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Highlights

- We develop a framework for literature in vaccine logistics.
- Within this framework, we discuss the recent literature.
- We characterize the unique particularities of the vaccine supply chain.
- Our review yields interesting directions for future research.

Literature Review - the vaccine supply chain

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Abstract

Vaccination is one of the most effective ways to prevent and/or control the outbreak of infectious diseases. This medical intervention also brings about many logistical questions. In the past years, the Operations Research/Operations Management community has shown a growing interest in the logistical aspects of vaccination. However, publications on vaccine logistics often focus on one specific logistical aspect. A broader framework is needed so that open research questions can be identified more easily and contributions are not overlooked.

In this literature review, we combine the priorities of the World Health Organization for creating a flexible and robust vaccine supply chain with an Operations Research/Operations Management supply chain perspective. We propose a classification for the literature on vaccine logistics to structure this relatively new field, and identify promising research directions. We classify the literature into the following four components: (1) product, (2) production, (3) allocation, and (4) distribution. Within the supply chain classification, we analyze the decision problems for existing outbreaks versus sudden outbreaks and developing countries versus developed countries. We identify unique characteristics of the vaccine supply chain: high uncertainty in both supply and demand; misalignment of objectives and decentralized decision making between supplier, public health organization and end customer; complex political decisions concerning allocation and the crucial importance of deciding and acting in time.

Keywords: supply chain management, vaccine, 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 aims at preventing a disease outbreak. Besides preventive vaccination, reactive vaccination 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 importance of vaccine logistics is demonstrated by the growing number of studies on the subject.

In this paper, we structure the literature on vaccine logistics, using the priority areas defined

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by the World Health Organization (WHO) (World Health Organization & PATH, 2011). These priority areas allow us to evaluate the current state of research on the vaccine supply chain and to identify promising directions that could be further explored to create a flexible and robust vaccine supply chain. We focus on the first three priorities of the WHO, as these are most related to Operations Research/Operations Management (OR/OM):

- Products and packaging
- Immunization supply system efficiency
- Environmental impact of immunization supply systems

The WHO clarifies these three priorities as follows: vaccine products and their packaging should be designed with characteristics that best suit the needs and constraints of countries; immunization supply systems should be designed to maximize effectiveness, agility, and integration with other supply systems, and to support continuous system improvement through learning, innovation, and leveraging synergies with other sectors; and the environmental impact of energy, materials, and processes used in immunization supply systems from the international to local levels should be assessed and minimized.

The OR/OM community is increasingly interested in vaccine logistics, which is indicated by the fact that around 90% of the papers discussed in this review date from 2005 and more than half from 2011 (cf., Appendix B). Despite this growing interest, the literature on vaccine logistics is somewhat scattered. Most papers focus on a one specific aspect of logistics (e.g., allocation or production) which has resulted in separate clusters of papers with few cross citations. Moreover, these papers direct little attention to the broader perspective of vaccine logistics, making the papers difficult to place in the correct context. This larger context is important, because improving a single aspect of logistics without aligning this with other aspects will only lead to minor overall improvements (Privett and Gonsalvez, 2014). A broad overview of vaccine logistics and the vaccine supply chain is lacking in the current literature, which makes it difficult to identify the opportunities for the OR/OM community.

We contribute to structuring the literature on vaccine logistics by integrating the WHO priorities with an OR/OM supply chain perspective. We split the second priority of the WHO (Immunization supply chain efficiency) into three parts, namely, production, allocation, and distribution, that each add to supply system efficiency. The environmental impact of supply systems has received little attention in the OR/OM community and will be discussed within our supply chain framework when relevant. We identify the following four components in the vaccine supply chain:

1. **Product** - *What kind of vaccine should be used?*
   A vaccine is administered to develop immunity to a certain disease. Before vaccination can take place, policy makers must decide which disease they are targeting and which vaccine will be used. Multiple vaccines might be available for the same disease, or the characteristics of the disease might not be known at the time of production. This leads to the problem of deciding on the composition of the vaccine. For example, the composition decision for the annual influenza shot is related to the strains of the influenza virus that should be included. Decisions about which vaccines should be used are also important for designing a vaccination program for multiple diseases. Policy makers must decide which diseases to include, which

vaccines to use, and how the vaccinations should be scheduled in the program. Finally, vaccines must be packaged properly, because they are sensitive to changes in temperature.

2. **Production** - *How many doses should be produced and when?*
   The production of vaccines is characterized by uncertainties in yield and production lead times, which can result in inefficiencies on the vaccine market. Market coordination 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, especially during sudden outbreaks. This creates an allocation problem: who should be vaccinated? Within a population, we 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 regions and/or countries can arise when an epidemic spreads across borders.

4. **Distribution** - *How should the vaccines be distributed?*
   The final step is distributing the vaccines from the manufacturer to the end-users. Inventory control decisions arise when deciding on the locations of vaccine stockpiles. Logistical questions related to the location, staffing levels, and layout of fixed distribution points come in play. Routing and scheduling problems occur when mobile facilities are used.

Throughout the paper, we consider alternative perspectives in addition to the supply chain perspective. These perspectives arise naturally from the discussed papers. One of these alternative perspectives is to investigate the decision problems that are involved in specific diseases. In Table 1 we classify the literature based on type of outbreaks, disease and component 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. Based on our bibliometric analysis in Chapter 3, we treat the studies on childhood vaccination separately.

	Product	**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	x
unspecified		x	x	x
Sudden outbreaks				
pandemic influenza			x	
unspecified			x	x
Bioterror attacks				
anthrax			x	
smallpox			x	
unspecified			x	x

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

Our supply chain perspective enables us to compare the vaccine supply chain to other supply chains. We observe that the vaccine supply chain has several unique characteristics, which leads to some general lessons for supply chains. Other aspects of the vaccine supply chain are also apparent in general supply chains (cf., Chopra and Meindl, 2007). Our analysis and structuring of the literature has led to the framework in Figure 1, which is discussed in Section 8. Using this framework, we integrate the papers discussed and synthesize their contributions. We see that the components 'Production' and 'Distribution' are comparable to other supply chains, 'Allocation' is unique to the vaccine supply chain and 'Product' is somewhat in between. Decisions about which product should be used play a role in every supply chain, but the composition decisions that are important in vaccination are unique.

	Product	**Production**	**Allocation**	**Distribution**
	What kind of vaccine should be used?	**How many doses should be produced and when?**	**Who should be vaccinated?**	**How should the vaccines be distributed?**
	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
Unique characteristics	- Decentralized decisions: product is determined by public health organizations, not by the supplier - Public health organizations are non-profit, whereas supplier is for-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 in most cases - Push process: initiated and performed in anticipation of end customer need - Decentralized decisions: 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 similar and unique characteristics.

Based on this framework we derive promising research directions. With the WHO priorities in mind, we identify how the vaccine supply chain should develop and what is still needed to achieve this development. We emphasize the importance of the supply chain perspective and the integration of the stages in the supply chain.

Within our classification of the vaccine supply chain, we structure and discuss 147 papers, 65 of which are from top OR/OM journals. We contribute by providing the first review that connects the logistical components of vaccination to develop an integrated view of the vaccine supply chain. We are aware of two reviews on related topics, but both have a rather different scope from ours. Dasaklis et al. (2012) extensively review epidemic control and discuss pharmaceutical and non-pharmaceutical interventions. They focus on unexpected disease outbreaks that occur naturally and those that are caused by a bioterror attack, but do not consider the logistical aspects related to seasonal influenza or other expected outbreaks. In contrast, we restrict ourselves to vaccination,

which is a special case of pharmaceutical interventions, and we consider all kinds of outbreaks (both expected and unexpected). Lemmens et al. (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 can deal with the characteristics of the rotavirus vaccine supply chain and they indicate some shortcomings.

The remainder of this paper is structured as follows. Section 2 discusses the search strategy and the characteristics of the included publications. In Section 3, we conduct a bibliometric analysis to cluster and visualize publications based on co-citations. In the remaining sections we discuss the four components of the supply chain: Product in Section 4, Production in Section 5, Allocation in Section 6 and Distribution in Section 7. We discuss our findings and present future research directions in Section 8 and close with conclusions in Section 9.

