Literature Review - the vaccine supply chain

Econometric Institute Report

Evelot Duijzer*, Willem van Jaarsveld and Rommert Dekker

January 30, 2017

EI2017-01

Abstract

Vaccination is one of the most effective ways to prevent the outbreak of an infectious disease. This medical intervention also brings about many logistical questions. In recent years, in the Operations Research/Operations Management community there is growing interest in the logistical aspects of vaccination. However, publications on this topic are somewhat scattered: most papers focus on particular logistical aspects only and a broad overview is missing. This potentially leads to contributions being overlooked and makes it difficult to identify open research questions.

In this literature review we use a supply chain perspective and propose a classification for the literature on vaccine logistics in order to structure this relatively new field and highlight promising research directions. Thereto we distinguish between the following four components: (1) composition, (2) production, (3) allocation and (4) distribution. We use this classification to derive the unique characteristics of the vaccine supply chain. We find that the vaccine supply chain can amongst others be characterized by high uncertainty in both supply and demand; asymmetry between supplier, public health organization and end customer; complex political decisions concerning allocation and the crucial importance of deciding and acting in time. Our review yields a framework for Operations Research/Operations Management research in vaccine logistics. Based on this framework we discuss for each component in the vaccine supply chain the related decision problems, the current status and future research possibilities.

Keywords: vaccine, supply chain, logistics, public health, global health

1 Introduction

Every year millions of people are vaccinated preventively: they receive the annual influenza shot, are included in childhood immunization programs or are vaccinated against other infectious diseases. Preventive vaccination takes place before a disease emerges and is meant to avoid an outbreak. Next to preventive vaccination there is also reactive vaccination that can take place during an outbreak of an infectious disease or in response to a bioterror attack. Although vaccination is a medical intervention, successful vaccination campaigns are impossible without good logistics. The growing literature on vaccine logistics demonstrates that this importance is increasingly being recognized.

The Operations Research/Operations Management (OR/OM) community faces a number of challenges within the field of vaccine logistics. This community is increasingly interested in health care logistics as

*Corresponding author: duijzer@ese.eur.nl

well as in vaccine logistics, which is indicated by the fact that around 90% of the papers discussed in this review dates from 2005 and onwards and more than half even from 2011 or later (see Appendix B for the exact numbers). Despite the growing interest, the literature on vaccine logistics is somewhat scattered. E.g., most papers focus on a particular aspect of logistics (e.g., allocation or production) which results in separate clusters of papers with few cross citations. Moreover, there is limited attention for the broader perspective of vaccine logistics in individual papers, such that these papers are difficult to place in the correct context. This larger context is important, because improving a single aspect of logistics without aligning with others will only lead to minor overall improvements (Privett & Gonsalvez, 2014). Current literature falls short in presenting a broad overview of vaccine logistics and the vaccine supply chain, which makes it difficult to see where opportunities lie for the OR/OM community.

We contribute as follows to structuring the literature on vaccine logistics and identifying avenues for future research. We develop a classification for the literature by taking a supply chain perspective and distinguish between the following four components in the vaccine supply chain:

1. **Composition** - *What kind of vaccine should be used?*
   A vaccine is administered to increase immunity against a certain disease. Before vaccination can take place policymakers have to decide which disease they are targeting at and which vaccine will be used. There might be multiple vaccines available for the same disease or the characteristics of the disease might not be known at the time of vaccination. This leads to the problem of deciding on the composition of the vaccine. For the annual influenza shot, for example, the composition decision is related to the strains of the influenza virus that should be included. Composition questions also play a role in designing a vaccination program for multiple diseases. Not only should be determined which diseases to include and which vaccines to use, but also when they are scheduled in the program.

2. **Production** - *How many doses should be produced?*
   Once a vaccine has been selected, it has to be produced. The production of vaccine is characterized by a high level of uncertainty in production yield and long production times. This potentially leads to inefficiencies on the vaccine market. Coordination on this market can improve the match between demand and supply.

3. **Allocation** - *Who should be vaccinated?*
   The available doses of vaccine are often insufficient to vaccinate the entire population. This brings about an allocation problem: who should be vaccinated? Within a population one can distinguish between high-risk and low-risk individuals, but also between high-transmission and low-transmission groups. Careful analysis is needed to determine which group(s) should be prioritized. Also (re)allocation problems among different countries can arise when an epidemic spreads across borders.

4. **Distribution** - *How to get the vaccines to the people?*
   Once vaccines are available and the allocation decision has been made, the actual distribution takes place. The doses of vaccine should be located somewhere, leading to inventory control decisions. In case of static distribution points, logistical questions related to the positioning and layout of these points come in play. For mobile medical teams that deliver medical support on various locations, routing and scheduling problems may be considered.

Within this classification we structure and discuss 66 papers, providing the first review that connects the different logistical components of vaccination in order to develop an integrated view of the vaccine supply chain. The analysis based on our classification results in several interesting insights. First, it shows that the vaccine supply chain has some specific characteristics: high uncertainty in both supply and demand; asymmetry between supplier, public health organisation and end customer; complex political decisions concerning allocation and the crucial importance of deciding and acting in time. Next to that, we observe that the OR/OM perspective brings high level models and insights on different aspects of the supply chain. OR tools such as mathematical modelling and optimization lead to general solutions and enable to study complex decision problems. As in other supply chains getting the right product to the right place in the right time is crucial for success. The right product is determined in the composition phase, allocation decisions are made to determine the right place and production and distribution processes guarantee that the vaccines arrive there in time. Finally, by analyzing the vaccine supply chain, we also learn about supply chains in general. Chopra and Meindl (2007) present an overview of supply chain characteristics and related decision problems of which some also appear in the vaccine supply chain. However, other aspects of the vaccine supply chain are relatively unique. We propose the framework in Figure 1 to summarize our findings. With this framework we integrate the discussed papers and synthesize their contributions. We see that the components 'Production' and 'Distribution' are comparable to other supply chains, whereas 'Composition' and 'Allocation' are unique for the vaccine supply chain.

	Composition	**Production**	**Allocation**	**Distribution**
	What kind of product to use?	**How many products to produce and when?**	**Who should get the product?**	**How to get the products to the people?**
	Right product (decision)	*Right product (realization), Right time*	*Right place (decision)*	*Right place (realization), Right time*
Similarities	- Product development (R&D)	- Long production time - Uncertain demand - Pull process: initiated by the customer (i.e., public health organisation) - Uncertain yields		- Inventory control - Facility location - Routing - Supply chain design - Perishable product - Temperature controlled chain
Particularities	- Asymmetry: product is determined by public health organisations, not by the supplier - Public health organisations are non-profit, whereas supplier is full profit - Product changes very frequently (yearly for annual influenza vaccine) - Product decision is made under time pressure and high demand uncertainty	- Demand externalities due to disease dynamics and the protective power of vaccinations for non-vaccinated people	- Complex decision making: political interests, equity considerations - End customer (i.e., \`patient') does not pay for the product - Push process: initiated and performed in anticipation of end customer need - Asymmetry: end customer has no power in this phase	- Mass distribution under time pressure

Figure 1: Framework - Classification of the vaccine supply chain and overview of its particularities.

Our literature review shows some promising research directions. We observe that, in particular for the higher levels of the supply chain, there are rarely any studies on sudden outbreaks. Future research could focus on questions related to the development and production of vaccines for sudden outbreaks, e.g., pandemic influenza, SARS, MERS. Another topic that could be further elaborated is the distributed decision making in the supply chain, which appears in several forms. There are policy makers involved who decide on the vaccine composition and allocation, suppliers produce these vaccines, other organisations take care of the distribution and there is an end customer (i.e., the 'patient') who gets vaccinated. Every party in this process has different objectives and can make its own decisions. Further research is needed to study the effects of this asymmetry on the supply chain and on the vaccine coverage level.

To summarize, our contribution is structuring the vaccine logistics literature. Our review yields a framework for OR/OM research in vaccine logistics, and based on this framework we develop an integrated view on the vaccine supply chain and identify avenues for future research.

We are aware of two reviews on related topics, but both have a rather different scope from ours. Dasaklis, Pappis, and Rachaniotis (2012) write an extensive review on epidemic control. Both pharmaceutical and non-pharmaceutical interventions are taken into account. As the focus is on unexpected outbreaks with a natural cause or due to a bioterror attack, logistical aspects related to seasonal influenza or other expected outbreaks are not taken into account. In contrast, we restrict ourselves to pharmaceutical interventions, more specifically vaccination, and we consider all kinds of outbreaks (both expected and unexpected). Lemmens, Decouttere, Vandaele, and Bernuzzi (2016) review general models on supply chain network design (SCND) and apply their findings to the vaccine supply chain of the rotavirus vaccine. They primarily consider the distribution phase and, to a lesser extent, the production phase. The authors investigate whether the current literature on SCND is able to deal with the characteristics of the rotavirus vaccine supply chain and they indicate a number of points where there are shortcomings.

The remainder of this paper is structured as follows. We start in Section 2 with a short discussion on the search strategy and the characteristics of the included publications. In Section 3 we perform a bibliometric analysis to cluster and visualize the publications based on co-citations. In the remaining sections we discuss the four components of the supply chain: Composition in Section 4, Production in Section 5, Allocation in Section 6 and Distribution in Section 7. We close with conclusions in Section 8.

2 Search strategy

The following search strategy is used. We have searched the journal databases of the top 20 journals in the category 'Operations Research and Management Science' of Thomson Reuters InCites Journal Citation Reports. The journals are ranked based on Article Influence Score and the ranking is presented in Appendix A. These journal databases have been searched using the keywords 'vaccination' and 'vaccine'. This resulted in 261 unique publications in total. The publications that were not scientific articles were disregarded. This applied to 43 publications, for example editorial statements, descriptions of award winners and book reviews. Out of the 218 remaining publications 87 were disregarded because of the lack of any health care related terminology in either title, abstract or keywords. These publications for example mentioned vaccination once as an example in the main text, or cited papers with one of the keywords in the title. We were left with 131 papers, which have been studied in more detail. After careful reading another 65 publications were disregarded because the topics did not match the scope of this literature review, in most of those cases vaccination was mentioned just once as an example. This review discusses the remaining 66 publications in the OR/OM community that deal with topics related to vaccination. We also review supporting literature: e.g., from the epidemiological or health economics community and other relevant literature that we found through citation analysis.

3 Bibliometric analysis

Before we discuss the papers on vaccine supply chains in detail, we perform a bibliometric analysis of the papers included in this review. The contribution of this bibliometric analysis is twofold: (1) it supports the classification of the literature that we use in the remainder of the paper and (2) it indicates some subfields. We use the database of the Web of Science^{TM} Core Collection to gather information (search date June 30, 2016). This paper reviews 66 studies of which 61 are found in this database and are hence included in the bibliometric analysis. The five papers that are not included are listed in Appendix C. We use VOSViewer (cf., Van Eck and Waltman (2007) and www.vosviewer.com), a software tool well-established in the field of bibliometric analysis. This tool is used to structure and visualize the papers based on co-citations. VOSViewer constructs a map in which the publications are represented by labelled nodes. The map contains only the most important publications, for others the labels are omitted to avoid overlapping labels. The distances between the nodes are based on bibliographic coupling, i.e., the number of references that publications share. Hence, the closer two publications are in the map, the more shared references they have. The *weight* of a publication is measured as the total bibliographic coupling with all other publications. Node size and font size of the labels are used to express this weight. Next to the construction of the map, VOSviewer also supports clustering of the publications using a clustering algorithm. This algorithm assigns weights to each combination of publications dependent on the bibliographic coupling. The optimal clustering is determined by minimizing a weighted distance function, where the distance between publications depends on wether they are in the same cluster or not. In the map different colors are used to distinguish between the publications in the different clusters.

