **15**(6).

Rahmandad, H. and J. Sterman (2008). "Heterogeneity and network structure in the dynamics of diffusion: Comparing agent-based and differential equation models." Management Science **54**(5): 998-1014.

Ratnayake, R. (2011). "Training in epidemiology and disease control for humanitarian emergencies." Journal of Epidemiology and Community Health **65**(2): 98-99.

Rebmann, T., B. Citarella, et al. (2011). "Personal protective equipment use and allocation in home health during disasters." American Journal of Infection Control **39**(10): 823-831.

Ren, Y., F. Órdoñez, et al. (2013). "Optimal resource allocation response to a smallpox outbreak." Computers and Industrial Engineering **66**(2): 325-337.

Richards, C. F., J. L. Burstein, et al. (1999). "Emergency physicians and biological terrorism." Annals of Emergency Medicine **34**(2): 183-190.

Richter, A. and S. Khan (2009). "Pilot model: Judging alternate modes of dispensing prophylaxis in Los Angeles County." Interfaces **39**(3): 228-240.

Riley, S. and N. M. Ferguson (2006). "Smallpox transmission and control: Spatial dynamics in Great Britain." Proceedings of the National Academy of Sciences of the United States of America **103**(33): 12637-12642.

Riley, S., C. Fraser, et al. (2003). "Transmission dynamics of the etiological agent of SARS in Hong Kong: Impact of public health interventions." Science **300**(5627): 1961-1966.

Rodger, A. J., M. Toole, et al. (2002). "DOTS-based tuberculosis treatment and-control during civil conflict and an HIV epidemic, Churachandpur District, India." Bulletin of the World Health Organization **80**(6): 451-456.

Rolland, E., F. Checchi, et al. (2006). "Operational response to malaria epidemics: Are rapid diagnostic tests cost-effective?" Tropical Medicine and International Health **11**(4): 398-408.

Rottkemper, B., K. Fischer, et al. (2012). "A transshipment model for distribution and inventory relocation under uncertainty in humanitarian operations." Socio-Economic Planning Sciences **46**(1): 98-109.

Rottkemper, B., K. Fischer, et al. (2011). "Inventory relocation for overlapping disaster settings in humanitarian operations." OR Spectrum **33**(3): 721-749.

Rowland, M. and F. Nosten (2001). "Malaria epidemiology and control in refugee camps and complex emergencies." Annals of Tropical Medicine and Parasitology **95**(8): 741-754.

Salama, P., F. Assefa, et al. (2001). "Malnutrition, measles, mortality, and the humanitarian response during a famine in Ethiopia." Journal of the American Medical Association **286**(5): 563-571.

Salama, P., P. Spiegel, et al. (2004). "Lessons learned from complex emergencies over past decade." Lancet **364**(9447): 1801-1813.

Samsuzzoha, M., M. Singh, et al. (2012). "A numerical study on an influenza epidemic model with vaccination and diffusion." Applied Mathematics and Computation **219**(1): 122-141.

Samsuzzoha, M., M. Singh, et al. (2013). "Uncertainty and sensitivity analysis of the basic reproduction number of a vaccinated epidemic model of influenza." Applied Mathematical Modelling **37**(3): 903-915.

References

Sander, B., A. Nizam, et al. (2009). "Economic evaluation of influenza pandemic mitigation strategies in the United States using a stochastic microsimulation transmission model." Value in Health **12**(2): 226-233.

Sato, H. (2011). "Countermeasures and vaccination against terrorism using smallpox: Pre-event and post-event smallpox vaccination and its contraindications." Environmental Health and Preventive Medicine **16**(5): 281-289.

Sato, H. and Y. Sakurai (2012). "The contribution of residents who cooperate with ring-vaccination measures against smallpox epidemic." Disaster Medicine and Public Health Preparedness **6**(3): 270-276.

