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“A Systematic Literature Review on Combined Routing-Scheduling Problems Featuring Medical Products With a Limited Lifetime

With Special Consideration of Production and Appointment Scheduling”

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Abstract English

This thesis provides a systematic collection, review and analysis of literature on routing-scheduling problems (RSPs) in the healthcare (HC) domain, specifically for perishable medical products. The optimisation of combined RSPs presents numerous challenges but has not been systematically explored. As this study shows, the recent COVID-19 pandemic has prompted an enormous spike in research in the field of operations research (OR) in HC. The purpose of this systematic survey is to help organize and classify, for the first time, the available material to provide a point of departure for further research. The current state of the art is summarized, trends are highlighted, and future research directions are suggested. Clusters are formed around the medical products blood, biological specimens, pharmaceuticals, and cancer medication. The various ways in which the limited lifetime requirements affect these products are categorised and compared. Objectives, solution methods, problem settings and other parameters are contrasted. The related topics of home healthcare, the emergency setting, drone usage and medical waste management receive additional attention. Production and appointment scheduling are given special consideration. It is shown that production scheduling is frequently optimised together with vehicle routing, especially for cancer medication, and its techniques inspire methods to better handle lifetime constraints. Meanwhile, appointment scheduling has not often been combined with routing, but offers potential for future improvements of operations.

Abstract German

Diese Arbeit widmet sich mit der Sammlung, Zusammenfassung und Auswertung von Literatur im Bereich der Routing-Scheduling Probleme (RSPs), welche sich mit dem Transport verderblicher Medizinprodukte befassen. Die gleichzeitige Optimierung von Touren- und Sequenzplanung stellt eine besondere Herausforderung dar, die noch nicht systematisch aufgearbeitet wurde. Wie diese Arbeit zeigt, löste die COVID-19 Pandemie überdies eine Publikationswelle im Bereich der Operations Research (OR) im Gesundheitsbereich (HC) aus. Der Zweck dieses systematischen Überblicks ist daher, das verfügbare Material erstmalig zu organisieren und zu klassifizieren, um einen Startpunkt zur weiterführenden Forschung zu bieten. Der aktuelle Forschungsstand wird präsentiert, Trends hervorgehoben und künftige Forschungsschwerpunkte vorgeschlagen. Während der Analyse des Materials bildeten sich Kategorien um die Medizinprodukte Blut, biologische Proben, Medikamente und Krebsmedikamente. Wie die eingeschränkte Lagerfähigkeit diese Produkte beeinflusst, wird herausgearbeitet. Zielsetzungen, Methoden, Problem- und Publikationsumfelder u.Ä. werden kritisch verglichen. Verwandte Themen, die besondere Aufmerksamkeit erhalten, sind häusliche Krankenpflege, Notsituationen, Drohnen und medizinischer Abfall. Produktions- und Terminplanung werden untersucht. Dabei fällt auf, dass die Produktion insbesondere von Krebsmedikamenten häufig gemeinsam mit dem anschließenden Transport optimiert wird. Zudem werden Methoden der Produktionsplanung angewendet, um den Umgang mit schnell verderblichen Medizinprodukten effizienter zu gestalten. Termin- und Transportplanung indessen werden bisher selten miteinander kombiniert, würden jedoch Potenzial für künftige Verbesserungen der Abläufe bieten.

Overview

Table 1: Important abbreviations

Abbreviation	Definition
AS	Appointment Scheduling
(B)SC	(Blood) Supply Chain
HC(SCM)	Health Care (Supply Chain Management)
HHC	Home Health Care
LMICs	Low- and Middle-Income Countries
OM	Operations Management
OR	Operations Research
PS	Production Scheduling
P&D	Pickup and Delivery
RS(P)	Routing-Scheduling (Problem)
SC(M)	Supply Chain (Management)
SLR	Systematic Literature Review
SR(P)	Scheduling-Routing (Problem)
TSP	Traveling Salesman Problem
UAV	Unmanned Aerial Vehicle
VRP(-TW)	Vehicle Routing Problem (with Time Win-dows)
WHO	World Health Organization