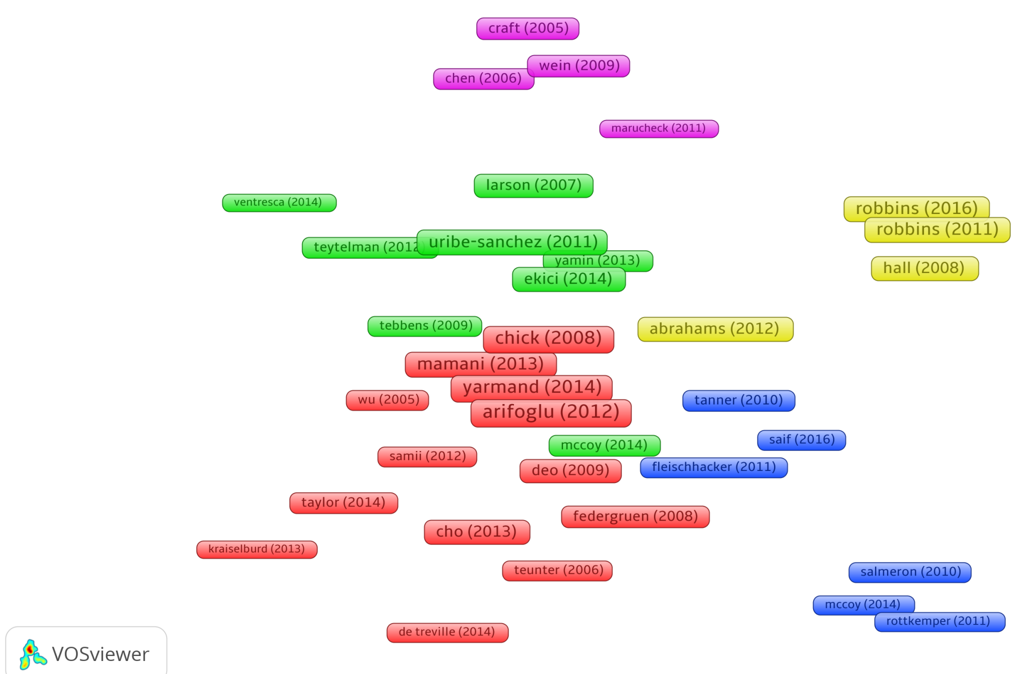

Figure 2: Mapping of the publications in this review, with node and font size representing the weight of a publication. The different colors represent the clusters.

The map in Figure 2 contains five clusters. If we analyze these clusters in more detail, we observe that the publications in each cluster are related by topic. Roughly, the clusters can be described as follows.

The purple cluster on top contains papers that study allocation problems in the context of bioterror response and one paper on safety and security. The yellow cluster in the top right corner captures part of the papers on vaccine composition, more precisely on childhood vaccination programmes. There is not really a central theme that connects the publications in the blue cluster, although most of them are related to vaccine distribution, focusing either on inventory control or supply chain design. The red cluster in the lower left corner is largely formed by publications in the INFORMS journals on influenza vaccine composition and production. Finally the green cluster in the top left consist of papers that discuss resource allocation or disease modelling. We thus conclude that Figure 2 roughly confirms our structuring of the different components of the supply chain. The way we subdivide the publications over these components qualitatively coincides with the clusters in the mapping. We also see some small subfields with a specific focus, such as bioterror response and childhood vaccination programmes. We have included these subfields in the broader components of the supply chain.

In this review we classify articles based on the component of supply chain that they consider. Alternatively, one could classify papers based on the disease or type of outbreak. In Table 1 we derive the relation between diseases and components of the supply chain. A cross in the table indicates that there are studies in this review that consider the combination of disease and supply chain component. The table shows that only allocation problems are studied for both existing/expected outbreaks and sudden outbreaks. For the other components the logistical questions are mainly studied for existing/expected outbreaks. The message derived from the table can be a little bit distorted, as there are also some studies that do not specify which disease they target at. These studies are mainly related to the distribution of vaccines and in particular to supply chain design.

	Composition	**Production**	**Allocation**	**Distribution**
Childhood vaccination	x			
Existing/expected outbreaks				
seasonal influenza	x	x	x	x
HIV/AIDS	x	x	x	x
malaria		x	x	x
tuberculosis			x	x
Sudden outbreaks				
anthrax			x	
pandemic influenza			x	
smallpox			x	

Table 1: Classification of studies based on type of vaccination and position in the supply chain.

4 Composition

The composition of a vaccine or vaccination programs brings about optimization problems which are discussed in this section. In Section 4.1 we focus on vaccine composition, in particular on the annual influenza vaccine. Every year policy makers have to decide which virus types to include in the influenza vaccine. Due to long production times, this decision has to be made under high uncertainty with little information about the characteristics of the coming influenza season. This results in the trade-off between deciding early based on limited information or deferring the decision to learn more. In Section 4.2 we shift attention from single vaccines to entire vaccination programs. We discuss the combinatorial problems that are related to the design of these programs, mainly focusing on childhood vaccination. Childhood vaccination programs intend to immunize a child against a number of infectious diseases by scheduling multiple vaccination moments during a certain period of time. Since there are different vaccines available which immunize each against a certain combination of diseases, constructing an effective and affordable childhood vaccination program is a challenging scheduling problem.

4.1 Vaccine composition

The problem of vaccine composition has been studied in particular for the annual influenza vaccine. There exist multiple types of the influenza virus and mutations might lead to new types. Every year the World Health Organization (WHO) advices on which virus types to include in the influenza vaccine (Gerdil, 2003; Silva et al., 2015). This combination of included virus types is called the *vaccine composition*. Because of the long production times, the composition of the vaccine must be determined well before the influenza season starts in order to produce a sufficient number of doses. At the decision moment the most prevalent strains in the coming influenza season are still unknown, although surveillance data may be used to make predictions. Wu, Wein, and Perelson (2005) discuss the 'follow policy', where the forecasted epidemic strain is included in the annual vaccine. The authors investigate whether this policy can be improved by including the antigenic history of the vaccinees, which consists of the strains to which the individual has been exposed in the past. A dynamic program is formulated to determine the optimal vaccine composition based on the antigenic history in sequential time periods. The results conclude that the follow policy is only slightly suboptimal and is therefore recommended to be continued. To gather more information about the coming influenza season it could be beneficial to defer the decision on the vaccine composition. Deferring the decision on the vaccine composition reduces uncertainty and could lead to better decisions on which strains to include in the vaccine. However, there is also a deadline before which the vaccines should be produced. Waiting too long thus reduces the available time for production, potentially leading to higher production costs. Kornish and Keeney (2008) study this trade-off and formulate a commit-or-defer model. Conditions on the optimal decision are derived using dynamic programming. Cho (2010) extends the work of Kornish and Keeney (2008) by including production yield uncertainties. Decision makers have to decide on retaining the current vaccine or shifting to updated compositions. The latter may have more production yield uncertainty. The objective is to maximize expected social welfare which is comprised of social benefits and social costs. The costs include the production costs, which are related to production yield uncertainties. A discrete time model is proposed with three possible decisions at every time: select the current vaccine strain, update to the most prevalent new strain or postpone decision making to the next period. Özaltın, Prokopyev, Schaefer, and Roberts (2011) allow for choosing among multiple possible strains for the vaccine, not only the most prevalent one. A multi-stage stochastic mixed integer model is formulated to integrate the composition decision and the timing of this decision. The results show that selecting a less prevalent strain might be beneficial, if this strain has higher production yields for example.

An innovative application of OR is presented by Maher and Murray (2016). They look at gene sequencing in HIV to identify structures that could potentially be used for vaccine development. A vaccine should target those antibodies that are responsible for the early stages of HIV. The authors use integer programming to characterize the key antibodies that determine the differences between initial and chronic sequences of the virus. Porco and Blower (1998) also consider HIV vaccination and formulate a simulation model to control two subtypes of HIV. A prophylactic vaccine is considered that is effective for one type and results in vaccineinduced cross immunity for the other. Dependent on the characteristics of the vaccine the authors determine whether mass vaccination leads to eradication of both HIV subtypes or to the existence of one or two of the types.

4.2 Designing vaccination programs

Not only the composition of a single vaccine results in optimization problems, but also the composition or design of an entire vaccination program. Childhood vaccination programs are a classical example of which the design results in large combinatorial problems. A childhood vaccination program consists of both a selection of diseases and vaccines and a schedule of the administered doses. A number of vaccine preventable diseases could be included and every selection brings about its own costs and benefits. To avoid that children need numerous injections, multiple vaccines can be combined into a single injection, a so-called 'combination vaccine'. Combination vaccines are not only beneficial, they also have potential negative side effects. An injection with multiple vaccines might overwhelm the immune system and can result in overdoses of vaccine antigen. Hall, Jacobson, and Sewell (2008) express the adverse effects of extraimmunization in terms of costs and aim to minimize the total costs of the childhood vaccination program. To solve the resulting combinatorial problem a solution method based on dynamic programming is proposed as well as heuristics. Once a vaccination program has been designed, not all children will adhere to this program. Due to parental misunderstanding or logistical difficulties vaccinations may be delayed or even missed. In those cases a catch-up vaccination schedule must be constructed. Engineer, Keskinocak, and Pickering (2009) propose a dynamic programming algorithm to construct catch-up schedules within a short amount of time. Based on this algorithm Smalley, Keskinocak, Engineer, and Pickering (2011) provide a decision tool that constructs the best catch-up schedule based on the vaccination history and age of a child.

Public health facilities and governments can buy the required vaccines for childhood vaccination programmes on the pediatric vaccine market. Robbins and Jacobson (2011) study the pediatric vaccine market from the perspective of the federal government which can negotiate prices and quantities with vaccine producers. The authors formulate a MINLP formulation which minimizes the costs of immunizing a full birth cohort while guaranteeing a sufficient profit for producers to stimulate research and development. Robbins, Jacobson, Shanbhag, and Behzad (2014) differentiate between the multiple vaccines offered on the market, where each vaccine contains one or more antigens. They study the problem where every customer (i.e., public health facility) wants to purchase at least one of each antigen while minimizing cost. This leads to a set covering game and conditions for the existence of equilibria are discussed. Robbins and Lunday (2016) extend Robbins et al. (2014) and formulate a bilevel mathematical program with the upper level consisting of the manufacturer and the customer on the lower level. The manufacturer wants to maximize profit and faces a pricing problem for the produced vaccines. The customer can choose among a set of available vaccines each of which immunizes against one or more diseases. The objective of the customer is to minimize cost while selecting a number of vaccines that together immunize against a set of diseases. The authors propose three heuristics to solve the problem.