2. Search strategy

The following search strategy is used in our review. We used the keywords 'vaccination' and 'vaccine' to search 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 (see Appendix A). Our keywords have a rather unique meaning. A thesaurus does not provide words with a similar meaning. The search resulted in 285 unique publications in total. We disregarded 45 publications that were not scientific articles, such as editorial statements, descriptions of award winners and book reviews. Out of the 240 remaining publications, 96 were disregarded because of the lack of any health care related terminology in either the title, the abstract, or in the keywords. We were left with 144 papers, which we studied in more detail. After careful reading another 79 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, or the publication had little relation to the supply chain. This review discusses the remaining 65 publications in the top OR/OM journals that deal with topics related to vaccination. We also review supporting literature such as studies from the epidemiological or health economics community, and other relevant literature that we found through citation analysis. This resulted in including over 40 publications from various fields, including Immunology, Mathematical & Computational Biology and Medicine. For these streams of literature, we adopted a pragmatic approach, and the list of included papers is not exhaustive. We mainly included studies that use a quantitative approach.

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 March 20, 2017). This paper reviews 65 studies of which 59 are found in this database and are hence included in the bibliometric analysis. The six 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 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 labeled 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. Besides 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 whether they are in the same cluster or not. In the map, 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, which are related by topic. Roughly, the clusters can be described as follows. The yellow cluster in the top left corner captures part of the papers in the component 'Product', more precisely on childhood vaccination programs. Publications in the purple cluster in the right upper corner have no obvious connection. However, most of them are related to the distribution phase of the vaccine supply chain, ranging from supply chain design to inventory decisions. The green cluster in the bottom right corner comprises papers that discuss allocation problems for unexpected outbreaks, either pandemics or bioterror attacks. The red and blue cluster are similar and include publications in the INFORMS journals on influenza vaccine composition and production. We thus conclude that Figure 2 roughly confirms our structuring of the four 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 programs. We have included these subfields in the broader components of the supply chain.

4. Product

The first decision in the vaccine supply chain is the choice for the right product: Which vaccine should be used? For some diseases (e.g., HIV/AIDS) there are no available vaccines, for others (i.e., seasonal influenza) a new vaccine needs to be developed every year. Decision problems arise regarding the design of such vaccines. For other diseases, including the ones in childhood vaccination programs, multiple suitable vaccines are often available. Decision makers have to decide on the vaccines to use and on the program in which these vaccines are included.

The right vaccine is a vaccine that is designed with characteristics that best suit the needs and constraints of countries (World Health Organization & PATH, 2011). A vaccine should primarily have the desired characteristics in terms of immunization. However, other aspects, such as the volume and the temperature at which it must be stored, can largely influence the supply chain. Such characteristics play a role particularly in developing countries, where (cold) storage capacity is limited. Following the terminology of the WHO priorities, we refer to these characteristics as the 'packaging' of the vaccine.

In this section, we study the decision problems related to designing the right product. In Section 4.1 we focus on vaccine composition, i.e., on designing a vaccine that can immunize against the targeted disease. Section 4.2 discusses vaccine selection, i.e., selecting the right vaccine from multiple vaccines available. Finally, in Section 4.3 we study the decision problems related to packaging of vaccines.

4.1. Vaccine composition

The main goal of a vaccine is to induce immunity to a disease. To design a vaccine that achieves this goal, it is important to know the characteristics of the disease you are immunizing against. For ongoing outbreaks (e.g., AIDS, malaria) we can study the characteristics of the disease that is causing the outbreak. However, this is not the case for sudden outbreaks (e.g., pandemic influenza) or for outbreaks that are caused by bioterror attacks. Outbreaks of seasonal influenza bring about an extra challenge: Even though we know that these outbreaks occur yearly, the virus strains that cause these outbreaks change every year. This leads to the following categorization of diseases: (1) diseases with unknown characteristics that are certain to break out in the near future (seasonal influenza), (2) diseases with unknown characteristics that could suddenly break out (e.g., pandemic influenza). Note that there is also a third category, namely diseases with known characteristics. We do not consider these diseases here, because the decision problem regarding the vaccine composition does not play a role for these diseases. There either is already a vaccine available, or it is still under development.

The first category comprises diseases with unknown characteristics but that are known to appear in the future. Seasonal influenza is the most studied example in this group. Every year there is an outbreak of seasonal influenza, but policy makers do not know beforehand which influenza virus strain will be dominant in the coming season. There exist multiple strains of the influenza virus and mutations might lead to new strains. In designing the annual influenza vaccine, policy makers therefore must decide which virus strains to include in the vaccine based on forecasts. Due to long production times for vaccines, this decision must 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 and deferring the decision to learn more. Every year the World Health Organization (WHO) advises on which virus strains should be included in the influenza vaccine (Gerdil, 2003; Silva et al., 2015). This combination of included virus strains is called the *vaccine composition*. 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 et al. (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, i.e., the strains to which the individual has been exposed in the past. They formulate a dynamic program to determine the optimal vaccine composition based on the antigenic history in sequential periods. The results show that the follow policy is only slightly suboptimal and the authors therefore recommend the continued use of this policy. The timing of the composition decision is crucial as it has a direct effect on the production time of the vaccine and therefore on its availability. On the one hand, it could be beneficial to defer the decision and gather more information about the coming influenza season. This reduces uncertainty and could lead to better decisions about which strains to include in the vaccine. On the other hand, postponing the decision reduces the available time for production of the vaccine, 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 also using dynamic programming. Their results can be used to evaluate what-if questions related to changes in vaccine production rates, effectiveness of the vaccines, dominant strains that cause the influenza outbreak, and its expected severity.

Cho (2010) extends the work of Kornish and Keeney (2008) by including production yield uncertainties. Decision makers must decide on retaining the current vaccine or shifting to updated compositions. The latter may involve more production yield uncertainty. The objective is to maximize expected social welfare, which comprises social benefits and social costs. The costs include production costs, which are related to production yield uncertainties. The authors propose a discrete-time decision model with three possible decisions at each time: select the current vaccine strain, update to the most prevalent new strain, or postpone decision making to the next period. The main contribution of their work is that they include the effects of the composition decision on the next step in the supply chain: the production of vaccines. Özaltın et al. (2011) also consider uncertain yields and allow for choosing among multiple possible strains for the vaccine, not only the most prevalent one. They formulate a multi-stage stochastic mixed integer model 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. Dai et al. (2016) note that vaccine manufacturers tend to start production before the vaccination composition has been determined to improve their delivery performance. Early production is risky, because the final composition decision may be different than expected. Furthermore, the health care provider benefits most from early production and prompt delivery, not the manufacturer. Dai et al. (2016) therefore propose supply chain contracts between the vaccine manufacturer and the health care provider to provide an incentive for the manufacturer to start production early, even before the vaccine composition decision has been made. Their work contains both elements of vaccine composition and vaccine production, and is discussed more extensively in Section 5.2.

We now consider the second group of diseases, which comprises disease with unknown characteristics that could suddenly break out. Designing vaccines for these diseases suffers from two

types of uncertainty. It is not certain what type of disease will cause the outbreak nor do we know when there will be an outbreak, if at all. The current policy for sudden outbreaks is therefore to design a vaccine only after an outbreak has emerged. This is, for example, the case for pandemic influenza (Özaltın et al., 2011). However, acting when the outbreak has already happened might result in many infections, due the long lead times for vaccine production. Decision makers can therefore decide to stockpile vaccines in order to prepare for a pandemic. Several researchers in the medical/epidemiological community have discussed the development of a 'pre-pandemic' vaccine for influenza (e.g., Jennings et al., 2008; Stöhr, 2010; Scorza et al., 2016). Such a vaccine is tailored to the vaccine strain(s) that is (are) most likely to cause the next influenza pandemic. These virus strains currently only cause outbreaks in animals, but could cause a threat to humans as well. It is difficult to determine in advance how effective such a pre-pandemic vaccine will be, because virus strains need genetic changes to establish effective human-to-human transmission. Arinaminpathy et al. (2012) show that pre-pandemic vaccination can protect a population against pandemic influenza, and can also have considerable influence on seasonal influenza evolution.

4.2. Vaccine selection

If a vaccine or multiple vaccines are already available for a certain disease, policy makers must determine which vaccine to use. A significant proportion of annual vaccinations occurs in childhood vaccination programs. Public health facilities and governments can buy the required vaccines for childhood vaccination programs on the pediatric vaccine market. Robbins and Jacobson (2011) study the pediatric vaccine market from the perspective of the federal government that can negotiate prices and quantities with vaccine producers. The authors propose a MINLP formulation that minimizes the costs of immunizing a full birth cohort, while guaranteeing a sufficient profit for producers to stimulate research and development. Robbins et al. (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.