1. Introduction

The healthcare (HC) industry presents an important, multifaceted, and growing research environment. Even before the recent COVID-19 pandemic, healthcare expenditures were on the rise (e.g., Di Mascolo et al. 2021:1, Dobrzykowski et al. 2014:514), and early evidence of the pandemic's effect shows a steep increase of public spendings: Among the key messages of the 2021 Global Report by the World Health Organization (WHO), it reads that "[g]lobal spending on health more than doubled in real terms over the past two decades, reaching US$ 8.5 trillion in 2019, or 9.8% of global GDP" (WHO 2021:vi).[1] As for estimations on the pandemic effect, based on data from 22 (mostly high-income) countries, the WHO states that healthcare spendings "rose substantially in 2020, more than in previous years" and that "most current health spending on COVID-19 went to treatment costs, followed by testing/tracing and medical goods" (WHO 2021:vii). This last two points are important as this thesis aims to survey literature on routing-scheduling problems (RSPs)[2] featuring perishable medical products, including PCR-tests and vaccines, for example.

Several papers tried to pinpoint the reasons for the rise of HC expenditures. Among these causes is the increase in patients in absolute terms linked to both the growth of the world population in general as well as the increase of chronic illnesses (e.g., Vieira et al. 2016:1, Entezari and Mahootchi 2021:3692), partly caused by the increase of life expectancy and the health risks that come with age (e.g., Haitam et al. 2021:345, Entezari and Mahootchi 2021:3693). Other reasons are the high costs and limited availability of medical resources (Abdalkareem et al. 2021:445, Vieira et al. 2016:1f, Schmid and Dörner 2014:59), including treatment facilities, staff, and medication. Yet, in the medical field, where patients' lives are at stake, a healthcare service provider that concentrates on cost reduction alone will not prevail. One must keep in mind other crucial aspects, like access to and quality of healthcare service, timely delivery of medical assistance, and of course patient satisfaction (Abdalkareem et al. 2021:445, Dobrzykowski et al 2014:514, Fikar and Hirsch 2017:86, Schmid and Dörner 2014:59, Vieira et al. 2016:1). These concepts will be mentioned and elaborated throughout the thesis.

All these factors – the increase in HC spendings, the simultaneous growth of demand for HC services and patients' expectations, etc. – promote the need for cost-effective, well-functioning and reliable HC systems (Ahmadi-Javid et al. 2017:3, Marynissen and Demeulemeester 2019:407). Increasing the efficiency of healthcare operations and processes is of great benefit to many actors along the healthcare supply chain (Marynissen and Demeulemeester 2019:407). Rather than taking a strategic approach to supply chain optimization, I chose to focus on RSPs for which the operational planning level is most relevant. As operations research (OR)[3] "provides numerous methodologies and solution techniques to simultaneously reduce costs and improve access to healthcare services" (Ahmadi-Javid et al 2017:3), the benefits that result from applying OR in the medical field have widely been recognized in the literature (e.g., Abdalkareem et al. 2021:445, Vieira et al 2016:2, Dobrzykowski et al 2014:514). Diwas Singh et al. (2020:74) describe the focus of the literature of healthcare operations management as "the efficient allocation of critical resources, the design and organization of effective delivery systems, and the use of technology in enabling new innovative models of care delivery." This thesis touches on all of these aspects, but especially the first and the second.

The main aim of this thesis is to review literature on routing-scheduling problems in the medical field, specifically those featuring perishable medical products. In addition to the effects of the

[1]The report goes on to highlight global inequalities, with high-income countries accounting for about 80% of these spendings. In high-income countries, governments finance around 70% of health expenditures, whereas low-income countries' primary sources of HC expenditures are out-of-pocket spendings and external aid.
[2]RSPs and other aspects of relevance will be presented in chapter 2.1.
[3]For a definition of OR in relation to HC, please refer to Vieira et al. (2016:2).