While combination vaccines are preferred in high-income countries, they are often not affordable in low-income countries. Proano, Jacobson, and Zhang (2012) study the 'antigen-bundling pricing' problem which determines for a set of producers which combination vaccines to produce, how many to supply to each market and for what price, in order to maximize total profit and consumer surplus. The authors propose a constructive heuristic to solve the problem. Based on their solutions they conclude that organisations as the WHO could serve as an intermediary to encourage the introduction of affordable vaccines for developing countries.

4.3 Discussion

We notice that the literature on vaccine composition and childhood vaccination mainly focuses on expected outbreaks in developed countries. Studies on the composition of a vaccine all consider seasonal influenza. The derived methods and results could also be applied to vaccines for pandemic influenza. However, the current policy for pandemic influenza is to design a vaccine after an outbreak has emerged (Özaltın et al., 2011). On the one hand this makes sense, as it is difficult to prepare for an outbreak of which you do not know the timing and disease characteristics. But on the other hand, acting only when the outbreak has emerged might result in many infections, due the long production times of an influenza vaccine (Gerdil, 2003). It would therefore be interesting to extend the literature on vaccine composition to pandemic influenza.

The works on childhood immunization programmes consider developed countries, with one exception being Proano et al. (2012). In general, in developed countries one can expect that a designed program can be executed as planned. In case children miss certain vaccinations, a catch-up schedule can be constructed (Engineer et al., 2009; Smalley et al., 2011). However, in developing countries childhood vaccination programmes face many more operational limitations. For example, in rural areas medical staff visits villages occasionally, which implies that all medical procedures are performed at the same time in a village. The OR/OM community can contribute in studying the design of childhood vaccination programmes in such environments.

Current studies are still behind in using models for disease progression to evaluate the effects of a vaccine. They assume that the number of cases is known (Kornish & Keeney, 2008) or use very general functions to express the social benefits of vaccination (Cho, 2010). There are some studies in the OR/OM community that focus in particular on models for disease progression, without the specific context of vaccine composition. R. C. Larson (2007) introduces the problem of influenza disease modelling and disease control to the Operations Research community. Some models are presented as a starting point to encourage the OR community to work on this field. Teytelman and Larson (2012) generalize one of these models and build a discrete time model to model the spread of influenza in a heterogeneous population. Aleman, Wibisono, and Schwartz (2011) propose an agent-based modelling approach to model a disease outbreak. These kind of models could be used to better evaluate the effects of a certain vaccine composition.

5 Production

The production of vaccine is characterized by long production times, a short immunization season and frequent changes in vaccine composition. Furthermore, vaccine production suffers from yield uncertainty. Especially the uncertain yields are one of the main causes for the undersupply on the vaccine market (Chick, Mamani, & Simchi-Levi, 2008; Deo & Corbett, 2009). An important question for the production of vaccine is therefore to determine how producers can deal with these uncertainties and how the vaccine market can be coordinated. OR tools such as mechanism design and game theory are useful in studying this coordination problem. Section 5.1 studies the characteristics of the vaccine market and coordination of this market. In Section 5.2 we discuss a few studies that consider other topics related to vaccine production.

5.1 Market coordination

Chick et al. (2008) show that a lack of coordination on the vaccine market for annual influenza leads to high production risks for the manufacturers of vaccines. Without government intervention the vaccine coverage is below the socially optimal level. Different types of contracts are studied in order to align the incentives of both governments and manufacturers. The authors show that a cost-sharing contract, in which the risks for yield uncertainty are shared, is able to globally optimize vaccine supply. Arifoğlu, Deo, and Iravani (2012) extend Chick et al. (2008) to include rational consumer behavior. Vaccination brings about a positive externality effect because it reduces the infection risk for individuals that are close contacts of the vaccinee. Next to that, negative externality effects can occur: self-interested individuals ignore that vaccinating high-risk individuals is more beneficial when supply is limited. The vaccine market suffers from inefficiencies because of these disregarded externality effects on the demand side and the yield uncertainty on the supply side. Arifoğlu et al. (2012) model the vaccine market as a game between the manufacturer and the individuals and study the effect of government interventions either on the demand or on the supply side.

Mamani, Chick, and Simchi-Levi (2013) study the case of multiple countries which each purchase an amount of vaccines. These vaccines are all distributed before the epidemic emerges. The amount of vaccines ordered and distributed in one country can influence the evolution of an outbreak in another country due to transmission across the borders. A contract is proposed to reduce inefficiencies in this respect. The results show that a lack of coordination leads to a shortage of vaccines in some regions and an excess in others. Adida, Dey, and Mamani (2013) extend the coordination of the vaccine market to contracts that affect both the supply and the demand side. They show that a fixed two-part subsidy is not able to align the quantity and pricing decisions simultaneously. A two-part menu is proposed with subsidies depending on the vaccination coverage. The analysis shows that this subsidy menu can result in a socially optimal level of vaccine coverage.

The randomness in both production yield and demand results in uncertainty for a vaccine supplier. Federgruen and Yang (2008) study a decision maker who has to satisfy the uncertain demand for a single season from several suppliers. The planning problem that he faces relates to determining how much to order from which suppliers, taking into account the uncertain yield of the suppliers. Goal is cost minimization while guaranteeing that the uncertain demand is satisfied with a certain probability. The authors motivate their model by the case of influenza vaccine delivery, where a unexpected drop-out of one of the two suppliers in 2004 lead to a significant reduction in the US vaccine stockpile. Federgruen and Yang (2009) analyze a supply chain where suppliers can influence their uncertain yields. The vaccine supply chain is used as an illustration throughout the paper and the equilibrium of the total market is analyzed.

Another way to manage the supply chain uncertainties is to adjust the pricing and selling strategy. Cho and Tang (2013) study three selling strategies: advance, regular and dynamic selling. In the first two strategies selling and price setting takes place respectively before or after demand and supply are realized. The authors show that the dynamic strategy, which combines advance and regular selling, is preferred by the manufacturer. Eskandarzadeh, Eshghi, and Bahramgiri (2016) extend this work to controlling the risk of the producer in the case that the price is set before the yield is realized. The authors study a production planning problem for a risk averse producer and propose a solution algorithm. They illustrate their solution approach for an influenza producer and determine the optimal price and production quantities for different risk profiles. Begen, Pun, and Yan (2016) analyze the effects and potential benefits of reducing supply or demand uncertainty. Results show that supply uncertainty reduction effort is more efficient.

The long lead times in vaccine production are another factor complicating market coordination. De Treville et al. (2014) investigate the costs of different lead times and analyze three supply chains, including the GlaxoSmithKline vaccine supply chain. This company bids on a tender and learns only a few months before delivery whether or not the tender was won. Due to the long production times of vaccines, the production has started well before knowing the outcome of the tender. Shortening lead times allows the company to start production at a later time when the estimated probability of winning the tender is higher. The results show that investing in lead time reduction is beneficial and accordingly managers have extensively explored ways to achieve this. Dai, Cho, and Zhang (2016) study the case where the supplier has little incentive to start production early as the retailer benefits the most from on time delivery. Late delivery can result in an influenza vaccine shortage, even though supply is sufficient. Existing supply contracts are shown to fail in coordinating this supply chain and a new contract is proposed that both coordinates the supply chain and allows for flexible profit division.

There are sometimes donors who are willing to subsidize the vaccine production process in order to increase access to health care in developing countries. Taylor and Xiao (2014) consider malaria vaccinations and study donor subsidies that are either dedicated to increasing the sales or lowering the production cost. The latter can be done via a purchase subsidy. A model is formulated where the donor wants to maximize the average sales to customers under a budget constraint. The optimal size and type of subsidies dependent on the perishability of the product are determined. The results show that for products with a long shelf life a donor should only subsidize purchases. Levi, Perakis, and Romero (2016) complement this work on subsidizing malaria medication by studying the setting of a central planner who aims to increase the market consumption. The authors study the effectiveness of a uniform copayment and derive conditions when this is optimal. The two papers together show that policy makers should not only consider subsidizing the manufacturer. Instead, allocating uniform subsidies to individual firms can (more) efficiently increase market consumption. The most effective malaria treatment nowadays uses medication for which artemisia leaves are used in the production process. The market of this agricultural product is characterized by high volatility in supply and price, which directly influences the market for malaria medication. Kazaz, Webster, and Yadav (2016) develop a model for the artemisia supply chain to study the consequences of several interventions to reduce the volatility in the market. They show for example that improving the average yield or offering a support price has significant impact.

5.2 Other topics

There are some other topics related to the production of vaccines that are studied in the literature. These papers focus on development of new vaccines or on packaging questions and are discussed below.

Ding and Eliashberg (2002) study the pipeline problem for new development of products. This problem concerns a company that has to decide in which products to invest, while it is still uncertain whether the development will be successful. The authors motivate their problem with describing potential approaches for developing an HIV vaccine. The model assists policy makers in deciding in which of these approaches they should invest.

A different aspect of the production of vaccines, namely the bottling, is discussed by Teunter and Flapper (2006). After production vaccine is stored in a tank, in which rework is still possible. Before vaccines can be sold a number of tests need to be performed. Manufacturers have to decide on the timing of bottling vaccines: This can be done before test results are available, partially before and after or only after the results are known. Quick bottling reduces the required tank capacity, but also limits the possibilities of rework and hence possibly leads to lost sales. The paper compares four bottling alternatives and presents closed form expressions for important performance criteria for each of the alternatives. The results show for which types of vaccines postponing bottling is beneficial.

A. J. Fleischhacker and Zhao (2011) consider the supply chain for medical trials. This supply chain suffers from the risk of a sudden drop in demand, when the trial is halted because of unsafe medication. This characteristic brings about a trade-off: using smaller lot sizes reduces the potential waste, but increases the setup costs. The authors study an extension of the Wagner-Whitin model (Wagner & Whitin, 1958) and show that their results can have a significant impact if the failure probability and the setup costs are high and inventory costs are relatively low.

5.3 Discussion

The vaccine supply chain is characterized by asymmetry in multiple dimensions: the producer does not design its own product and the end user is not the one paying for the product. Furthermore, the buyers of vaccines are often non-profit organisations whereas suppliers are full profit companies (Herlin & Pazirandeh, 2012). This requires a lot of coordination on the market, which is studied by the discussed papers. Most papers on production study seasonal influenza, for which the production time is uncertain due to biological processes and quality and safety tests (Gerdil, 2003).

When considering the classification in Table 1 it is interesting to observe that there are no studies in the OR/OM literature regarding the production of vaccines for sudden outbreaks. Future research is highly needed in this important area. When facing a sudden outbreak, either with natural cause or due to a bioterror attack, it is important to know beforehand how many vaccines to produce, where and when. Time plays a very crucial role in that case: it is important to react quickly to a sudden outbreak, but the production lead times are uncertain and the demand might drop over time if vaccines arrive too late. Hence, decisions have to be made under time pressure. The OR/OM community can aid decision makers in these complex decisions by designing production plans for sudden outbreaks.