Seddiq, K., D. A. Enarson, et al. (2014). "Implementing a successful tuberculosis programme within primary care services in a conflict area using the stop TB strategy: Afghanistan case study." Conflict and Health **8**(1).

Sharp, T. W., F. M. Burkle Jr, et al. (2002). "Challenges and opportunities for humanitarian relief in Afghanistan." Clinical Infectious Diseases **34**(SUPPL. 5): S215-S228.

Sheather, J. and T. Shah (2011). "Ethical dilemmas in medical humanitarian practice: Cases for reflection from Mèdecins Sans Frontières." Journal of Medical Ethics **37**(3): 162-165.

Shen, Z., M. M. Dessouky, et al. (2009). "A two-stage vehicle routing model for large-scale bioterrorism emergencies." Networks **54**(4): 255-269.

Shih, W. (1974). "A new application of incremental analysis in resource allocations." Operational Research Quarterly **25**(4): 587-597.

Shih, W. (1977). "Branch and bound procedure for a class of discrete resource allocation problems with several constraints." Operational Research Quarterly **28**(2): 439-451.

Shope, R. (1991). "Global Climate Change and Infectious-Diseases." Environmental Health Perspectives **96**: 171-174.

Siddiqui, M. R. and W. J. Edmunds (2008). "Cost-effectiveness of antiviral stockpiling and near-patient testing for potential influenza pandemic." Emerging Infectious Diseases **14**(2): 267-274.

Spencer, S., A. D. Grant, et al. (2004). "Malaria in camps for internally-displaced persons in Uganda: Evaluation of an insecticide-treated bednet distribution programme." Transactions of the Royal Society of Tropical Medicine and Hygiene **98**(12): 719-727.

Stein, M. L., J. W. Rudge, et al. (2012). "Development of a resource modelling tool to support decision makers in pandemic influenza preparedness: The AsiaFluCap Simulator." BMC Public Health: 870.

Strikas, R. A., L. J. Neff, et al. (2008). "US civilian smallpox preparedness and response program, 2003." Clinical Infectious Diseases **46**(SUPPL. 3): S157-S167.

Sypsa, V., I. Pavlopoulou, et al. (2009). "Use of an inactivated vaccine in mitigating pandemic influenza A(H1N1) spread: a modelling study to assess the impact of vaccination timing and prioritisation strategies." Euro surveillance : bulletin européen sur les maladies transmissibles = European communicable disease bulletin **14**(41): 19356.

Tappero, J. W. and R. V. Tauxe (2011). "Lessons learned during public health response to cholera epidemic in Haiti and the Dominican Republic." Emerging Infectious Diseases **17**(11): 2087-2093.

Taylor, D. and S. Pettit (2009). "A consideration of the relevance of lean supply chain concepts for humanitarian aid provision." International Journal of Services, Technology and Management **12**(4): 430-444.

Thieren, M. (2005). "Health information systems in humanitarian emergencies." Bulletin of the World Health Organization **83**(8): 584-589.

Thomas, A. and L. Kopczak (2007). "Life-saving supply chains." Building Supply Chain Excellence in Emerging Economies: 93-111.

References

Tong, A., K. Flemming, et al. (2012). "Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ." BMC Medical Research Methodology **12**.

Tong, J., O. Valverde, et al. (2011). "Challenges of controlling sleeping sickness in areas of violent conflict: Experience in the Democratic Republic of Congo." Conflict and Health **5**(1).

Toole, M. J. and R. J. Waldman (1997). The public health aspects of complex emergencies and refugee situations. **18:** 283-312.

Tuite, A. R., D. N. Fisman, et al. (2010). "Optimal pandemic influenza vaccine allocation strategies for the Canadian population." PLoS ONE **5**(5).

Tumpey, T. M., C. F. Basler, et al. (2005). "Characterization of the reconstructed 1918 Spanish influenza pandemic virus." Science **310**(5745): 77-80.

U.S. Agency for International Development (2009). Laboratory logistics handbook: a guide to designing and managing laboratory logistics systems. Retrieved April 18, 2010 from http://pdf.usaid.gov/pdf_docs/PNADP082.pdf.