Once decision makers have decided which vaccines should be used, a vaccination program must be designed, which involves solving combinatorial problems. A classic example of such large combinatorial problems is the design of childhood vaccination programs. These programs aim at immunizing children against a number of infectious diseases by scheduling multiple vaccination moments during a certain period. Since there are different vaccines available, each which immunize against a certain combination of diseases, developing an effective and affordable childhood vaccination program is a challenging scheduling problem. Multiple vaccines can be combined into a single injection or a 'combination vaccine' so that children need only one injection. 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 et al. (2008) examine the adverse effects of extra immunization in terms of costs, and aim to minimize

the total costs of the childhood vaccination program. To solve the resulting combinatorial problem, they propose a solution method based on dynamic programming 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 these cases, a catch-up vaccination schedule must be made. Engineer et al. (2009) propose a dynamic programming algorithm to construct catch-up schedules within a short time. Based on this algorithm Smalley et al. (2011) provide a decision tool that constructs the best catch-up schedule given the vaccination history and the age of a child.

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

4.3. Packaging

The WHO emphasizes the importance of designing vaccine packages with the right characteristics. Vaccines are packaged in vials, which are small glass or plastic bottles that can contain liquid medicine, such as vaccine. The number of doses per vial influences the required storage capacity and the wastage of vaccine. Determining the vial size is particularly challenging in developing countries where people are vaccinated often in small communities and where it is extremely difficult to predict the number of people that will show up for an immunization session. Consequently, determining the number of doses needed is complicated, which often results in partially used vials and lost doses. In the epidemiological community, several studies evaluate the effects of changing the vaccine vial size on the supply chain. Lee et al. (2010) develop a general spreadsheet model to evaluate the effects of changing vial sizes on the costs in the supply chain (inventory costs, disposal costs, costs of administering vaccines and costs of doses wasted). They show that the optimal vial size depends on patient demand. If the demand is high, bigger vials are preferred, and the reduced wastage costs outweigh the increased medical waste and storage requirements. If demand is low, smaller vial sizes are preferred. Lee et al. (2011) and Assi et al. (2011) use discrete event simulation models for respectively Niger, and for Thailand's Tang province to analyze the best vial size for measles vaccine. They conclude that it is not beneficial to replace the currently used 10-dose vial with smaller vial sizes, even though the waste of vaccines could be reduced. Dhamodharan and Proano (2012) apply optimization techniques to this problem and determine the optimal vial size. They use a Monte Carlo Simulation model to account for stochastic demand, and solve an integer programming problem to find optimal ordering policies and the best vial size. Their model can generally be applied by decision makers.

Besides the vial size, also the storage conditions of vaccines have an important impact on the supply chain. In developing countries, cold storage capacity is scarce and electricity to provide refrigeration is often unreliable. Lee et al. (2012) study the effects of making vaccines thermostable, meaning that cold storage is no longer required. They develop a large discrete event simulation model for the Niger vaccine supply chain. Their results show that even making a single vaccine thermostable reduces the pressure in the bottlenecks in the supply chain and thereby improves the availability for other vaccines as well.

4.4. Discussion

In this section, we analyzed the decision problems related to vaccine composition, selection and packaging. We observe that many studies in the OR/OM community focus on expected outbreaks in developed countries. Studies on vaccine composition all consider seasonal influenza, which is a yearly recurrent outbreak. It would be interesting to study how the derived methods and results could be applied to vaccines for pandemic influenza, especially given the discussion on developing a pandemic vaccine. Developing a pre-pandemic vaccine is different from the seasonal influenza composition problem in many aspects. Pandemic virus strains are difficult to characterize, especially those which are currently only sporadically infecting humans. Besides, the uncertainty regarding the timing of the next pandemic complicates the commit-or-defer decision, because the consequences of deferring cannot easily be determined. We also note that pandemic vaccines, when administered on a large scale, potentially also change the seasonal influenza evolution and consequently the decisions on seasonal influenza vaccines (Arinaminpathy et al., 2012).

Studies on childhood immunization programs mostly focus on developed countries, with one exception being Proano et al. (2012) who primarily focus on the pricing problem for a specific type of vaccine. In general, we expect that designed vaccination programs can be executed as planned in developed countries. If children miss certain vaccinations, catch-up schedules can be generated (Engineer et al., 2009; Smalley et al., 2011). However, in developing countries, childhood vaccination programs 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. The WHO emphasizes that a growing number of vaccines will be available for low-income countries in the coming years. It is therefore of interest to determine how these new vaccines should be integrated in existing childhood vaccination schedules and which catch-up schedules should be used. The OR/OM community can contribute by analyzing these scheduling problems, which are characterized by high uncertainty in many dimensions (e.g., show-up rate of children, availability of vaccines).

Although current studies on vaccine composition use advanced OR techniques such as dynamic programming or stochastic programming, they are somewhat behind in using models for disease progression to evaluate the effects of a vaccine. They assume that the number of cases is known (Kornish and Keeney, 2008) or use very general functions to express the social benefits of vaccination (Cho, 2010). More advanced models for disease progression are available in the epidemiological literature, but also in the OR/OM community (e.g., Larson, 2007; Teytelman and Larson, 2012; Aleman et al., 2011). Further research should incorporate these disease progression models into the vaccine composition decision, because evaluating the time course of an epidemic is essential to properly quantify the impact of vaccination.

In Section 4.3, we emphasized the importance of designing packaging with the desired characteristics. In the epidemiological community, some studies focus on determining a good vial size and on evaluating the effects of the vial size on the supply chain. However, the results of these studies are often very case specific. The OR/OM community can contribute to these decision problems with their general models and supply chain perspective. Another important characteristic of vaccines is their required storage temperature. Liquid vaccines typically need to be stored at a temperature of 2 to 8 degrees Celsius and the storage of vaccines is therefore sometimes referred to as the 'cold chain'. Recent research shows that novel approaches and technologies are being developed to allow vaccines to be stored at higher temperatures (e.g., Chen and Kristensen, 2009; Wang et al., 2013). Future research could evaluate the effects of making vaccines thermostable on the entire supply

chain. Lee et al. (2012) analyze this using a detailed simulation model for Niger, and the OR/OM community can provide more general insights by using general supply chain models. Another interesting research direction is coordinating the discussion between manufacturers and public health decision makers on determining the desired characteristics of a vaccine. These two parties have their own interest, and coordination might be needed. Solutions have been proposed for related coordination problems on vaccine production (see Section 5.2) and further research could extend these solution methods to the packaging of vaccines.

5. Production

The production of vaccine is characterized by several types of uncertainty. In the production phase, multiple stakeholders are involved including for-profit manufacturers and non-profit governments, and public health organizations. All these stakeholders have their own interest and are affected by the uncertainties differently. The production process itself has a long production time and suffers from yield uncertainty. In addition, the demand for vaccines is highly uncertain. For example, the immunization period for seasonal influenza is short and there are frequent changes in the vaccine composition. Section 5.1 discusses these uncertainties and examines how they can be reduced. Uncertain yields are one of the main causes for the undersupply on the vaccine market (Chick et al., 2008; Deo and Corbett, 2009). As vaccines are public goods with positive externalities, governments and other non-profit organizations may want to influence the vaccine market to achieve a social optimum. We distinguish two ways to achieve this: via market coordination or through funding. Section 5.2 focuses on market coordination, which mainly plays a role in developing countries. Section 5.3 deals with funding, which is also of importance for developing countries.

5.1. Production uncertainties

Various uncertainties occur in vaccine production. The most eminent are the natural uncertainties that are related to the production process. For example, influenza vaccines are grown in embryonated eggs, which is a process that is characterized by uncertain production yields. An additional complicating factor for influenza vaccines is that they last for only one season, in contrast to other vaccines. They can therefore be seen as one-time newsvendor products, whereas other vaccines resemble perishable products (Chick et al., 2008). Malaria vaccines are also produced through natural production processes that suffer from yield uncertainties. The most effective malaria treatment uses medication that is produced using artemisia leaves. The supply and price of this agricultural product is highly volatile, which directly influences the market for malaria medication (Kazaz et al., 2016).

The safety and quality regulations for vaccines also contribute to yield uncertainty. Vaccines must undergo rigourous and extensive testing before entering the market. After vaccine is produced, it is stored in a tank, and vaccine manufacturers must decide when to bottle vaccines. The bottling can be done before the test results are available, partially before and after, or after the results are known. Early bottling reduces the required tank capacity, but also limits the possibilities of rework, which could lead to lost sales. Teunter and Flapper (2006) compare four bottling alternatives and present closed form expressions for important performance criteria for each of the alternatives. Based on the results, they propose for which types of vaccines postponing bottling is beneficial.

Another uncertainty is related to fluctuations in vaccine demand. On the one hand, there is the demand from the governments or public health organizations. This demand can be regulated

via tenders. Vaccine producers can bid, but only find out wether they have won the tender a few months before delivery. Due to the long production times of vaccines, production must start well before the contract is awarded. Shortening lead times allows the company to start production later, when the estimated probability of winning the tender is higher. De Treville et al. (2014) study the GlaxoSmithKline vaccine supply chain. They show that investing in lead time reduction is beneficial and report that managers have extensively explored ways to achieve this. Demand also comes from individuals, who can decide themselves whether or not to be vaccinated. In developed countries, this demand is dependent on the perceived risk of becoming infected and the perceived safety of the vaccine. Public health organizations and governments should consider this individual demand when deciding how many vaccines to order.