6 Allocation

The allocation of vaccines is a resource allocation problem. Vaccines are scarce and decision makers face the difficult decision of determining who is entitled to be vaccinated and who is not. In Section 6.1 we discuss the case of multiple decision makers. These decision makers can either decide to act selfishly and keep their own vaccine stockpile or they can decide to allocate some vaccines to other populations in order to reduce transmission across borders. Besides the decision of the individual decision maker, we can also study the coordination between them. When there is complete coordination, the situation collapses to a single decision maker, which is studied in Section 6.2. In that case the decision problems that arise are related to allocating over multiple sub-populations (e.g., regions or age-groups). Other studies differentiate between people that are very vulnerable to the disease and those who contribute heavily to the spread. The allocation problem is to determine which groups should be vaccinated and which groups not. Often different allocation schemes are compared in terms of disease related characteristics, such as the number of infected individuals. In Section 6.3 we review a class of papers that uses cost-effectiveness analysis to compare different vaccine allocations. This approach assigns costs to both the intervention and the achieved health benefit. Studies then determine which interventions are cost effective: i.e., for which interventions are the benefits higher than the cost?

Finally, in Section 6.4 we review a class of papers that considers allocating limited resources in case of a bioterror attack. That situation is characterized by a lot of uncertainty regarding the location of the attack, the number of victims et cetera.

6.1 Multiple decision makers

The decision on the allocation of funds for HIV prevention is a multilevel decision problem. The allocation over multiple regions is decided globally, but the regions themselves decide on the allocation over the several risk-groups within their region. Lasry, Zaric, and Carter (2007) study this multilevel decision problem and compare an equity-based heuristic with the optimal allocation. The equitable allocation allocates proportionally with respect to numbers of infected cases. The objective in the optimal allocation is to minimize the number of new infections. The results show that if optimization can only be applied to one level, it can better be the lower decision level than the upper level.

Sun, Yang, and de Véricourt (2009) use game theory to study the allocation of vaccine stockpiles among different countries. Prior to an outbreak every country is assumed to have its own vaccine stockpile. During an outbreak countries face the question whether or not they are willing to give up parts of their stockpile to help other countries in containing the epidemic. A Reed-Frost model is used to describe the spread of an epidemic and only the initial stage of epidemic growth is considered. The authors study Nash equilibria and compare the situation with and without a central planner, such as the WHO. In addition to Sun et al. (2009), Mamani et al. (2013) evaluate the entire time course of the epidemic. They study multiple countries that each want to minimize total costs related to number of infections and allocated vaccines. A contract is proposed to achieve system optimality.

6.2 Central coordination

In case of a single decision maker, allocation decisions are related to prioritizing between multiple subgroups. These subgroups correspond for example to geographical regions or age groups. Policy makers have to decide which subgroups to vaccinate.

Uribe-Sánchez, Savachkin, Santana, Prieto-Santa, and Das (2011) construct a simulation model and determine the resource allocation that limits the impact of ongoing epidemics and the potential impact of new outbreaks in multiple regions. Yarmand, Ivy, Denton, and Lloyd (2014) study a two-stage decision framework for vaccine allocation over multiple locations. In the first stage a predefined amount of vaccines is allocated to every location. The second stage decision is based on the outcome of the first stage allocation: the epidemic is either contained or not. The authors show that their problem can be reformulated as a news vendor type of model.

Outside the Operations Research literature there are many papers that consider vaccine allocation over multiple regions (e.g., Araz, Galvani, & Meyers, 2012; Keeling & Shattock, 2012; Matrajt, Halloran, & Longini Jr, 2013; Wu, Riley, & Leung, 2007). These papers make little use of OR tools such as optimization, but usually use approaches such as scenario analysis or enumeration. Some of them cluster the population in smaller groups, such as communities or households (e.g., F. Ball, Britton, & Lyne, 2004; F. Ball & Lyne, 2006; F. G. Ball & Lyne, 2002; Becker & Starczak, 1997; Tanner, Sattenspiel, & Ntaimo, 2008). Tanner and Ntaimo (2010) present a technological extension to Tanner et al. (2008) to solve stochastic problems with joint chance constraints. They add new optimality cuts to the problem and apply branch-and-cut. Using test instances on vaccine allocation developed in Tanner et al. (2008) they show that the new method significantly reduces computation time and is also able to derive solutions for larger instances.

The papers discussed so far did not assume a special structure on the connection between the different regions. In contrast to these papers, there are also some studies that consider network models, where a graph is used to represent regions (or individuals) and their connections. Ventresca and Aleman (2014b) consider a network structure and investigate the optimal removal of nodes. When the network represent a population, node removal can be interpreted as either vaccination or quarantining. More theoretical work on link or node removal can be found in Arulselvan, Commander, Elefteriadou, and Pardalos (2009); Nandi and Medal (2016); Ventresca (2012); Ventresca and Aleman (2014a).

Dividing the population based on geographical criteria, results in physical distance between the groups. This distance enables to consider limited or no interaction between the groups. Ignoring interaction is not possible when the population is grouped based on age or disease specific characteristics, because it is exactly the interaction between these groups that significantly contributes to the spread of a disease. Many studies in the medical/epidemiological literature consider vaccine allocation over different age-groups (e.g., Goldstein et al., 2009; Medlock & Galvani, 2009; Mylius, Hagenaars, Lugnér, & Wallinga, 2008; Patel, Jr., & Halloran, 2005; Wallinga, van Boven, & Lipsitch, 2010). Others differentiate between vulnerable groups and more active groups, who contribute to the spread of the disease (e.g., Dushoff et al., 2007; Goldstein, Wallinga, & Lipsitch, 2012; E. K. Lee, Yuan, Pietz, Benecke, & Burel, 2015; Matrajt & Longini Jr, 2010).

In some situations it is not the vaccine stockpile that is limiting the vaccine coverage, but the participation of the population in vaccination programmes. Yamin and Gavious (2013) study how the level of influenza coverage can be increased using a game model with a central planner who can give a financial incentive given to encourage people to get vaccinated. Results indicate that the incentives should be higher for non-elderly as well as in years when the seasonal influenza is less contagious. The more vulnerable groups, such as the elderly, will benefit from the increased coverage in the groups that contribute significantly to transmission.

6.3 Cost-effectiveness

Vaccine allocations are not only compared in terms of infected cases or other health care related performance criteria, but also in terms of costs or other socioeconomic factors.

Parker (1983) combines medical and socioeconomic development programmes to reduce cases of malaria. The authors formulate a resource allocation model where the optimal selection is made out of several intervention programmes. The novelty of this paper lies in the fact that socioeconomic measurements are included in the multiobjective approach such as infant mortality rate, calorie intake levels, and degree of standard housing and potable water.

Frerichs and Prawda (1975) develop a simulation model for the spread of rabies. Several vaccination strategies are analyzed with the model and compared based on their cost-effectiveness. The authors show that a vaccination strategy in which vaccination teams consecutively visit regions that have the highest risk of contributing to new rabies cases is most cost-effective. Edwards, Shachter, and Owens (1998) study the cost-effectiveness of HIV programmes in relation to behavioral changes. Rauner (2002) develops a decision support system to determine which prevention programmes for HIV are cost-effective. They include the option to vaccinate people, although an effective HIV vaccine is not available up to now. Tebbens and Thompson (2009) analyze different decision rules for the allocation of resources for eradicable diseases. A model for two diseases is considered and the effects of switching priorities from one disease to another are investigated using cost-effectiveness analysis. The results show that a long-term strategy is more cost-effective than regularly switching priorities to the most pressing disease. Hutton, Brandeau, and So (2011) study the cost-effectiveness of screening, treatment and vaccination programmes for hepatitis B. The results have influenced policy makers and have resulted in increased screening and catch-up vaccination for children. Dimitrov, Moffett, Morton, and Sarkar (2013) combine models for determining cost-effectiveness, disease burden and intervention delivery. They determine the optimal actions under budget constraints using Markov Decision Processes. The model not only advices what vaccination strategy to use, but also presents detailed geographic intervention plans and informs where to locate the supply centers. The top-down approach results in a decision support tool, which is illustrated for a case study of malaria in Nigeria. Thompson, Tebbens, Pallansch, Wassilak, and Cochi (2015) analyze the efforts that are needed to attain polio eradication. A simple allocation model is used to choose among a set of possible allocations those options that either minimize the incremental cost-effectiveness ratio or maximize net benefit.

Some studies do not explicitly perform a cost-effectiveness analysis, but take the costs for the considered interventions into account differently. Reveller, Lynn, and Feldmann (1969) focus on cost minimization while achieving a certain reduction in disease incidence. The authors propose a linear approximation of the transmission model for tuberculosis. Linear programming is used with the objective of minimizing the total costs of the intervention strategy. Four schedules for the reduction of active tuberculosis cases are given and for each schedule the optimal intervention is determined. These interventions consist both of vaccination and prophylaxis. Denysiuk, Silva, and Torres (2015) combine costs and disease related measures in a multiobjective optimization problem for tuberculosis. The goal is to minimize both costs for the active infections as well as the costs of the control strategy. To determine the optimal intervention the authors apply optimal control theory using a transmission model consisting of a set of differential equations.

Cost-effectiveness of vaccination programmes is widely studied in communities outside OR/OM. In the health economics literature and the epidemiological literature this approach is often used (e.g., Jit, Brisson, Portnoy, & Hutubessy, 2014; Jit, Choi, & Edmunds, 2008; Siddiqui & Edmunds, 2008).

6.4 Bioterror or emergency response

There is a class of papers that focuses on a specific allocation problem: the allocation of scarce resources after a bioterror attack or an unexpected emergency.

We first discuss papers focusing on (responses to) bioterror attacks. Craft, Wein, and Wilkins (2005) study a response plan against an anthrax attack. An extensive model is considered that consists among others of a disease progression model, queueing models for antibiotics distribution and queueing model for hospitalization. This model is a simplification of the model proposed by Wein, Craft, and Kaplan (2003) and is used to estimate the number of infections and the number of deaths resulting from the attack. Their results show that the fraction of deaths among infected people is more or less constant. Based on these results policy makers decided to focus on lowering the proportion of deaths instead of the actual number, also motivated by the fact that it is very difficult to predict the magnitude of an attack. Chen, Carley, Fridsma, Kaminsky, and Yahja (2006) focus only on the transmission model in case of an anthrax attack. The authors compare an agent-based and a population based simulation model for the evaluation of disease progression after a bioterror attack. The more complex agent-based model is aligned with the simple model such that the former can be used to derive policy recommendations in more detail. Miller, Randolph, and Patterson (2006) evaluate different intervention strategies including vaccination and social distancing after a smallpox attack. A case study for San Antonio Texas is considered and policy recommendations are derived. Berman and Gavious (2007) also take the perspective of the terrorist who plans to commit the attack into account. A two-player game is formulated that models the interaction between a terrorist and the state.