UNICEF (2012). Guidance note on the use of Oral Cholera Vaccines for UNICEF. Retrieved November 13, 2013 from http://www.unicef.org/immunization/files/UNICEF_OCV_Guidance_20_July2012_final.pdf.

Uribe-Sánchez, A., A. Savachkin, et al. (2011). "A predictive decision-aid methodology for dynamic mitigation of influenza pandemics." OR Spectrum **33**(3): 751-786.

Valenciano, M., D. Coulombier, et al. (2003). "Challenges for Communicable Disease Surveillance and Control in Southern Iraq, April-June 2003." Journal of the American Medical Association **290**(5): 654-658.

Van Der Wichmann, C. P., M. L. Stein, et al. (2013). "Choosing pandemic parameters for pandemic preparedness planning: A comparison of pandemic scenarios prior to and following the influenza A(H1N1) 2009 pandemic." Health Policy **109**(1): 52-62.

Van Wassenhove, L. N. (2006). "Blackett memorial lecture humanitarian aid logistics: Supply chain management in high gear." Journal of the Operational Research Society **57**(5): 475-489.

Vijayaraghavan, M., F. Lievano, et al. (2006). "Economic evaluation of measles catch-up and follow-up campaigns in Afghanistan in 2002 and 2003." Disasters **30**(2): 256-269.

Von Seidlein, L., M. Jiddawi, et al. (2013). "The value of and challenges for cholera vaccines in Africa." Journal of Infectious Diseases **208**(SUPPL. 1): S8-S14.

Waldor, M. K., P. J. Hotez, et al. (2010). "A national cholera vaccine stockpile - A new humanitarian and diplomatic resource." New England Journal of Medicine **363**(24): 2279-2282.

Wallinga, J., M. Van Bovena, et al. (2010). "Optimizing infectious disease interventions during an emerging epidemic." Proceedings of the National Academy of Sciences of the United States of America **107**(2): 923-928.

Wang, H., X. Wang, et al. (2009). "Optimal material distribution decisions based on epidemic diffusion rule and stochastic latent period for emergency rescue." International Journal of Mathematics in Operational Research **1**(1): 76-96.

Wang, S., F. de Véricourt, et al. (2009). "Decentralized resource allocation to control an epidemic: A game theoretic approach." Mathematical Biosciences **222**(1): 1-12.

Waring, S. C. and B. J. Brown (2005). "The threat of communicable diseases following natural disasters: A public health response." Disaster Management and Response **3**(2): 41-47.

Watson, J. T., M. Gayer, et al. (2007). "Epidemics after natural disasters." Emerging Infectious Diseases **13**(1): 1-5.

Weil, A. A., L. C. Ivers, et al. (2012). "Cholera: Lessons from Haiti and beyond." Current Infectious Disease Reports **14**(1): 1-8.

References

Wein, L., D. Craft, et al. (2003). "Emergency response to an anthrax attack." Proceedings of the National Academy of Sciences of the United States of America **100**(7): 4346.

Whitworth, M. H. (2006). "Designing the response to an anthrax attack." Interfaces **36**(6): 562-568.

Wichmann, O., P. Stöcker, et al. (2010). "Pandemic influenza A(H1N1) 2009 breakthrough infections and estimates of vaccine effectiveness in Germany 2009-2010." Eurosurveillance **15**(18): 1-4.

World Health Organization (1999). WHO Guidelines for Epidemic Preparedness and Response to Measles Outbreaks. Retrieved November 12, 2013 from http://www.who.int/csr/resources/publications/measles/whocdscsrisr991.pdf?ua=1

World Health Organization (2005). Communicable disease control in emergencies: a field manual edited by M. A. Connolly. Retrieved April 08, 2010 from http://whqlibdoc.who.int/publications/2005/9241546166_eng.pdf?ua=1.