Vaccine manufacturers have several options to reduce the uncertainty resulting from the randomness in both production yield and demand. Begen et al. (2016) analyze the effects and potential benefits of reducing supply or demand uncertainty. Results show that reducing supply uncertainty is more efficient. It can be reduced by influencing uncertain yields. Federgruen and Yang (2009) investigate suppliers that influence their uncertain yields, and use the vaccine supply chain as an example throughout the paper. They analyze the equilibrium of the total market. Kazaz et al. (2016) determine how uncertainty can be reduced in the production process of malaria vaccines, a process in which artemisia leaves are used. They develop a model for the artemisia supply chain to study the consequences of several interventions to reduce market volatility. For example, they show that improving the average yield or offering a support price has significant impact.

Another way to manage supply chain uncertainties is to adjust pricing and selling strategies. 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 manufacturers prefer the dynamic strategy, which combines advance and regular selling. Eskandarzadeh et al. (2016) extend this work to controlling the risk of the producer if 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.

Production uncertainty also affects the public health decision maker. Federgruen and Yang (2008) study such a decision maker who must satisfy the uncertain demand for a single season from several suppliers. The planning problem is to determine how much to order from which supplier, considering the suppliers' uncertain yield. The 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 an unexpected drop-out of one of the two suppliers in 2004 lead to a significant reduction in the US vaccine stockpile.

5.2. Market coordination

Vaccines are public goods with positive externalities. Governments and public health organizations therefore want to achieve high immunization levels. However, due to supply and production uncertainties, the quantity of vaccines produced may be below socially optimal levels. Via contracts and subsidies, governments can try to coordinate the vaccine market. Tools such as mechanism design and game theory are useful in studying this coordination problem. Chick et al. (2008) show that a lack of coordination on the vaccine market for annual influenza leads to high production risks for vaccine manufacturers. Without government intervention, the vaccine coverage is below

the socially optimal level. The authors study various types of contracts to align the incentives of both governments and manufacturers. They show that a cost-sharing contract, in which the risks for yield uncertainty are shared, can globally optimize vaccine supply. Arifoğlu et al. (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. Negative externality effects can also occur: self-interested individuals ignore that vaccinating high-risk individuals is more beneficial when supply is limited. The positive externalities can lead to free-riding, when individuals do not get vaccinated because they expect to benefit from the vaccination of others (Ibuka et al., 2014). The vaccine market suffers from inefficiencies because of these disregarded externality effects on the demand side and yield uncertainties 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 supply or on the demand side. Adida et al. (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. They propose a two-part menu 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 need for coordination on the vaccine market is the result of misalignment of objectives and decentralized decision making: that which is beneficial for the supplier is often not beneficial for the public health organization and vice versa. This also applies to the timing of production. The supplier has little incentive to start production early, because the public health organization benefits most from on time delivery. Late delivery can result in a vaccine shortage, even though supply is sufficient. Dai et al. (2016) show that existing supply contracts fail in coordinating the supply chain in this respect. They propose a new contract that coordinates the supply chain and allows for flexible profit division. Besides asymmetry in interests, there is also asymmetry in information. Chick et al. (2017) contribute to this stream of literature by explicitly considering this asymmetric information. They consider a government that wants to minimize expected social costs and a for-profit manufacturer who has private information about his productivity. The study shows that the manufacturer can command information rent from the government, due to the asymmetric information. The authors propose a menu of contracts that minimizes the overall costs of the government.

5.3. Funding

Besides market coordination, funding or sponsoring also has an impact on the vaccine market. Sometimes donors are willing to subsidize the vaccine production process to increase access to health care in developing countries. Taylor and Xiao (2014) consider malaria vaccinations and study donor subsidies that aim to either increase the sales or lower the production costs. The latter can be done via a purchase subsidy. They formulate a model where the donor wants to maximize average sales to customers under a budget constraint and determine the optimal size and type of subsidies dependent on the perishability of the product. The results show a donor should only subsidize purchases for products with a long shelf life. Levi et al. (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 uniform copayments and derive conditions when this is optimal. The two papers together show that policy makers should not only consider subsidizing the manufacturer, but should also allocate uniform subsidies to individual firms to increase market consumption.

Vaccines are examples of public interest goods. Demirci and Erkip (2017) study the supply chain for public interest goods in which a central authority wants to maximize utility in society. They develop a model that determines how much the central authority should invest in demand-increasing strategies and how much in rebates that increase the revenue per unit sold. They formulate a bilevel program that also considers the manufacturers profit. Results show that applying the model outcomes can considerably increase utility. Berenguer et al. (2016) consider subsidy programs that target either a not-for-profit firm or a for-profit firm. Their results show that a limited budget available for subsidies is best spent when a not-for-profit firm is subsidized.

Despite the funding for vaccines, many developing countries are often confronted with stockouts. Gallien et al. (2016) develop a discrete event simulation model based on historical data to study the relationship between drug availability and the fund disbursement policy of the global health organization 'The Global Fund to Fight AIDS, Tuberculosis and Malaria'. They find that adjusting the disbursement amounts to make them compatible with the duration of monitoring periods has a higher potential to reduce expected stockouts than using regional buffer stocks or bridge financing (i.e., providing funds for the period between grant approval and disbursement).

5.4. Discussion

The vaccine supply chain is characterized by misalignment of objectives and decentralized decision making in multiple dimensions: manufacturers do not fully design their own products and end users are typically not the ones paying for the product. Furthermore, the buyers of vaccines are often non-profit organizations, whereas suppliers are for-profit companies (Herlin and Pazirandeh, 2012). Supply chain asymmetries have inspired research on market coordination mechanisms.

Most papers on production study seasonal influenza. Vaccine production for seasonal influenza suffers from uncertain production times due to biological processes and quality and safety tests (Gerdil, 2003). New technologies have recently been developed to reduce the production uncertainties of vaccines. One of these technologies is the development of cell-based instead of egg-based production processes for vaccines, in which vaccines are developed from animal cells (Centers for Disease Control and Prevention, 2016). One of the main advantages of cell-based production over egg-based production is that the production process can start more rapidly. These new developments will affect the decision problems related to influenza vaccine composition and vaccine production. Further research should therefore incorporate these new developments to help decision makers to prepare for the changes that new technologies will bring about.

When considering the classification in Table 1, we observe that no studies in the OR/OM literature are related to the production of vaccines for sudden outbreaks. Although the timing of production is perhaps less of a question for sudden outbreaks (production should start immediately), it is important to think about a production plan (where, how much). Such a plan can be executed in case of a sudden outbreak and should be part of a broader pandemic preparedness plan. Time plays a very crucial role: it is important to react quickly to a sudden outbreak, but lead times are uncertain and demand might drop over time if vaccines arrive too late. Decisions must be made under time pressure. The 2017 update of the Pandemic Response Plan of the U.S. Department of Health and Human services states that influenza vaccine manufacturing capacity should be sufficient to deliver doses of vaccine within 12 weeks after the declaration of the pandemic (U.S. Department of Health and Human Services, 2017). To achieve this, pandemic production plans could also investigate stockpiling supplies for vaccine manufacturing so that production can start as quickly as possible. The OR/OM community can aid decision makers in these complex decisions by designing production plans for sudden outbreaks.

Furthermore, it is important for decision makers to think about how much they are willing to invest in the production of vaccines for sudden outbreaks. In case of an emergency, two responses are possible: (1) use the existing stockpile and (2) start production for more vaccines. We see these two aspects in some US pandemic response plans, which describe the importance of stockpiling prepandemic vaccines and investing in vaccine manufacturing capacity (U.S. Department of Health and Human Services, 2005; Homeland Security Council, 2006; U.S. Department of Health and Human Services, 2017). However, apart from a recent working paper (Duijzer et al., 2017a) little to no research has been conducted on the budget allocation problem that results from the trade-off between these two aspects. This problem is typical for sudden outbreaks, because uncertainty regarding the timing of the outbreak and the disease causing it complicate the analysis of the trade-off between stockpiling and reserving production capacity. Studying this trade-off provides an interesting research direction.

In Section 5.3, we discussed the role of funding in vaccination. Gallien et al. (2016) interestingly show that the way funding is organized can significantly influence the supply chain. Their work might provide a good starting point for future research in this direction. The retrospective results of Gallien et al. (2016) can be used to redesign current funding programs and design new ones. Also with the development of new and more costly vaccines, it is becoming increasingly important to investigate who should pay for these vaccines (Seib et al., 2017).