The state is able to locate facilities that contain the resources to respond to an attack. The terrorist will commit an attack at a certain location. Available resources will then be transported through the network via shortest paths. The authors formulate a leader-follower game where the state acts first and best strategies for both players are derived. A special case of a bioterror attack, namely on an airport, is considered by Berman, Gavious, and Menezes (2012). In that setting the authors study the allocation of limited emergency resources. An approximation of an SEIR model is used to determine the number of cases dependent on the allocated resources. An optimization problem is constructed to find the allocation that minimizes the number of cases.

Next to response plans for bioterror attacks, there are other emergency situations related to infections that require complex decision making. Wein (2009) discusses four topics related to homeland security: response to a bioterror attach either with anthrax or on the food supply chain, the control of pandemic influenza and border analyses to keep terrorists out of the country. The author discusses the contributions made in these four areas and shows that applying operations research methods in these fields is useful to quantify the effects of an attack and to derive policy implications. Fogli and Guida (2013) design a decision support system for emergency management using the novel approach of knowledge-centered design. This approach iteratively updates the knowledge about the domain and the users of the decision support system and adjusts the support system accordingly. The authors illustrate their results with a case study for pandemic influenza, where important decisions are for example how to plan emergency vaccination and vaccine distribution.

Models for emergency response often use complex OR techniques and advanced software which may hinder implementation or application. To avoid these obstacles Herrmann (2008) derives spread sheet models which can be used by decision makers to evaluate multiple response plans.

6.5 Discussion

The allocation of vaccines differs slightly from the other components in the vaccine supply chain. In contrast to the production and distribution of vaccines, allocation is not a tangible process but a decision problem on a higher level. As can be seen in Table 1 allocation is the only component of the supply chain that is studied for both expected/existing outbreaks and sudden outbreaks. A possible explanation for this is that the allocation problem is quite general and can be studied for multiple situations and types of diseases with comparable models. Papers that study vaccine allocation all assume that there is a stockpile available. For sudden outbreaks or in response to a bioterror attack, this might be problematic (see our discussion in Section 5.3).

As mentioned in the previous sections the topic of vaccine allocation is extensively studied in the epidemiological literature. Although there is already some work in the OR/OM community on this topic, the epidemiological literature could benefit from further applying OR/OM tools. The high level modelling and use of optimization methods have potential to result in insights and understanding of the complex allocation problems that could not be obtained with simulation or numerical methods (cf., Duijzer, Van Jaarsveld, Wallinga, & Dekker, 2015). Furthermore, with OR tools explicit solutions of optimal allocations or efficient solutions approaches can be derived (cf., Duijzer, Van Jaarsveld, Wallinga, & Dekker, 2016). As data is scarce and model parameters are difficult to determine for disease transmission models, these results are very valuable when performing sensitivity analyses.

The asymmetry in the vaccine supply chain also plays a role in the allocation phase. Where decision makers specify the allocation, individuals can have multiple reasons not to participate. Vaccine hesitancy or vaccine refusal is studied a lot in the medical/epidemiological literature (H. J. Larson, Jarrett, Eckersberger, Smith, & Paterson, 2014; Omer, Salmon, Orenstein, Dehart, & Halsey, 2009), but hardly incorporated in the OR/OM papers on allocation. As the attitude towards vaccination might differ across (sub)populations, this might affect the allocation decision. Future research is needed to incorporate this aspect.

7 Distribution

The distribution of vaccines involves many logistical questions on the operational level. Vaccines can either be distributed through fixed locations, so-called 'points of dispensing' (PODs), or via mobile facilities, respectively discussed in Section 7.1 and 7.2. PODs bring about many logistical questions ranging from facility location, to staffing levels and facility lay-out. When mobile facilities or mobile medical teams are used, routing problems play a role.

In Section 7.3 we consider the inventory control of vaccines. When policy makers decide to keep vaccine stockpiles, they have to decide how large these stockpiles should be and where they should be located. We close with discussing studies on supply chain design in Section 7.4. These studies take into account characteristics like the perishability of vaccine and the fact that vaccines should be kept in a temperature controlled environment.

7.1 Points of dispensing

Pandemic response plans often include the setup of local clinics for the distribution of medication and vaccines.

We discuss a stream of research that considers the logistical questions related to these clinics. Whitworth (2006) uses simulation models to design a response plan for a bioterror attack. The author analyzes candidate points, design and staffing levels of PODs for a specific case study of one community. Aaby, Herrmann, Jordan, Treadwell, and Wood (2006) develop a discrete-event simulation model to study the layout and organization of vaccination clinics for Montgomery County. Richter and Khan (2009) compare different ways to dispense prophylaxis to the population in a metropolitan area. Using multi-criteria decision analysis the authors show that the current method of drive-thru is outperformed by distribution via postal offices or via commercial pharmacies. E. K. Lee, Chen, Pietz, and Benecke (2009); E. K. Lee, Maheshwary, Mason, and Glisson (2006); E. K. Lee, Pietz, Benecke, Mason, and Burel (2013) develop the emergency response decision tool RealOpt© for PODs that are used in response to bioterrorist attacks or pandemics. This tool supports the decision making with respect to locating the facilities, determining the required labor resources and the floor plans of the facilities. RealOpt© has been used for numerous events, including anthrax preparedness and seasonal influenza. Luangkesorn, Norman, Zhuang, Falbo, and Sysko (2012) use queueing and simulation models to study the design and lay-out of health care centers for prevention and screening in Abu Dhabi. Various designs are compared in terms of utilization and waiting time. Based on the results an adjusted design is proposed that reduces the size of the area needed for waiting. McCoy and Johnson (2014) design clinic capacity while incorporating adherence, which is assumed to depend on the travel distance to the facility. They study a clinic which has a fixed budget that can be allocated over a number of time periods. During these time periods the epidemic continues to spread with a speed dependent on the allocation decisions. An optimization problem is formulated where the size of the infected population is minimized restricted by the budget constraint. For two special cases of adherence the solution is determined analytically. The results show that incorporating adherence may significantly improve outcomes. Ramirez-Nafarrate, Lyon, Fowler, and Araz (2015) simultaneously study the location problem and capacity planning for points of care. A mathematical program is formulated and a solution approach is proposed based on a genetic algorithm. The results show that simultaneously determining location, staffing and population assignment can reduce waiting times compared to sequential decision making. Ekici, Keskinocak, and Swann (2014) focus specifically on food distribution during a pandemic. A disease spread model is used and combined with a facility location model for the location problem of food distribution points. To find close to optimal solutions a heuristic is proposed which can help policymakers in preparing for a pandemic.

Finally, we discuss a paper on travel vaccines. These vaccines are for travellers in order to protect them against diseases that are prevalent in their destination country. The demand for these vaccines is relatively low, which brings about the following trade-off. Vaccines come in vials and multi-dose vials are cheaper, but potentially result in waste as vaccine spoils rapidly. Abrahams and Ragsdale (2012) study the scheduling problem for a travel clinic that aims to minimize the total cost of the vaccination schedule while taking scheduling preferences of the patients into account. The results show that their method results in significantly lower costs compared to simple scheduling heuristics.

7.2 Mobile facilities

The central question for mobile facilities is how to route them, which is studied in the following two OM papers. Halper and Raghavan (2011) define the mobile facility routing problem, with moving facilities to serve demand at different nodes in a network. A facility at a node can serve a subset of all the other nodes, for example those within a certain distance. The demand for every node is assumed to depend on time. The satisfied demand thus depends on the routing schedule. For multiple facilities the problem is NP-hard and a heuristic is proposed to solve the problem. An application of this problem is in the routing of mobile medical facilities or teams. Rachaniotis, Dasaklis, and Pappis (2012) study this routing problem, with the significant simplification of only one mobile medical team. This team consecutively visits subpopulations in which an epidemic is ongoing. The authors determine the optimal order for visiting the subpopulations such that the total number of new infections is minimized. The optimal schedule significantly outperforms random scheduling.

The organisation Riders for Health provides reliable transportation to health care workers in sub-Saharan Africa, who are then able to visit more rural areas to provide medical care such as vaccination. McCoy and Lee (2014) investigate the balance between equity and effectiveness for this organisation. They propose a model that can aid decision makers in deciding to which region newly available vehicles should be allocated.

7.3 Inventory control

Inventory of vaccines can be used to deal with uncertainties in demand and supply. Jacobson, Sewell, and Proano (2006) consider inventory control for pediatric vaccines in the United States. The current stockpiles are sufficient to handle disruptions in production that last for around 6 months. However, when disruptions last longer the inventory level is inadequate. This potentially leads to underimmunization and consequently to epidemic outbreaks. The risk of epidemics could be reduced by making moderate investments in inventories. Samii, Pibernik, Yadav, and Vereecke (2012) connect allocation schemes for influenza vaccines to inventory control policies. Three allocation schemes are compared that all reserve a proportion of the available vaccines for the high-risk groups, but differ in the way the unreserved proportion is allocated. Every allocation scheme is related to an inventory control policy and the corresponding service levels and fill rates are determined.

We next discuss some papers that focus on inventories for disaster response. Salmerón and Apte (2010) consider pre-disaster planning for a general type of disaster. A two stage stochastic programming formulation is proposed to minimize the expected casualties. The first stage is related to building capacity, whereas the second stage considers the logistics of the problem, related to transporting victims and resources. The analysis reflects the importance of using stochastic models, because of the uncertainty in the location of the disaster. In addition to pre-disaster planning, one can also study the situation *during* a disaster when resources might need to be (re)distributed. Arora, Raghu, and Vinze (2010) consider this problem and include both delivery from a central stockpile and lateral transshipments. The authors assume the available stockpile to be limited and do not take into account newly produced and supplied inventories. Rottkemper, Fischer, Blecken, and Danne (2011) consider a similar model, but assume an unlimited inventory at the central depot. The paper studies the relocation of inventories in case of an emergency in certain areas. In these areas the demand for relief goods then suddenly increases, but at the same time ongoing operations in other areas must continue. The authors formulate an inventory relocation model and solve it using a rolling horizon to incorporate uncertainties. To illustrate the policy recommendations that can be generated, a case for meningitis vaccine in Burundi is used.

A. Fleischhacker, Ninh, and Zhao (2015) study clinical trial supply chains. As patient recruitment is a bottleneck in clinical trials policy makers require a very high service level for the supply of medication to avoid shortages. The authors formulate a multi-echelon inventory model and develop a solution method. The results show that when clinical trials become more global it becomes more important to think about where to position inventory. The optimal strategy lies between holding all inventories centrally and pushing everything to the sites.

7.4 Supply Chain Design

Peterson et al. (2009) consider the possibilities for statistical thinking in the changes that the pharmaceutical industry is facing. These changes are for example the increasing global competition, the need for faster drug-development and new quality regulations. Based on four case studies the paper shows that statisticians can help in improving quality and efficiency in the pharmaceutical industry. Also product safety and security is an important aspect of pharmaceutical supply chains. Marucheck, Greis, Mena, and Cai (2011) argue that this technological topic has also many operational aspects. The authors illustrate some risks for several supply chains, including the pharmaceutical supply chain. One of the main risks is the long supply chain with many activities at different location. Other problems are the risk of counterfeiting or the case of stockpiling medication with the goal to sell at higher prices when shortages occur. The paper presents four focus areas for the Operations Management community to contribute to safety and security in supply chains, including supplier relations and product life cycle management.