medication's limited shelf life, I will shine a special light on the production and/or appointment scheduling aspects in these papers. I want to look for patterns and then highlight the key characteristics of each problem type, the difficulties researchers face, and in what ways integrating different processes and supply chain stages creates potential benefits for healthcare operations. My aim is to compare different models; to try and build categories; to identify which methods are applied most frequently or yield the best results. Further, I hope to identify gaps in research, current trends and maybe even some brand-new breakthroughs or promising approaches to long-known problems. I aspire to conduct this survey in a very strict and systematic way. Full transparency is the guiding principle by which I intend to search for and select the publications. I want to provide in-depth information on my search process and the papers I found, analyse the relevance of various keyword combination and how on-topic they proved to be upon further examination. The purpose of this is to simplify and guide future research on the topic; to allow students and scientists to conduct their own studies more efficiently through the help of my paper.

In order to achieve this, I shall try and answer the following research question(s): What is the state of art in routing-scheduling problems in healthcare in combination with perishable medical products, and in particular with production/appointment scheduling? How do the existing papers relate to each other and what are the challenges and potentials for future research?

My hypothesis is that it might be difficult to find papers that meet all the inclusion criteria, as combined RSPs are not (yet) widely studied (chapter 2.1). Choosing a healthcare focus instead of more traditionally studied fresh consumer goods like foods, flowers or newspapers might additionally complicate the literature search. The reason I chose this particular focus is that, according to my next hypothesis, the recent COVID-19 pandemic has led to a spike in interest in healthcare-related topics. From among the medical field, I believe I will find most literature on the production and delivery of pharmaceutical products, which I consider to be the largest and most diverse product group. Hypotheses regarding production and appointment scheduling in particular will be put forth in chapter 2.2 and checked against the evidence in chapters 5.9 and 5.10.

The remainder of this paper is structured as follows: In chapter 2, I will introduce some concepts of relevance to this thesis. First, I shall provide a description of combined routing-scheduling problems, then give insight into the characteristics I have chosen, namely production and appointment scheduling as well as product perishability. In chapter 3 I present the methodology used to conduct my survey: the systematic literature review. In the second subchapter, I will provide a detailed explanation of how my research has been conducted. Subsequently, I shall dive into the topic at hand: Chapter 4 divides my reference papers into groups. These clusters are formed around the medical product, the reasons for which are explained at the beginning of the chapter. In each subchapter, the product background and specificities are explained, followed by a problem description, before each paper is presented individually. In chapter 5, at the heart of my thesis, the most extensive and important part can be found: the analysis and systematization of the publications I found. I study different aspects of the reference papers (objective functions, solution approaches, etc.) in a comparative way. I hope to uncover patters and opportunities for further synergies. In chapter 6 I will critically review what I have done in this thesis, including the weaknesses of my search processes and potential future improvements, comment on the state of art, and point out relevant research directions. During my concluding remarks in chapter 7, I shall sum up my findings. Part 8, finally, contains a complete list of my references, both the reference papers analysed in chapters 4 and 5, as well as all publications cited in this work, followed by an appendix.

2. Aspects of Relevance in this Work

In this section, without going into too much detail, I would like to shortly introduce some concepts of relevance to this thesis. The purpose of this chapter is to clear up any confusion related to terminology and hopefully show why I have chosen this particular set of aspects as the focus of my literature review.

2.1 Combined Routing-Scheduling Problems in Health Care

The integrated routing-scheduling problem combines the routing aspects from the vehicle routing problem (VRP) with the scheduling of (usually daily or weekly) operation plans. It is "mainly seen as an application of the *Multi-Travelling Salesman Problem* (MTSP) or the *Vehicle Routing Problem* (VRP) with Time Windows, […], and thus it is NP-Hard and challenging for OR researchers" (Euchi et al. 2022:353). While the route planning determines the sequence of customer visits and maps the paths, scheduling optimizes the exact timings of the visits or tasks to be performed (Yücel 2013A:504). Moons et al. (2017:225), by the example of integrated production scheduling and distribution problems, demonstrate how the two problems influence one another, how "optimizing a single problem independently disregards the requirements and constraints of the other", and how a coordinated approach is necessary to find an overall optimal solution.