6. Allocation

Before the vaccines can be distributed, governments or public health organizations must decide how the available vaccines will be allocated. Vaccines are scarce, particularly during unexpected outbreaks. Therefore, decision makers face a complex resource allocation problem in which they must determine who is entitled to be vaccinated and who is not. The vaccine allocation problem thus has an important ethical dimension, unlike other resource allocation problems. One of the most crucial ethical issues in vaccine allocation is the fact that equity and efficiency are often competing objectives. An allocation that significantly reduces the total number of infections, might be very unequitable (cf., Keeling and Shattock, 2012; Teytelman and Larson, 2013). The OR/OM community does not resolve these ethical issues, but provides support in the decision making process. The final decision is made by public health organizations such as the Centers for Disease Control and Prevention in the US who have detailed ethical guidelines (e.g., Kinlaw and Levine, 2007). We are aware of the ethical dimensions in vaccine allocation, but restrict attention to the logistical challenges in the remainder of this section.

In order to determine the optimal vaccine allocation, epidemic models are used. With these models, decision makers can analyze the effects of a certain allocation strategy on the time course of the epidemic, on the number of infections et cetera. There are roughly two types of epidemic models that are often used: simulation models and differential equation models. Simulation models can capture many realistic aspects of a population and of the transmission process. These models are computationally intensive and studies that use these models therefore rely on scenario analysis of a number of predetermined vaccination strategies. On the other hand, the analytical structure of differential equation models can enable to derive structural insights into the optimal allocation. Previous studies have shown that differential equation models and simulation models harmonize quite well (Ajelli et al., 2010) and that the policy advice derived from these two modeling approaches can be comparable, despite differences in the predictions of the time course of the epidemic (Rahmandad and Sterman, 2008; Dalgıç et al., 2017).

In some situations, multiple decision makers are involved in vaccine allocation decisions. These decision makers can, for example, correspond to multiple countries or regions. They can decide either to act selfishly and keep their own vaccine stockpile, or to allocate some vaccines to other populations to reduce transmission across borders. Section 6.1 discusses coordination among multiple decision makers. Section 6.2 examines situations where there is just one decision maker, for example, a government or global health organization. In these cases, the vaccine allocation decision involves determining which subpopulations (e.g., regions or age groups) should be prioritized. Often different allocation schemes are primarily compared in terms of disease related characteristics, such as the number of infected individuals. Section 6.3 discusses another way of analyzing vaccine allocations, namely by using cost-effectiveness analysis. Most studies on vaccine allocation consider allocations to fight natural outbreaks of infectious diseases. In contrast, Section 6.4 reviews a class of papers that considers allocating limited resources in case of a bioterror attack. Preparing for an attack is complex, because of the uncertainties involved, for example, the location of the attack and the number of victims.

6.1. Multiple decision makers

In some situations, multiple decision makers are involved in deciding on the allocation of vaccines or other scarce health resources. These decision makers can be at the same hierarchical level and must therefore come to a decision together. Alternatively, they may be at different hierarchical levels and their decisions are made consecutively. An example of such a multilevel decision problem is the situation where the allocation over multiple regions is decided globally, but the regions themselves decide on the allocation over the several risk-groups within their region. This situation occurs in the United States, where the Centers for Disease Control and Prevention (CDC) allocates vaccines to the states and every state decides individually on the allocation within their state. This multilevel decision problem is not studied in the vaccine literature, but Lasry et al. (2007) analyze the same problem for the allocation of funds for HIV prevention. Since no vaccine is currently available for HIV, funds are spent on general interventions that reduce transmission. The authors 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 analysis shows that if optimization can only be applied to one level, better results are obtained if the lower level is optimized instead of the upper level.

Coordination might be needed if the decision makers are all at the same hierarchical level. Sun et al. (2009) use game theory to coordinate 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 of whether they are willing to give up parts of their stockpile to help other countries in containing the epidemic. The authors use a Reed-Frost model to describe the spread of an epidemic and only consider the initial stage of epidemic growth. They 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. The quantity of vaccines ordered and distributed in one country can influence the evolution of an outbreak in another country due to cross-border transmission. They study multiple countries that each want to minimize total costs related to the number of infections and allocated vaccines. A contract is proposed to achieve system optimality. The results show that a lack of coordination leads to a shortage of vaccines in some regions and to an excess in others.

6.2. Central coordination

In case of a single decision maker, allocation decisions involve prioritizing among multiple subgroups. These subgroups can correspond to geographical regions or to age groups. Policy makers must decide which subgroups to vaccinate. The main difference between distinguishing between regions or age groups is the role of interaction between the subgroups. Interaction between geographical regions plays a much smaller role in the transmission of an infectious disease than interaction between age groups.

Regions. Outside the OR/OM literature many papers consider vaccine allocation over multiple regions (e.g., Wu et al., 2007; Araz et al., 2012; Keeling and Shattock, 2012; Matrajt et al., 2013). These papers make little use of OR tools such as optimization, but usually use scenario analysis or enumeration. Many studies in the literature show that prioritizing some regions over others can substantially reduce infections, but in practice a pro-rata strategy is often preferred because of its simplicity, robustness, and uncontroversiality. A common finding is that regions should be prioritized in which it is possible to prevent many infections. These are regions that are still pre-peak or regions with a small population, such that the vaccine stockpile is large enough to achieve sufficient protection. Some studies cluster the population in smaller groups, such as communities or households (e.g., Becker and Starczak, 1997; Ball and Lyne, 2002; Ball et al., 2004; Ball and Lyne, 2006; Tanner et al., 2008). These studies advocate for the *equalizing strategy*, which is a strategy that leaves the same number of people susceptible in each household. This implies that proportionally more people are vaccinated in larger households.

Within the OR/OM community there is more emphasis on developing models and solution methods. 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. They show that the new method significantly reduces computation time and can derive solutions for larger instances of the vaccine allocation problem. Other techniques used in the OR/OM community for solving vaccine allocation problems are simulation or stochastic programming. For example, Uribe-Sánchez et al. (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. Teytelman and Larson (2013) develop several heuristics to allocate a limited vaccine stockpile over the states of the US to fight an influenza outbreak. They evaluate their heuristics by using Monte Carlo Simulation. Their results show that their telescope-to-the-future algorithm, which considers regional differences, is best at reducing infections. Yarmand et al. (2014) study a two-stage stochastic programming decision framework for vaccine allocation over multiple locations. In the first stage, a predefined quantity 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 newsvendor type of model.

The papers discussed so far do not assume a special structure on the connection between the different regions. In contrast to these papers, some studies also 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 represents 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 et al. (2009); Ventresca (2012); Ventresca and Aleman (2014a); Nandi and Medal (2016).

Age groups. Dividing the population based on geographical criteria, results in physical distance between the groups. This distance allows us to consider limited or no interaction between 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 age groups (e.g., Patel et al., 2005; Mylius et al., 2008; Medlock and Galvani, 2009; Goldstein et al., 2009; Wallinga et al., 2010; Dalgıç et al., 2017). Most of these studies find that the highest priority should be given to (school)-children, especially if vaccines are available in the initial phase of the epidemic. Vaccinating children is effective, because they are most likely to transmit infections to their parents. Other studies explicitly differentiate between vulnerable groups and more active groups, who contribute to the spread of the disease (e.g., Dushoff et al., 2007; Matrajt and Longini Jr, 2010; Goldstein et al., 2012; Lee et al., 2015b). They often find that high transmission groups should be prioritized when vaccination takes place early in the outbreak. Since the high transmission groups mainly consist of children, these results are line with the results on vaccine allocation over age groups. When vaccination takes place in a declining epidemic, it is often better to focus on the high-risk adults.

In some situations, it is not the vaccine stockpile that limits the vaccine coverage, but the participation of the population in vaccination programs. 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 to encourage people to get vaccinated. Results indicate that the incentives should be higher for non-elderly and in times seasonal influenza is less contagious. The more vulnerable groups, such as the elderly, benefit from the increased coverage in the groups that contribute significantly to transmission.