One of the characteristics of pharmaceuticals is that they are perishable. Masoumi, Yu, and Nagurney (2012) takes this into account when studying a supply chain network model. The model incorporates multiple firms that are competing in different market, with the product flows on their supply chain networks as strategies. The authors present an algorithm to find supply chain equilibria. Chung and Kwon (2016) extend this work and derive insightful supply chain decision rules from the necessary conditions for the equilibria. Pishvaee, Razmi, and Torabi (2014) proposes a method to design a sustainable medical supply chain taking into account the complete life cycle of medical supplies and waste. Careful design of the medical waste supply chain is in particular critical for supplies that have been used for infectious patients, where the risk of further transmission is always imminent. Saif and Elhedhli (2016) also take environmental considerations into account when studying the design of a cold supply chain, i.e., a supply chain for goods that have to stay in a temperature controlled environment such as vaccines. They illustrate their model for the vaccine supply chain in Ontario and show that there is a trade-off between transportation costs and inventory costs.

7.5 Discussion

Time is of high importance in the vaccine supply chain, also in the distribution phase. When vaccines are distributed during an outbreak it is crucial that the distribution can be done efficiently and quickly to avoid an explosive increase in infections. Large scale vaccination campaigns, also known as mass vaccination campaigns, can be used in case of a sudden outbreak with natural cause or due to a bioterror attack (Kaplan, Craft, & Wein, 2002). Performing a mass vaccination campaign is a huge logistical challenge with decision problems related to vaccination locations, facility lay-out, the order in which the population is vaccinated, staffing levels. The decision tool RealOpt© is an important contribution towards solving some of these decision problems, but the OR/OM community can further contribute here. In particular, from our overview we observe that there are quite some studies on vaccine allocation for sudden outbreaks, but the literature on how to actually distribute vaccines according to this allocation is limited. This gap in literature provides research opportunities for the OR/OM community.

Kaufmann, Miller, and Cheyne (2011) state that the vaccine supply chain in low and middle income countries consists of two segments: (1) the process of sending vaccines to the receiving country and (2) the distribution of vaccines from the entrance in the receiving country to inventory points and finally to the health care provider. The first segment partly takes place in developed countries, whereas the second segment is completely organized within the developing countries. The discussion on the design of the chain particularly plays a role in developing countries. In these countries the supply chains are often insufficiently able to incorporate the introduction of new vaccines. This is partly due to a lack of coordination between the multiple supply chain levels with each their own stockpiles. In the epidemiological literature there are quite some papers that study this coordination and the redesign of the supply chain (Assi et al., 2013; Brown et al., 2014; B. Y. Lee et al., 2015). But within the OR/OM community this topic has not been considered yet. Since this community has experience in studying supply chains, there are research opportunities to apply this knowledge to the vaccine supply chain.

8 Conclusions

In this review we discuss publications on the vaccine supply chain. This topic originates in the epidemiological community, but has recently also found its way into the OR/OM community. By analyzing the different aspects of the vaccine supply chain, we connect the logistical questions that play a role in vaccination.

Based on our extensive literature review we conclude that the vaccine supply chain can benefit from the OR/OM perspective and ample examples of interesting studies are presented in this paper. The OR/OM community can contribute in different dimensions to improving the vaccine supply chain in both developed and developing countries. Kraiselburd and Yadav (2013) argue that one of the main causes for the limited access to health care and medication in developing countries is a lack of careful supply chain design. Often these supply chains originate from decades ago and are not sufficiently able to keep up with the increase in available vaccines. The OR/OM community has experience in presenting an integrated view over a whole supply chain and in formally defining decision problems. These problems can be studied with OR tools to gain insights and to derive specific decision support systems.

When analyzing current literature some observations repeatedly appear over the different components of the supply chain. Firstly, we see that time is of crucial importance: composition decisions have to be made under time pressure, production is subject to uncertain production times and swift response is needed in case of an outbreak. The combination of time pressure and extreme uncertainty, which is especially the case for sudden outbreaks, complicates decision making processes. Future research should focus on these aspects to aid decision makers in these processes. Secondly, we notice that there is a gap in literature regarding research on sudden outbreaks and the first two stages of the supply chain (composition and production) (see also Table 1). Further research is needed to address questions regarding the development and production of vaccines for sudden outbreaks. Thirdly, the discussed papers are mainly considering isolated aspects of the supply chain in developed countries. Future research could therefore focus on strengthening the connection between consecutive components. Privett and Gonsalvez (2014) emphasize that advanced improvement in a single aspect of the global health supply chain without focusing on the coordination will only lead to minor overall improvements. Finally, the vaccine supply chain is affected by the consequences of distributed decision making. Coordination between policy makers and suppliers is relatively well studied, but the role of the end customer (i.e., the 'patient') is hardly taken into account. As vaccine hesitancy or even vaccine refusal will directly affect the effects of vaccination, future research should incorporate this aspect in the models.

The papers discussed in this review show the valuable contribution that the OR/OM community has already made to logistical problems in vaccination. Further research in this area is promising and we present interesting research directions for problems that play a role in developed countries or in developing countries. The growing availability of vaccines in developing countries results in ample opportunities to use expertise on logistics and supply chains, such that medical developments will not be hindered by logistical constraints.

References

Aaby, K., Herrmann, J. W., Jordan, C. S., Treadwell, M., & Wood, K. (2006). Montgomery County's Public Health Service Uses Operations Research to Plan Emergency Mass Dispensing and Vaccination Clinics. *Interfaces*, *36*(6), 569-579.

Abrahams, A. S., & Ragsdale, C. T. (2012). A decision support system for patient scheduling in travel vaccine administration. *Decision Support Systems*, *54*(1), 215–225.

Adida, E., Dey, D., & Mamani, H. (2013). Operational issues and network effects in vaccine markets. *European Journal of Operational Research*, *231*(2), 414 - 427.

Aleman, D. M., Wibisono, T. G., & Schwartz, B. (2011). A nonhomogeneous agent-based simulation approach to modeling the spread of disease in a pandemic outbreak. *Interfaces*, *41*(3), 301–315.

Araz, O. M., Galvani, A., & Meyers, L. A. (2012). Geographic prioritization of distributing pandemic influenza vaccines. *Health Care Management Science*, *15*(3), 175–187.

Arifoğlu, K., Deo, S., & Iravani, S. M. R. (2012). Consumption Externality and Yield Uncertainty in the Influenza Vaccine Supply Chain: Interventions in Demand and Supply Sides. *Management Science*, *58*(6), 1072-1091.

Arora, H., Raghu, T., & Vinze, A. (2010). Resource allocation for demand surge mitigation during disaster response. *Decision Support Systems*, *50*(1), 304–315.

Arulselvan, A., Commander, C. W., Elefteriadou, L., & Pardalos, P. M. (2009). Detecting critical nodes in sparse graphs. *Computers & Operations Research*, *36*(7), 2193–2200.

Assi, T.-M., Brown, S. T., Kone, S., Norman, B. A., Djibo, A., Connor, D. L., ... Lee, B. Y. (2013). Removing the regional level from the Niger vaccine supply chain. *Vaccine*, *31*(26), 2828 - 2834.

Ball, F., Britton, T., & Lyne, O. (2004). Stochastic multitype epidemics in a community of households: estimation and form of optimal vaccination schemes. *Mathematical Biosciences*, *191*(1), 19–40.

Ball, F., & Lyne, O. (2006). Optimal vaccination schemes for epidemics among a population of households, with application to variola minor in Brazil. *Statistical Methods in Medical Research*, *15*(5), 481–497.

Ball, F. G., & Lyne, O. D. (2002). Optimal vaccination policies for stochastic epidemics among a population of households. *Mathematical Biosciences*, *177*, 333–354.

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

Begen, M. A., Pun, H., & Yan, X. (2016). Supply and demand uncertainty reduction efforts and cost comparison. *International Journal of Production Economics*. doi: doi:10.1016/j.ijpe.2016.07.013

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

Berman, O., Gavious, A., & Menezes, M. B. (2012). Optimal response against bioterror attack on airport terminal. *European Journal of Operational Research*, *219*(2), 415 - 424.

Brown, S. T., Schreiber, B., Cakouros, B. E., Wateska, A. R., Dicko, H. M., Connor, D. L., ... Lee, B. Y. (2014). The benefits of redesigning Benin's vaccine supply chain. *Vaccine*, *32*(32), 4097 - 4103.

Chen, L.-C., Carley, K. M., Fridsma, D., Kaminsky, B., & Yahja, A. (2006). Model alignment of anthrax attack simulations. *Decision Support Systems*, *41*(3), 654–668.

Chick, S. E., Mamani, H., & Simchi-Levi, D. (2008). Supply Chain Coordination and Influenza Vaccination. *Operations Research*, *56*(6), 1493-1506.

Cho, S.-H. (2010). The Optimal Composition of Influenza Vaccines Subject to Random Production Yields. *Manufacturing & Service Operations Management*, *12*(2), 256-277.

Cho, S.-H., & Tang, C. S. (2013). Advance selling in a supply chain under uncertain supply and demand. *Manufacturing & Service Operations Management*, *15*(2), 305–319.

Chopra, S., & Meindl, P. (2007). Supply chain management. Strategy, planning & operation. In *Das summa summarum des management* (pp. 265–275). Springer.

Chung, S. H., & Kwon, C. (2016). Integrated supply chain management for perishable products: Dynamics and oligopolistic competition perspectives with application to pharmaceuticals. *International Journal of Production Economics*, *179*, 117–129.

Craft, D. L., Wein, L. M., & Wilkins, A. H. (2005). Analyzing bioterror response logistics: The case of anthrax. *Management Science*, *51*(5), 679-694.

Dai, T., Cho, S.-H., & Zhang, F. (2016). Contracting for on-time delivery in the US influenza vaccine supply chain. *Manufacturing & Service Operations Management*, *18*(3), 332-346.

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

Denysiuk, R., Silva, C. J., & Torres, D. F. (2015). Multiobjective approach to optimal control for a tuberculosis model. *Optimization Methods and Software*, *30*(5), 893–910.

Deo, S., & Corbett, C. J. (2009). Cournot Competition Under Yield Uncertainty: The Case of the U.S. Influenza Vaccine Market. *Manufacturing & Service Operations Management*, *11*(4), 563-576.

De Treville, S., Bicer, I., Chavez-Demoulin, V., Hagspiel, V., Schürhoff, N., Tasserit, C., & Wager, S. (2014). Valuing lead time. *Journal of Operations Management*, *32*(6), 337–346.

Dimitrov, N. B., Moffett, A., Morton, D. P., & Sarkar, S. (2013). Selecting malaria interventions: A top-down approach. *Computers & Operations Research*, *40*(9), 2229–2240.

Ding, M., & Eliashberg, J. (2002). Structuring the new product development pipeline. *Management Science*, *48*(3), 343–363.