World Health Organization (2005). Malaria control in complex emergencies : an inter-agency field handbook. Retrieved September 6, 2013 from http://whqlibdoc.who.int/publications/2005/924159389X_eng.pdf?ua=1.

World Health Organization (2006). Use of the two-dose oral cholera vaccine in the context of a major natural disaster. Report of a mass vaccination campaign in Aceh Province, Indonesia, 2005. Retrieved November 14, 2013 from http://www.who.int/topics/cholera/publications/final_tsunami.pdf.

World Health Organization (2007). Tuberculosis care and control in refugee and displaced populations: an interagency field manual. – 2nd ed. / edited by M.A. Connolly, M. Gayer and S. Ottmani. Retrieved September 12, 2013 from http://apps.who.int/iris/bitstream/10665/43661/1/9789241595421_eng.pdf?ua=1.

World Health Organization (2007). WHO position paper on cholera vaccine use in Iraq, 05 October 2007.

World Health Organization (2008). Communicable disease alert and response for mass gatherings: key considerations. Retrieved February 09, 2010, from http://www.who.int/csr/Mass_gatherings2.pdf

World Health Organization (2010). "Cholera vaccines: WHO position paper. Weekly Epidemiological Record, 85(13):117–128. Retrieved March 17, 2013 from http://www.who.int/wer/2010/wer8513.pdf ".

World Health Organization (2012). Outbreak surveillance and response in humanitarian emergencies. WHO guidelines for EWARN implementation. Retrieved November 14, 2013 from http://whqlibdoc.who.int/hq/2012/WHO_HSE_GAR_DCE_2012_1_eng.pdf.

World Health Organization (2012). WHO Consultation on oral cholera vaccine (OCV) stockpile strategic framework: potential objectives and possible policy options. Geneva: Department of Immunization, Vaccines and Biologicals, World Health Organization; (WHO/IVB/12.05). Retrieved November 7, 2013 from http://www.who.int/immunization/documents/innovation/WHO_IVB_12.05/en/.

World Health Organization (2012). WHO Technical Working Group on creation of an oral cholera vaccine stockpile. Retrieved November 5, 2013 from http://www.who.int/iris/bitstream/10665/75240/1/WHO_HSE_PED_2012_2_eng.pdf.

World Health Organization (2013). SAGE Working Group on Vaccination in Humanitarian Emergencies. Vaccination in Acute Humanitarian Emergencies: a Framework for Decision-Making. Retrieved November 14, 2013 from http://www.who.int/iris/bitstream/10665/92462/1/WHO_IVB_13.07_eng.pdf.

Yaesoubi, R. and T. Cohen (2011). "Dynamic health policies for controlling the spread of emerging infections: Influenza as an example." PLoS ONE **6**(9).

References

Yang, Y., P. M. Atkinson, et al. (2011). "Analysis of CDC social control measures using an agent-based simulation of an influenza epidemic in a city." BMC Infectious Diseases **11**.

Yarmand, H., J. S. Ivy, et al. (2014). "Optimal two-phase vaccine allocation to geographically different regions under uncertainty." European Journal of Operational Research **233**(1): 208-219.

Zenihana, T. and H. Ishikawa (2010). "Effectiveness assessment of countermeasures against bioterrorist smallpox attacks in Japan using an individual-based model." Environmental Health and Preventive Medicine **15**(2): 84-93.

Zhao, L. and L. Sun (2008). Emergency service modes of supply chains with replenishment sources. 5th International Conference on Service Systems and Service Management, ICSSSM'08. , Melbourne.

Zhao, W. and R. Han (2010). Optimal model of emergency relief supplies distribution in anti-bioterrorism system. International Conference on Logistics Systems and Intelligent Management, ICLSIM 2010, Harbin.

Zhou, L. and M. Fan (2012). "Dynamics of an SIR epidemic model with limited medical resources revisited." Nonlinear Analysis: Real World Applications **13**(1): 312-324.