6.3. Cost-effectiveness

Cost-effectiveness analysis is a way to compare vaccine allocations differently than in terms of infected cases or other health care related performance criteria. This approach assigns costs to both the intervention and the achieved health benefit and determines which interventions are cost effective (i.e., the benefits are higher than the cost). Cost-effectiveness of vaccination programs has been widely studied in communities outside the OR/OM community. In the health economics literature and the epidemiological literature this approach is often used (e.g., Siddiqui and Edmunds, 2008; Jit et al., 2008, 2014). Also within the OR/OM community, there are some studies that use cost-effectiveness analysis. Epidemic models are used to determine the effect of certain interventions on the time course of an epidemic, and on the number of infected cases etc. Some studies aim at comparing a predefined set of interventions and determine which are cost-effective (Frerichs and Prawda, 1975; Edwards et al., 1998; Rauner, 2002; Hutton et al., 2011). Others try to find the optimal actions under budget constraints (Dimitrov et al., 2013). The latter paper makes use of Markov Decision Processes and not only advises what vaccination strategy to use, but also presents detailed geographic intervention plans and suggests locations for the supply centers.

Instead of conducting a cost-effectiveness analysis, some studies consider the costs for the considered interventions or other socioeconomic measures differently. Parker (1983) uses a multiobjective approach and includes socioeconomic measurements such as infant mortality rates, calorie intake levels, and the degree of standard housing and potable water. Reveller et al. (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. They consider four schedules for the reduction of active tuberculosis cases and determine the optimal intervention for each schedule. These interventions consist of both vaccination and prophylaxis, where the latter refers to medication that reduces the severity of (potential) infection. Denysiuk et al. (2015) also study tuberculosis, but combine costs and disease-related measures in a multiobjective optimization problem. The goal is to minimize the 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.

The allocation of vaccines has been studied for a broad range of diseases, which is also apparent from the papers that apply cost-effectiveness analyses to analyze vaccine allocations. Already in the OR/OM community there are studies on hepatitis B (Hutton et al., 2011), HIV (Edwards et al., 1998; Rauner, 2002), malaria (Parker, 1983; Dimitrov et al., 2013), polio (Thompson et al., 2015), rabies (Frerichs and Prawda, 1975), and tuberculosis (Reveller et al., 1969; Denysiuk et al., 2015).

In most cases, the goal of a vaccination program is to contain an outbreak. However, policy makers even strive for complete eradication for some diseases. Tebbens and Thompson (2009) use a model for two diseases to analyze several decision rules for the allocation of resources for eradicable diseases. They investigate the effects of switching priorities from one disease to another 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. Thompson et al. (2015) analyze the efforts that are needed to attain polio eradication. They develop a simple allocation model to choose among a set of possible allocations those options that either minimize the incremental cost-effectiveness ratio or maximize net benefit.

6.4. Bioterror

In this section, we analyze the allocation of vaccines and other scarce health resources in case of a bioterror attack. Allocation decisions in this case must be made under high time pressure and suffer from uncertainty in many dimensions (e.g., location of attack/outbreak, magnitude, and severity of outbreak).

A bioterror attack is a form of terrorism where infectious viruses or bacteria are intentionally released. Examples are the anthrax attacks in the United States in 2001. After these attacks, several studies developed response plans for a new anthrax attack. To evaluate these response plans, various types of models are proposed for the transmission of anthrax and the effect of vaccination and other interventions. These models include queueing models (e.g., Wein et al., 2003; Craft et al., 2005) and agent-based models (e.g., Chen et al., 2006). Craft et al. (2005) analyze the situation with and without preattack vaccination and compare the number of infections and the number of deaths resulting from the attack. Their results show that preattack vaccination is beneficial not only for the vaccinated people: Also the unvaccinated people benefit from it, because they can receive antibiotics faster after the attack. This results in additional lives saved and therefore the authors recommend to consider preattack vaccination. Next to anthrax attacks, there are also some studies on vaccine allocation after a smallpox attack. Miller et al. (2006) propose a discrete event simulation to evaluate various intervention strategies including vaccination and social distancing. They consider a case study for San Antonio, Texas and show that the most robust response plan contains a mixture of public health interventions. Berman et al. (2012) discuss a bioterror attack on an airport and study the allocation of limited emergency resources (i.e., human resources and vaccines). They consider a one-time allocation decision in which reallocation of resources is not

incorporated, motivated by the fact that people should be vaccinated quickly after contact with an infectious person and that moving vaccinators is not efficient. Under certain assumptions, the resource allocation problem of minimizing the number of cases is convex, and they propose a greedy algorithm to find the optimal allocation.

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 at a higher level. As can be seen in Table 1, allocation is the only component of the supply chain that is studied for expected/existing outbreaks, sudden outbreaks and bioterror attacks. 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. Naturally, papers that study vaccine allocation 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 5.4). In these cases, it could be interesting to study the allocation of vaccines that become available in batches over time.

As mentioned in the previous sections, the topic of vaccine allocation has been studied extensively in the epidemiological literature. Although the OR/OM community has conducted some research on this topic, the epidemiological literature could benefit from further applying OR tools. The high-level modeling and use of optimization methods in the OR/OM community may lead to insights and a better understanding of the complex allocation problems that can not be obtained with simulation or numerical methods (cf., Duijzer et al., 2017b). Furthermore, explicit solutions of optimal allocations or efficient solutions approaches can be derived with OR tools (cf., Duijzer et al., 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 misalignment of objectives, and in particular the decentralized decision making 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 has received extensive attention in the medical/epidemiological literature (Omer et al., 2009; Larson et al., 2014), but has hardly been incorporated in 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.

The decision problems that we discussed in Section 6.4 are closely related to the decision problems in disaster management and humanitarian logistics (e.g., Altay and Green, 2006; Tomasini et al., 2009; Kunz and Reiner, 2012; Galindo and Batta, 2013; Leiras et al., 2014). This field focuses on organizing the supply of relief items in case of a disaster, which includes setting up preparedness plans (e.g., Duran et al., 2013) and coordinating among multiple parties (e.g., Ergun et al., 2014). The models and results in this field could also be useful for the allocation and distribution of vaccines after unexpected outbreaks.

7. Distribution

In this section, we analyze the final component of the vaccine supply chain: the distribution phase. In this phase, the vaccines are distributed from the manufacturer to the end user (i.e., the 'patient'). The distribution of vaccines involves many logistical questions on the operational level. First, it is important to determine how this part of the chain must be organized. How many layers

are needed in the chain and where should hubs and storage locations be positioned? Section 7.1 discusses the design of the vaccine supply chain. Section 7.2 examines inventory control for vaccines. When policy makers decide to keep vaccine stockpiles, they must decide how large these stockpiles should be and where they should be located. Finally, the vaccines should be distributed to the end user. Section 7.3 discusses distribution through fixed locations or 'points of dispensing' (PODs), and Section 7.4 examines vaccine distribution via mobile facilities. Distribution through PODs raises many logistical questions including facility location, staffing levels, and facility layout. When mobile facilities or mobile medical teams are used, routing problems play a role.

7.1. Supply chain design

In the past years, the number of vaccines that is available for low- and middle-income countries has increased considerably and this trend is expected to continue in the coming years. Vaccine supply chains in these countries cannot keep up with this increase without investments in the logistic systems. Kaufmann et al. (2011) distinguish two segments in the vaccine supply chain in low- and middle-income countries: (1) the segment that moves vaccines to the receiving country and (2) the segment that distributes the vaccines within the receiving country, from the point of entry via national and local storage points to the health care provider. The first segment partly takes place in developed countries, whereas the second segment takes place in developing countries. The authors recommend that coordination between the two segments of the vaccine supply chain should be improved. Zaffran et al. (2013) and Privett and Gonsalvez (2014) discuss the main challenges for the vaccine supply chain in developing countries. They address the importance of coordination, motivated personnel and information systems to improve decision making. Privett and Gonsalvez (2014) emphasize that improving single aspects of the supply chain without focusing on coordination will only lead to minor overall improvements. Marucheck et al. (2011) focus on product safety and security and 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 various locations. Other problems include the risk of counterfeiting or of stockpiling medication with the aim of selling it at a higher price when shortages occur. The authors identify four focus areas where the OR/OM community can contribute to safety and security in supply chains, including supplier relations and product life cycle management.

In Section 4.3 we saw that the product characteristics of vaccines can have a major impact on the supply chain. This is particularly true for the perishability of vaccines and the fact that they should be kept in a temperature controlled environment. Masoumi et al. (2012) consider the perishability of products when studying a supply chain network model. The model incorporates multiple firms that compete in different markets, 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 et al. (2014) propose a method to design a sustainable medical supply chain, considering the complete life cycle of medical supplies and waste. Careful design of the medical waste supply chain is 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, such as vaccines, that should be stored in a temperature controlled environment. 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.

In the epidemiological literature, numerous studies have analyzed the design of the vaccine supply chain and the multiple storage levels. Many of these studies use a similar approach in which a simulation model is developed for a specific country, for example, using HERMES software (highly extensible resource for modeling supply chains) (e.g., Haidari et al., 2013; Assi et al., 2012, 2013). A common conclusion is that removing levels can reduce supply chain costs and increase vaccine availability (e.g., Assi et al., 2013; Brown et al., 2014; Lee et al., 2015a).