Duijzer, L. E., Van Jaarsveld, W. L., Wallinga, J., & Dekker, R. (2015). *Dose-optimal vaccine allocation over multiple populations* (Tech. Rep.). Econometric Institute, Erasmus School of Economics. Retrieved from `http://repub.eur.nl/pub/79212` (Report number: EI 2015-29)

Duijzer, L. E., Van Jaarsveld, W. L., Wallinga, J., & Dekker, R. (2016). *The most efficient critical vaccination coverage and its equivalence with maximizing the herd effect* (Tech. Rep.). Retrieved from `http://repub.eur.nl/pub/79912` (Report number: EI 2016-06)

Dushoff, J., Plotkin, J. B., Viboud, C., Simonsen, L., Miller, M., Loeb, M., & Earn, D. J. (2007). Vaccinating to Protect a Vulnerable Subpopulation. *PLoS Med*, *4*(5), e174.

Edwards, D. M., Shachter, R. D., & Owens, D. K. (1998). A Dynamic HIV-Transmission Model for Evaluating the Costs and Benefits of Vaccine Programs. *Interfaces*, *28*(3), 144-166.

Ekici, A., Keskinocak, P., & Swann, J. L. (2014). Modeling influenza pandemic and planning food distribution. *Manufacturing & Service Operations Management*, *16*(1), 11-27.

Engineer, F. G., Keskinocak, P., & Pickering, L. K. (2009). OR Practice: Catch-Up Scheduling for Childhood Vaccination. *Operations Research*, *57*(6), 1307-1319.

Eskandarzadeh, S., Eshghi, K., & Bahramgiri, M. (2016). Risk shaping in production planning problem with pricing under random yield. *European Journal of Operational Research*, *253*(1), 108–120.

Federgruen, A., & Yang, N. (2008). Selecting a portfolio of suppliers under demand and supply risks. *Operations Research*, *56*(4), 916–936.

Federgruen, A., & Yang, N. (2009). Competition under generalized attraction models: Applications to quality competition under yield uncertainty. *Management Science*, *55*(12), 2028–2043.

Fleischhacker, A., Ninh, A., & Zhao, Y. (2015). Positioning inventory in clinical trial supply chains. *Production and Operations Management*, *24*(6), 991–1011.

Fleischhacker, A. J., & Zhao, Y. (2011). Planning for demand failure: A dynamic lot size model for clinical trial supply chains. *European Journal of Operational Research*, *211*(3), 496 - 506.

Fogli, D., & Guida, G. (2013). Knowledge-centered design of decision support systems for emergency management. *Decision Support Systems*, *55*(1), 336–347.

Frerichs, R. R., & Prawda, J. (1975). A computer simulation model for the control of rabies in an urban area of Colombia. *Management Science*, *22*(4), 411–421.

Gerdil, C. (2003). The annual production cycle for influenza vaccine. *Vaccine*, *21*(16), 1776–1779.

Goldstein, E., Apolloni, A., Lewis, B., Miller, J., Macauley, M., Eubank, S., ... Wallinga, J. (2009). Distribution of vaccine/antivirals and the 'least spread line' in a stratified population. *Journal of the Royal Society Interface*, rsif20090393.

Goldstein, E., Wallinga, J., & Lipsitch, M. (2012). Vaccine allocation in a declining epidemic. *Journal of The Royal Society Interface*, *9*(76), 2798–2803.

Hall, S. N., Jacobson, S. H., & Sewell, E. C. (2008). An Analysis of Pediatric Vaccine Formulary Selection Problems. *Operations Research*, *56*(6), 1348-1365.

Halper, R., & Raghavan, S. (2011). The Mobile Facility Routing Problem. *Transportation Science*, *45*(3), 413-434.

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

Herrmann, J. W. (2008). Disseminating emergency preparedness planning models as automatically generated custom spreadsheets. *Interfaces*, *38*(4), 263–270.

Hutton, D. W., Brandeau, M. L., & So, S. K. (2011). Doing Good with Good OR: Supporting Cost-Effective Hepatitis B Interventions. *Interfaces*, *41*(3), 289-300.

Jacobson, S. H., Sewell, E. C., & Proano, R. A. (2006). An analysis of the pediatric vaccine supply shortage problem. *Health Care Management Science*, *9*(4), 371–389.

Jit, M., Brisson, M., Portnoy, A., & Hutubessy, R. (2014). Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. *The Lancet Global Health*, *2*(7), e406–e414.

Jit, M., Choi, Y. H., & Edmunds, W. J. (2008). Economic evaluation of human papillomavirus vaccination in the United Kingdom. *BMJ*, *337*, a769.

Kaplan, E. H., Craft, D. L., & Wein, L. M. (2002). Emergency response to a smallpox attack: the case for mass vaccination. *Proceedings of the National Academy of Sciences*, *99*(16), 10935–10940.

Kaufmann, J. R., Miller, R., & Cheyne, J. (2011). Vaccine Supply Chains Need To Be Better Funded And Strengthened, Or Lives Will Be At Risk. *Health Affairs*, *30*(6), 1113–1121.

Kazaz, B., Webster, S., & Yadav, P. (2016). Interventions for an artemisinin-based malaria medicine supply chain. *Production and Operations Management*, *25*, 1576 - 1600.

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

Kornish, L. J., & Keeney, R. L. (2008). Repeated Commit-or-Defer Decisions with a Deadline: The Influenza Vaccine Composition. *Operations Research*, *56*(3), 527-541.

Kraiselburd, S., & Yadav, P. (2013). Supply Chains and Global Health: An Imperative for Bringing Operations Management Scholarship into Action. *Production and Operations Management*, *22*(2), 377–381.

Larson, H. J., Jarrett, C., Eckersberger, E., Smith, D. M., & Paterson, P. (2014). Understanding vaccine hesitancy around vaccines and vaccination from a global perspective: a systematic review of published literature, 2007–2012. *Vaccine*, *32*(19), 2150–2159.

Larson, R. C. (2007). Simple models of influenza progression within a heterogeneous population. *Operations Research*, *55*(3), 399-412.

Lasry, A., Zaric, G. S., & Carter, M. W. (2007). Multi-level resource allocation for HIV prevention: A model for developing countries. *European Journal of Operational Research*, *180*(2), 786 - 799.

Lee, B. Y., Connor, D. L., Wateska, A. R., Norman, B. A., Rajgopal, J., Cakouros, B. E., ... Brown, S. T. (2015). Landscaping the structures of GAVI country vaccine supply chains and testing the effects of radical redesign. *Vaccine*, *33*(36), 4451 - 4458.

Lee, E. K., Chen, C.-H., Pietz, F., & Benecke, B. (2009). Modeling and Optimizing the Public-Health Infrastructure for Emergency Response. *Interfaces*, *39*(5), 476-490.

Lee, E. K., Maheshwary, S., Mason, J., & Glisson, W. (2006). Large-Scale Dispensing for Emergency Response to Bioterrorism and Infectious-Disease Outbreak. *Interfaces*, *36*(6), 591-607.

Lee, E. K., Pietz, F., Benecke, B., Mason, J., & Burel, G. (2013). Advancing Public Health and Medical Preparedness with Operations Research. *Interfaces*, *43*(1), 79-98.

Lee, E. K., Yuan, F., Pietz, F. H., Benecke, B. A., & Burel, G. (2015). Vaccine Prioritization for Effective Pandemic Response. *Interfaces*, *45*(5), 425-443.

Lemmens, S., Decouttere, C., Vandaele, N., & Bernuzzi, M. (2016). A review of integrated supply chain network design models: Key issues for vaccine supply chains. *Chemical Engineering Research and Design*, *109*, 366–384.

Levi, R., Perakis, G., & Romero, G. (2016). On the Effectiveness of Uniform Subsidies in Increasing Market Consumption. *Management Science*.

Luangkesorn, K. L., Norman, B. A., Zhuang, Y., Falbo, M., & Sysko, J. (2012). Practice Summaries: Designing Disease Prevention and Screening Centers in Abu Dhabi. *Interfaces*, *42*(4), 406-409.

Maher, S. J., & Murray, J. M. (2016). The unrooted set covering connected subgraph problem differentiating between HIV envelope sequences. *European Journal of Operational Research*, *248*(2), 668–680.

Mamani, H., Chick, S. E., & Simchi-Levi, D. (2013). A Game-Theoretic Model of International Influenza Vaccination Coordination. *Management Science*, *59*(7), 1650-1670.

Marucheck, A., Greis, N., Mena, C., & Cai, L. (2011). Product safety and security in the global supply chain: Issues, challenges and research opportunities. *Journal of Operations Management*, *29*(7), 707–720.

Masoumi, A. H., Yu, M., & Nagurney, A. (2012). A supply chain generalized network oligopoly model for pharmaceuticals under brand differentiation and perishability. *Transportation Research Part E: Logistics and Transportation Review*, *48*(4), 762–780.

Matrajt, L., Halloran, M. E., & Longini Jr, I. M. (2013). Optimal Vaccine Allocation for the Early Mitigation of Pandemic Influenza. *PLoS Computational Biology*, *9*(3), e1002964.

Matrajt, L., & Longini Jr, I. M. (2010). Optimizing Vaccine Allocation at Different Points in Time during an Epidemic. *PLoS ONE*, *5*(11), e13767.

McCoy, J. H., & Johnson, M. E. (2014). Clinic Capacity Management: Planning Treatment Programs that Incorporate Adherence. *Production and Operations Management*, *23*(1), 1–18.

McCoy, J. H., & Lee, H. L. (2014). Using fairness models to improve equity in health delivery fleet management. *Production and Operations Management*, *23*(6), 965–977.

Medlock, J., & Galvani, A. P. (2009). Optimizing Influenza Vaccine Distribution. *Science*, *325*(5948), 1705–1708.

Miller, G., Randolph, S., & Patterson, J. E. (2006). Responding to bioterrorist smallpox in san antonio. *Interfaces*, *36*(6), 580–590.

Mylius, S. D., Hagenaars, T. J., Lugnér, A. K., & Wallinga, J. (2008). Optimal allocation of pandemic influenza vaccine depends on age, risk and timing. *Vaccine*, *26*(29), 3742–3749.

Nandi, A. K., & Medal, H. R. (2016). Methods for removing links in a network to minimize the spread of infections. *Computers & Operations Research*, *69*, 10–24.

Omer, S. B., Salmon, D. A., Orenstein, W. A., Dehart, M. P., & Halsey, N. (2009). Vaccine refusal, mandatory immunization, and the risks of vaccine-preventable diseases. *New England Journal of Medicine*, *360*(19), 1981–1988.

Özaltın, O. Y., Prokopyev, O. A., Schaefer, A. J., & Roberts, M. S. (2011). Optimizing the Societal Benefits of the Annual Influenza Vaccine: A Stochastic Programming Approach. *Operations Research*, *59*(5), 1131-1143.

Parker, B. R. (1983). A program selection/resource allocation model for control of malaria and related parasitic diseases. *Computers & Operations Research*, *10*(4), 375–389.

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

Peterson, J. J., Snee, R. D., McAllister, P. R., Schofield, T. L., Carella, A. J., Hoerl, R. W., … others (2009). Statistics in pharmaceutical development and manufacturing/discussion/discussion/discussion/discussion/rejoinder. *Journal of Quality Technology*, *41*(2), 111.