The probably most well-known RSP in HC is the *Home Health Care* (HHC) or *Nurse Rostering* problem, wherein the nurses' working and the patients' visiting schedule will be optimized together with the routing of the vehicles that will transport the nurses from patient A to patient B. Keeping the patients' locations in mind in addition to their preferred service time windows will allow for much more efficient planning:

> *"The routing problem that considers the time window of each service, the frequency, the number of repetitions, and the duration of the service leads to routing and scheduling problems. The optimal routing and scheduling decisions could be very influential in reducing costs and satisfying the patients[.]" (Entezari and Mahootchi 2021: 3694)*

For more information on the home healthcare problem, please refer to chapter 6.2.1. SR-problems are not unique to the home care setting, however. Schmid and Dörner (2014) couple intra-hospital routing with appointment scheduling to improve both patient-centred objectives (the perceived inconvenience) as well as cost-related objectives (in terms of (e.g., operating room) idle times). Moreover, the scheduling aspect may also refer to a production-scheduling problem that either precedes or follows the VRP. This is of special relevance when medical products such as cancer medication are made to order and need to be freshly produced (see chapter 4.4). Ideally, they are not treated as individual problems, but optimized jointly. In their problem on intra-hospital medication production and delivery, Chen et al. (2021:3) write: "Medicine delivery is a complex task, because it requires coordination among departments, pharmacies, and the transport system. Medicine delivery should be investigated in an integrated way." Combining two such planning problems yields significant benefits despite the added effort (Moons et al. 2017:225). A more detailed introduction to appointment and production scheduling will be given in the next subchapter.

The RSP can also be addressed in the framework on an IRP: "The inventory routing problem (IRP), in which a supplier delivers products to a number of geographically dispersed customers, can provide integrated logistics solutions by simultaneously optimizing inventory management, vehicle routing, and delivery scheduling" (Liu et al. 2020:5). Not all combined RSPs include inventory management, however, especially not if the products in question have very short lifetimes and do not need storage.[4] Product perishability will be introduced in chapter 2.3 as it is one of the main elements in this thesis.

The integration of RSPs, which are already difficult to solve separately, seems to be relatively new in the literature (Robbes et al. 2022:790, Kergosien et al. 2017:288). Robbes et al. (2022:787) claim that "[n]umerous studies are available in the literature on production scheduling problems and distribution problems, but they are often solved independently. Recently, however, combined production-distribution problems have started to be studied at the operational level." Literature on RSPs in healthcare is scarce, especially for medical products rather than nurses (HHC problem) or patients (ambulance routing problem). In their review, Noorain et al. (2022), for example, only mention scheduling and routing in combination with HHC. Building on the works of Moons et al. (2017), who give an overview of combined production scheduling and vehicle routing problems, Robbes et al. (2022:788, Table 1) present the studies that have been conducted since then. However, they give no indication as to how they found or chose their reviewed literature, and neither they nor Moons et al. (2017) limit themselves to or even focus on the field of healthcare. Moons et al. (2017:225) stress that "[e]specially for perishable or time-sensitive goods, an integrated approach can be valuable". Among their examples, they name newspapers, food, ready-mixed concrete, industrial adhesive materials, and, finally, nuclear medicine, for which they know of only one example: Lee et al. (2014; presented in chapter 4.4.3). Other than that, they seem to be unaware of further publications that combine production scheduling and vehicle routing in a medical setting. Seven years earlier, Chen (2010:131) wrote a review on Integrated Production and Outbound Distribution Scheduling and raised the same point, but his survey did not mention healthcare products or the medical field at all. Therefore, I believe combined routing-scheduling problems in healthcare and especially in combination with perishable medical products to be an interesting field of study that could benefit from a systematic literature review.