To increase the efficiency of the vaccine supply chain, the WHO recommends integrating the supply chain with other health supply chains and possibly even with the private sector (World Health Organization & PATH, 2011). Yadav et al. (2014) study the possibilities of integration. Although integration is expected to increase efficiency, it also presents challenges as products can have different supply and demand characteristics. Several case studies illustrate examples of countries where integration of the supply chain has been implemented. Lydon et al. (2015) even go a step further and analyze the option of outsourcing some activities of the supply chain to the private sector. The authors present a case study from the Western Cape province in South Africa, where the storage and transport of vaccines was outsourced to a third party. The authors conclude that outsourcing can be beneficial, although it is highly important to consult all stakeholders in advance and to carefully determine which parts of the supply chain should be outsourced and to whom. These studies provide illustrations of successful integration from which lessons can be learnt on best practices.

7.2. Inventory control

Inventories of vaccines are used to guarantee supply system efficiency and to deal with uncertainties in demand and supply (see Section 5.1). For planned vaccination (e.g., seasonal influenza vaccination or pediatric vaccination) inventories can increase effectiveness. Jacobson et al. (2006) consider inventory control for pediatric vaccines in the United States. The current stockpiles are sufficient to handle disruptions in production that last up to six months. However, the inventory level is inadequate when disruptions last longer. This potentially leads to underimmunization and consequently to epidemic outbreaks. The risk of epidemics could be reduced by making moderate investments in inventories. Shrestha et al. (2010) develop a spreadsheet model for the inventory control of pediatric vaccines in the United States. This model can be used to evaluate stockpile sizes and potential shortages. Samii et al. (2012) connect allocation schemes for influenza vaccines to inventory control policies. They compare three allocation schemes that all reserve a proportion of the available vaccines for the high-risk groups, but differ in the way the unreserved proportion is allocated. Each allocation scheme is related to an inventory control policy and the corresponding service levels and fill rates are determined.

In case of sudden outbreaks, stockpiles of vaccines can increase agility, allowing for response. Several studies focus on inventories for disaster response. Salmerón and Apte (2010) consider pre-disaster planning for a general type of disaster. They propose a two-stage stochastic programming formulation to minimize 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. Arora et al. (2010) consider the (re)distribution of resources *during* a disaster and include both delivery from a central stockpile and lateral transhipments. The authors assume the available stockpile to be limited, but fail to consider newly produced and supplied inventories. Rottkemper et al. (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. They use a case for meningitis vaccine in Burundi to illustrate policy recommendations.

7.3. Points of Dispensing

In the final stage of the vaccine supply chain, the vaccines are distributed to the end users (i.e., the 'patients'). For vaccination in case of sudden outbreaks, pandemic response plans describe how this stage should be executed. These plans often include the setup of local clinics for the distribution of medication and vaccines, so-called Points-of-Dispensing (PODs). The literature on PODs does not primarily focus on vaccine distribution, but on medical supplies in general. We note that vaccines are more difficult to distribute than other medical supplies such as masks or oral medication, because administering vaccines is a relatively timely procedure that must be performed by qualified personnel. Nevertheless, the logistical decision problems that play a role for vaccine distribution and medical supply distribution are similar. Therefore, in this section and in Section 7.4, we review the literature on the distribution of medical supplies, without restricting ourselves to vaccines.

When designing PODs three major decision problems play a role: Where should they be located? What is the ideal layout? What are the required staffing levels? Some studies focus on one of these decision problems. For example, Ekici et al. (2014) look at facility location, Aaby et al. (2006) and Luangkesorn et al. (2012) focus on the design and layout of clinics and McCoy and Johnson (2014) evaluate clinic capacity. However, the decision problems on PODs are connected, and many studies analyze them together. Ramirez-Nafarrate et al. (2015) simultaneously study the location problem and capacity planning for points of care. They formulate a mathematical program and propose a solution approach 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. Lee et al. (2006, 2009, 2013) developed RealOpt©, an emergency response decision-support tool to be used in response to bioterrorist attacks or pandemics. This tool supports the decision-making process with respect to, for example, determining the facility locations, the layout of the facilities, and the required labor resources. RealOpt© is a generally applicable tool that has been used for numerous events, including anthrax preparedness and seasonal influenza.

Instead of developing a general model, some studies focus on case specific results. Aaby et al. (2006) consider vaccination clinics for Montgomery County and Luangkesorn et al. (2012) investigate health care centers for prevention and screening in Abu Dhabi. The latter paper uses queueing and simulation models and proposes an adjusted design that reduces the size of the waiting area. Decisions on location of clinics, layout and staffing levels directly affect the people that visit these clinics. Therefore, McCoy and Johnson (2014) explicitly take adherence into account, which is assumed to depend on the travel distance to the facility. They study a clinic that has a fixed budget that can be allocated over several time periods to assign capacity for patients. 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 under a budget restriction. The solution is determined analytically for two specific cases of adherence. The results show that incorporating adherence may significantly improve outcomes.

Most studies consider the setup of clinics in response to a pandemic and focus only on clinics that deliver medical services. Alternatively, Whitworth (2006) designs 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. Ekici et al. (2014) consider a pandemic, but focus on food distribution. The authors use a disease spread model combined with a facility location model for the location problem of food distribution points. To find close to optimal solutions, they propose a heuristic which can help policymakers in preparing for a pandemic. Although most studies analyze PODs to distribute medical supplies, there are also alternative distribution possibilities. Richter and Khan (2009) compare some of these alternatives to dispense prophylaxis to the population in a metropolitan area. Using multicriteria decision analysis, the authors show that the current method of drive-thru is outperformed by distribution via postal offices or via commercial pharmacies.

We next discuss the research in the OR/OM community on the distribution of vaccines in case of planned vaccination. In developing countries, populations can be hard to reach (see the next section), but in developed countries, this final stage of the supply chain does not involve major logistical problems. We already discussed childhood vaccination programs in Section 4.2, which account for a substantial part of the annual planned vaccinations in developed countries.

For completeness, we would like to mention another class of vaccines, namely travel vaccines, which also involve a scheduling problem. Travel vaccines are intended to protect travelers against diseases that are prevalent in their destination country. Although the decision problem related to travel vaccines does not coincide with the three important decision problems related to PODs, it is a supply chain decision problem related to distribution, and we therefore discuss it here. The demand for travel 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 the scheduling preferences of their patients into account. The results show that their method results in significantly lower costs compared to simple scheduling heuristics.

7.4. Mobile facilities

Although vaccines are preferably administered at PODs, in some situations it is more efficient to bring the vaccines to the people instead of the other way around. For example, this can apply to mass vaccination campaigns or vaccination in rural areas where mobile medical teams go from one location to another. The central question for such mobile teams is how to route them. 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 other nodes, for example, those within a certain distance. Demand of each node is assumed to depend on time. The satisfied demand thus depends on the routing schedule. In case of multiple facilities the routing problem is $\mathcal{NP}$-hard and a heuristic is proposed to solve the problem. Rachaniotis et al. (2012) study the same 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.

In developing countries, mobile medical teams are crucial in reaching rural areas. The organization Riders for Health provides reliable transportation for health care workers in sub-Saharan Africa, enabling them to visit more rural areas and provide medical care, such as vaccination. McCoy and Lee (2014) investigate the trade-off between equity and effectiveness for this organization.

They propose a model that can aid decision makers in allocating newly available vehicles to specific regions.

7.5. Discussion

Time is of great importance in the vaccine supply chain, especially during the distribution phase. During an outbreak, efficient and effective distribution is crucial to avoid an explosive increase in infections. Large-scale vaccination campaigns, also known as mass vaccination campaigns, are set up in case of a sudden outbreak with natural cause or due to a bioterror attack (Kaplan et al., 2002). Managing a mass vaccination campaign is a huge logistical challenge with decision problems related to issues such as vaccination locations, facility layout, the order in which the population is vaccinated, and staffing levels. The decision tool RealOpt© is an important contribution towards solving some of these decision problems and can potentially also be used to integrate allocation and distribution decisions. From our overview, we observe that there are quite some studies on vaccine allocation for sudden outbreaks, but that the literature on how to distribute vaccines according to this allocation is limited. Allocation decisions might have different effects on the operational level of vaccine distribution and some allocations might be easier to distribute than others. Current literature does not integrate these two decision problems, which provides research opportunities for the OR/OM community.