Pishvaee, M., Razmi, J., & Torabi, S. (2014). An accelerated benders decomposition algorithm for sustainable supply chain network design under uncertainty: A case study of medical needle and syringe supply chain. *Transportation Research Part E: Logistics and Transportation Review*, *67*, 14–38.

Porco, T. C., & Blower, S. M. (1998). Designing HIV vaccination policies: subtypes and cross-immunity. *Interfaces*, *28*(3), 167–190.

Privett, N., & Gonsalvez, D. (2014). The top ten global health supply chain issues: Perspectives from the field. *Operations Research for Health Care*, *3*(4), 226 - 230.

Proano, R. A., Jacobson, S. H., & Zhang, W. (2012). Making combination vaccines more accessible to low-income countries: The antigen bundle pricing problem. *Omega*, *40*(1), 53 - 64.

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*(1), 225 - 231.

Ramirez-Nafarrate, A., Lyon, J. D., Fowler, J. W., & Araz, O. M. (2015). Point-of-Dispensing Location and Capacity Optimization via a Decision Support System. *Production and Operations Management*, *24*(8), 1311–1328.

Rauner, M. S. (2002). Resource allocation for HIV/AIDS control programs: a model-based policy analysis. *OR Spectrum*, *24*(1), 99–124.

Reveller, C., Lynn, W., & Feldmann, F. (1969). An optimization model of tuberculosis epidemiology. *Management Science*, *16*(4), B–190.

Richter, A., & Khan, S. (2009). Pilot Model: Judging Alternate Modes of Dispensing Prophylaxis in Los Angeles County. *Interfaces*, *39*(3), 228-240.

Robbins, M. J., & Jacobson, S. H. (2011). Pediatric vaccine procurement policy: The monopsonist's problem. *Omega*, *39*(6), 589 - 597.

Robbins, M. J., Jacobson, S. H., Shanbhag, U. V., & Behzad, B. (2014). The Weighted Set Covering Game: A

Vaccine Pricing Model for Pediatric Immunization. *INFORMS Journal on Computing*, *26*(1), 183-198.

Robbins, M. J., & Lunday, B. J. (2016). A bilevel formulation of the pediatric vaccine pricing problem. *European Journal of Operational Research*, *248*(2), 634 - 645.

Rottkemper, B., Fischer, K., Blecken, A., & Danne, C. (2011). Inventory relocation for overlapping disaster settings in humanitarian operations. *OR spectrum*, *33*(3), 721–749.

Saif, A., & Elhedhli, S. (2016). Cold supply chain design with environmental considerations: A simulation-optimization approach. *European Journal of Operational Research*, *251*(1), 274–287.

Salmerón, J., & Apte, A. (2010). Stochastic Optimization for Natural Disaster Asset Prepositioning. *Production and Operations Management*, *19*(5), 561–574.

Samii, A.-B., Pibernik, R., Yadav, P., & Vereecke, A. (2012). Reservation and allocation policies for influenza vaccines. *European Journal of Operational Research*, *222*(3), 495 - 507.

Siddiqui, M. R., & Edmunds, W. J. (2008). Cost-effectiveness of antiviral stockpiling and near-patient testing for potential influenza pandemic. *Emerging infectious diseases*, *14*(2), 267–74.

Silva, M. L., Perrier, L., Cohen, J. M., Paget, W. J., Mosnier, A., & Späth, H. M. (2015). A literature review to identify factors that determine policies for influenza vaccination. *Health Policy*, *119*(6), 697 - 708.

Smalley, H. K., Keskinocak, P., Engineer, F. G., & Pickering, L. K. (2011). Universal Tool for Vaccine Scheduling: Applications for Children and Adults. *Interfaces*, *41*(5), 436-454.

Sun, P., Yang, L., & de Véricourt, F. (2009). Selfish Drug Allocation for Containing an International Influenza Pandemic at the Onset. *Operations Research*, *57*(6), 1320-1332.

Tanner, M. W., & Ntaimo, L. (2010). IIS branch-and-cut for joint chance-constrained stochastic programs and application to optimal vaccine allocation. *European Journal of Operational Research*, *207*(1), 290 - 296.

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

Taylor, T. A., & Xiao, W. (2014). Subsidizing the Distribution Channel: Donor Funding to Improve the Availability of Malaria Drugs. *Management Science*, *60*(10), 2461-2477.

Tebbens, R. J. D., & Thompson, K. M. (2009). Priority Shifting and the Dynamics of Managing Eradicable Infectious Diseases. *Management Science*, *55*(4), 650-663.

Teunter, R. H., & Flapper, S. D. P. (2006). A comparison of bottling alternatives in the pharmaceutical industry. *Journal of Operations Management*, *24*(3), 215 - 234.

Teytelman, A., & Larson, R. C. (2012). Modeling influenza progression within a continuous-attribute heterogeneous population. *European Journal of Operational Research*, *220*(1), 238 - 250.

Thompson, K. M., Tebbens, R. J. D., Pallansch, M. A., Wassilak, S. G., & Cochi, S. L. (2015). Polio Eradicators Use Integrated Analytical Models to Make Better Decisions. *Interfaces*, *45*(1), 5-25.

Uribe-Sánchez, A., Savachkin, A., Santana, A., Prieto-Santa, D., & Das, T. K. (2011). A predictive decision-aid methodology for dynamic mitigation of influenza pandemics. *OR Spectrum*, *33*(3), 751–786.

Van Eck, N. J., & Waltman, L. (2007). Vos: a new method for visualizing similarities between objects. In *Advances in data analysis* (pp. 299–306). Springer.

Ventresca, M. (2012). Global search algorithms using a combinatorial unranking-based problem representation for the critical node detection problem. *Computers & Operations Research*, *39*(11), 2763–2775.

Ventresca, M., & Aleman, D. (2014a). A derandomized approximation algorithm for the critical node detection problem. *Computers & Operations Research*, *43*, 261–270.

Ventresca, M., & Aleman, D. (2014b). A randomized algorithm with local search for containment of pandemic disease spread. *Computers & Operations Research*, *48*, 11 - 19.

Wagner, H. M., & Whitin, T. M. (1958). Dynamic version of the economic lot size model. *Management science*, *5*(1), 89–96.

Wallinga, J., van Boven, M., & Lipsitch, M. (2010). Optimizing infectious disease interventions during an emerging epidemic. *Proceedings of the National Academy of Sciences*, *107*(2), 923–928.

Wein, L. M. (2009). OR Forum-Homeland Security: From Mathematical Models to Policy Implementation: The 2008 Philip McCord Morse Lecture. *Operations Research*, *57*(4), 801–811.

Wein, L. M., Craft, D. L., & Kaplan, E. H. (2003). Emergency response to an anthrax attack. *Proceedings of the National Academy of Sciences*, *100*(7), 4346–4351.

Whitworth, M. H. (2006). Designing the response to an anthrax attack. *Interfaces*, *36*(6), 562–568.

Wu, J. T., Riley, S., & Leung, G. M. (2007). Spatial considerations for the allocation of pre-pandemic influenza vaccination in the United States. *Proceedings of the Royal Society of London B: Biological Sciences*, *274*(1627), 2811–2817.

Wu, J. T., Wein, L. M., & Perelson, A. S. (2005). Optimization of Influenza Vaccine Selection. *Operations Research*, *53*(3), 456-476.

Yamin, D., & Gavious, A. (2013). Incentives' effect in influenza vaccination policy. *Management Science*, *59*(12), 2667–2686.

Yarmand, H., Ivy, J. S., Denton, B., & Lloyd, A. L. (2014). Optimal two-phase vaccine allocation to geographically different regions under uncertainty. *European Journal of Operational Research*, *233*(1), 208 - 219.

Supplementary Material
Literature Review - the vaccine supply chain

Appendix A Journal list

For this review we considered the top 20 journals in the category 'Operations Research and Management Science' by Thomson Reuters' InCites Journal Citation Reports [1]. The following ranking is based on the Article Influence Score (AIS), with in brackets the number of papers discussed in this review:

- Management Science (11)
- Journal of Operations Management (3)
- Mathematical Programming (0)
- Operations Research (10)
- Mathematics of Operations Research (0)
- Manufacturing & Service Operations Management (5)
- Transportation Science (0)
- Transportation Research part B (0)
- Journal of Quality Technology (3)
- Omega - International Journal of Management Science (2)
- Systems & Control Letters (0)
- European Journal of Operational Research (11)
- Computational Optimization and Applications (0)
- Transportation Research part E (2)
- Production and Operations Management (7)
- OR Spectrum (3)
- INFORMS Journal on Computing (1)
- Decision Support Systems (4)
- Optimization Methods and Software (1)
- Computers & Operations Research (3)

Appendix B Chronological analysis of publications

The 66 publications are published between 1969 and 2016. 3 publications fall inside the time interval [1969-2000], 4 within the interval [2000-2005], 19 within the interval [2006-2010] and the remaining 42 publications date from [2011-2016]. The histogram in Figure 3 displays the number of publications over time.

Appendix C Bibliometric analysis

Five articles could not be found in the database of the Web of Science$^{\mathrm{TM}}$ Core Collection (search date June 30, 2016). The first four are the following: Reveller et al. (1969), Dai et al. (2016), Kazaz et al. (2016), Levi et al. (2016). In the database of the Journal of Quality Technology the publication Peterson et al. (2009) consists of three parts: the original paper, the discussions and the rejoinder. In counting the publications in Section 2 we have considered them as three separate publications. In the Web of Science database only the original paper and the rejoinder were found. So the fifth missing publication relates to the discussions parts of Peterson et al. (2009).

[1] See jcr.incites.thomsonreuters.com

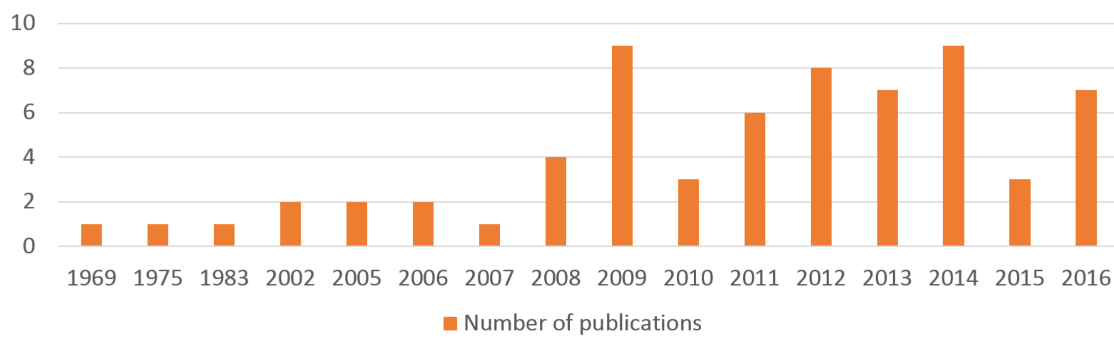

Figure 3: The relation between time and the publications on the vaccine supply chain that are reviewed in this paper.