The discussion on the design of the supply chain plays a major role in developing countries, where 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 that each have their own stockpiles. In the epidemiological literature, numerous studies have examined this coordination and the redesign of the supply chain (Assi et al., 2013; Brown et al., 2014; Lee et al., 2015a). However, this topic has not been considered yet within the OR/OM community. Since this community has experience in studying general supply chain models, there are research opportunities to apply this knowledge to the vaccine supply chain and to derive general insights on the structure of a robust vaccine supply chain. Our review of the vaccine supply chain, which identifies the important logistical problems that play a role, could serve as guideline.

The vaccine supply chain in developing countries would not only benefit from better design at the strategic level. Also on the tactical and operational level, there are challenging logistical decision problems related to keeping the vaccines at the right temperature, i.e., the 'cold chain'. Routing and inventory control decisions should consider this aspect to reduce wastage, because vaccines deteriorate quickly when exposed to temperatures that are too low or too high. Given the expertise of the OR/OM community in these areas, this provides a promising research direction for future studies.

In addition, future research could focus on the location of vaccine stockpiles in developing countries, as this has received little attention in the OR/OM community. When stockpiling vaccines for sudden outbreaks, such as the 2010 cholera outbreak in Haiti, it is important to determine where to locate these stockpiles. Small local stockpiles can quickly be used in the neighboring area, but bring about additional relocation time if an outbreak occurs elsewhere. On the other hand, large global stockpiles are very flexible, but also require transportation time to the outbreak location. Further research is needed to address these inventory control problems.

Studying the vaccine supply chain will lead to new perspectives on supply chain management in general. The vaccine supply chain differs significantly in developing and developed countries, especially in the distribution phase. The literature on inventory control should therefore also

focus on developing countries that often suffer from unreliable electricity systems and unreliable transportation.

8. Discussion and future research directions

The research in this literature review has led to some interesting observations. In Sections 4.4, 5.4, 6.5, and 7.5 we discussed the observations related to the individual components of the supply chain. In this section, we summarize and present common findings.

We analyzed vaccine logistics and developed a supply chain perspective. This has allowed us to structure different classes of papers that all study logistic decision problems related to vaccination. Our supply chain perspective also revealed the importance of integrated analyses. Namely, decisions made in one component of the supply chain affect the downward components. In the epidemic literature some case studies have already adopted a more integrated approach, e.g., the studies on the effects of vial size on the supply chain (see Section 4.3). However, these results are very case specific, and the OR/OM community can contribute with general models. The supply chain perspective can also aid governments and NGOs who want to invest in vaccine supply chains, for example, in developing countries. We present an overview of the supply chain challenges that should be considered when introducing new vaccines or improving existing chains. Focusing on the entire supply chain is expected to have more effect than optimizing individual components.

A second observation is the crucial importance of time (see also Figure 1): 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. Regarding research on sudden outbreaks, we see a gap in literature in the first two components of the supply chain ('Product' and 'Production') (see also Table 1). Further research is needed to address questions regarding the development and production of vaccines for sudden outbreaks.

Third, we see that the development of new technologies can have a large impact on the decision problems in the vaccine supply chain. The introduction of cell-based vaccines with shorter production times can change existing decision problems on vaccine composition and vaccine production. The development of thermostable vaccines also affects inventory control decisions and supply chain design. Other new technologies, such as the use of genomics for the development of vaccines, might generate new decision problems to which the OR/OM community can contribute.

The analysis of the vaccine supply chain is a contribution to general supply chain literature. We see two important aspects in which the vaccine supply chain differs from other supply chains. First, the vaccine supply chain is affected by the consequences of misaligned objectives and distributed decision making, which can also be seen in Figure 1. Many parties are involved in the vaccine supply chain, each with their own interests. The 'Product' and 'Production' components of the supply chain could be characterized as a pull-process in which public health organizations and governments request the vaccines from the manufacturer. However, the allocation and distribution phase are more related to a push-process where public health organizations determine the planning for the end user (i.e., the 'patient'). Much research has been conducted into the coordination between policy makers and manufacturers in the production phase, but coordination regarding the packaging of vaccines has received very little attention. Furthermore, the role of the end customer (i.e., the

'patient') has not been addressed sufficiently. As vaccine hesitancy and vaccine refusal directly affect the effects of vaccination, future research should incorporate this aspect in the models.

The second aspect in which the vaccine supply chain differs from many other supply chains is the quantitative difference between developed and developing countries. This difference is most apparent in the distribution phase. Since most vaccines need to be stored at low temperatures, reliable electricity systems to provide refrigeration is crucial. Unfortunately, such reliable systems are not available in many developing countries. Besides, transportation is often less reliable in developing countries, with poor road quality, frequent vehicle breakdowns and fuel shortages. Transportation of vaccines and medical teams is highly important, because it is the only way to reach communities in rural areas. The distribution of vaccines in developing countries thus brings about different decision problems than in developed countries. In extant supply chain literature, there is little attention for this difference. This is an avenue for future research.

9. 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 various aspects of the vaccine supply chain, we connect the logistical questions that play a role in vaccination. In short, we identify three main challenges for vaccine logistics: (1) increasing the efficiency and cost-effectiveness of the supply chain for planned vaccination (2) preparing for sudden outbreaks and (3) preparing for bioterror attacks.

Based on our extensive literature review we conclude that the vaccine supply chain can benefit from the OR/OM perspective, and we identify research opportunities for the OR/OM community. It can contribute in different dimensions to improving the vaccine supply chain in both developed and developing countries. For example, this 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. Besides, we see that the epidemiologic literature often makes use of case studies and scenario analysis. Although this approach provides case specific insights, decision makers could benefit from the more general OR/OM models and insights. General insights are particularly useful because similar decision problems occur for similar types of outbreaks (e.g., expected or sudden), even if the diseases might be different.

When analyzing current literature, some observations repeatedly occur over the four supply chain components. We see the importance of the supply chain perspective and the integration of the components. We also observe that time is of crucial importance, and that the time pressure combined with uncertainty makes decision problems more complex. Emerging technologies should be taken into account as well, because they can change current decision problems and generate new ones. We contribute to the supply chain literature by demonstrating the unique characteristics of the vaccine supply chain: misalignment of objectives and decentralized decision making between the various parties and the quantitative difference between developed and developing countries.

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 provide interesting research directions. 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.

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Appendices

Supplementary Material
Literature Review - optimization in 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 (11)
- Mathematics of Operations Research (0)
- Manufacturing & Service Operations Management (5)
- Transportation Science (0)
- Transportation Research part B (0)
- Journal of Quality Technology (0)
- Omega - International Journal of Management Science (3)
- Systems & Control Letters (0)
- European Journal of Operational Research (10)
- Computational Optimization and Applications (0)
- Transportation Research part E (2)
- Production and Operations Management (8)
- 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 65 publications are published between 1969 and 2017. 3 publications fall inside the time interval [1969-2000], 4 within the interval [2000-2005], 16 within the interval [2006-2010] and the remaining 42 publications date from [2011-2017]. The histogram in Figure 3 displays the number of publications over time.

Appendix C Bibliometric analysis

Six articles could not be found in the database of the Web of Science^{TM} Core Collection (search date March 20, 2017): Reveller et al. (1969), Berenguer et al. (2016), Gallien et al. (2016), Levi

[1] See jcr.incites.thomsonreuters.com

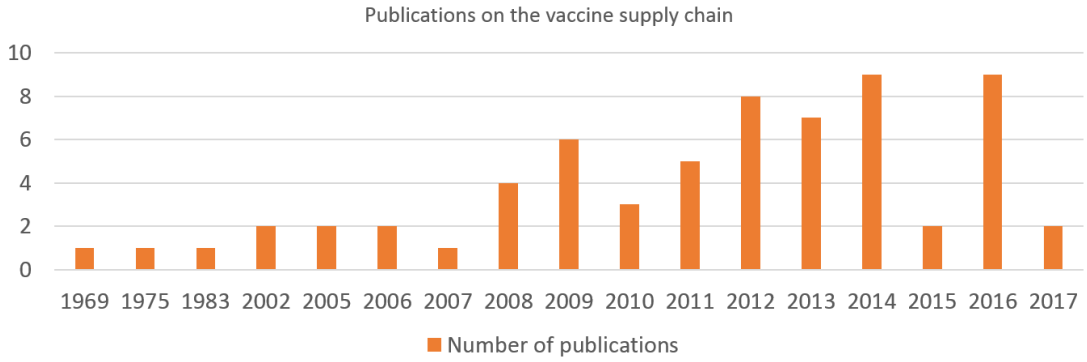

Figure 3: The relation between time and the publications on the vaccine supply chain that are reviewed in this paper.

et al. (2016), Demirci and Erkip (2017) and Chick et al. (2017). Accept from the first paper, all papers are very recent, which is probably the reason that they are not (yet) included in the database.