2.2 Production and Appointment Scheduling

Since this thesis is not concerned with human transportation but with the delivery of medical products, a production step is bound to form part of the supply chain. Shortly before or after transportation, medical products need to be produced or processed. Especially for time-sensitive products, considerable benefits can be yielded if there is no interruption between these two processes. The best way to achieve this is to optimize them jointly. The following citation shall serve as an example of the production echelon in a perishable medical product (blood) supply chain:

> *"Production: This takes place at a blood processing centre, where donated units of blood are tested and* separated into various components (red blood cells, platelets and plasma) as required. The production of platelets depends on the amount of time since the donation, as platelets must be separated from whole blood shortly after collection. This echelon ends with blood being packaged ready for distribution and moved to storage." (Williams et al. 2020:200)

Based on this example, I infer that production scheduling (PS) will be of particular importance if blood donations and blood processing are not performed in the same location. Further, I presume that in the reference papers analysed from chapter 4 onwards, this processing stage will frequently be integrated with the collection stage, but also with the distribution planning, possibly inventory decisions, and maybe even all of the above.

[4] At least not until they have undergone processing that may extend their shelf lives, as is the case with blood products. For more information, refer to chapter 4.1 on blood products.

Both blood donors and blood recipients might profit from appointment scheduling (AS) to avoid waiting times before their respective medical procedure. After all, Gupta and Denton (2008:800) write that "[a]ppointment scheduling systems lie at the intersection of efficiency and timely access to health services." They consider timely access crucial for both patient satisfaction and good medical outcomes. Abdalkareem et al. (2021:445) consider healthcare scheduling a particular challenge "due to high constraints and preferences, such as personnel requirements, resources limitation. Unlike any other institution, healthcare sectors are working around the clock. However, the lack of staffing and irregular working shifts leads to job dissatisfaction and might influence patient satisfaction." I believe that appointment scheduling will be most relevant if the end-customers are patients with particularly time-sensitive needs and treatments, like cancer patients. Gupta and Denton (2008:800) define appointment scheduling as "assigning a specific time when the patient is scheduled to start receiving care." The less the time of the treatment diverges from the planned starting time, the higher both the patient satisfaction and the chances of medical success will be. Among their other benefits, "[a]ppointment systems also smooth work flow, reduce crowding in waiting rooms and allow health systems to honor patient and provider preferences while matching supply and demand" (Gupta and Denton 2008:800f).

Production and appointment scheduling follow similar patterns. Much like in a production problem, in the appointment scheduling problem, feasible schedules that contain several operations and follow a certain sequence have to be planned. AS has thus repeatedly been compared to the job shop problem (Schmid and Dörner 2014:59, Vogl et al. 2019:138). In the operating room scheduling problem addressed by Schmid and Dörner (2014:59), for example, "every patient corresponds to a job and rooms to machines." When they speak of rooms, they refer to operating rooms or examination rooms where certain procedures are performed. These require special equipment that can only ever service one patient at a time, such as X-rays or MRIs. Depending on the type of treatment, a machine might also stand for a bed (chemotherapy), a chair (dialysis, blood donation) or other equipment that may only be utilized by one person at a time, similar to a machine scheduling problem. AS for patients is mostly applied in treatments with a bottleneck resource that needs to be used as efficiently as possible, including surgery and operating room scheduling (Schmid and Dörner 2014), chemotherapy (Garaix et al. 2020) or radiotherapy (Vieira et al. 2016, Vogl et al. 2019). Another relevant area of application is multi-appointment scheduling, wherein various, sometimes interrelated consultations and treatments are scheduled together. From the patients' point of view, the appointments (procedures or examinations; the tasks in a job shop problem) follow a strict, predetermined order. Certain tasks or appointments need to take precedence over others, like an examination before an operation or treatment. Two key concepts in AS and PS are feasibility and delays. For one, both in terms of routing and scheduling, the problem must be feasible and capacity limits need to be respected. Avoiding underutilization of bottleneck resources requires tightly packed schedules. The consequence is a strong need to avoid delays: If one appointment cannot start on time, the resulting delay affects all subsequent appointments. Delays raise operation costs while simultaneously lowering patient satisfaction, thus causing negative effects on two key objectives in this problem type.

My hypothesis is that in the healthcare context, with its focus on the patient, production and appointment scheduling will be of particular importance, both in the name of increasing service levels through reduced waiting times: efficient production scheduling allows for reducing actual waiting times (thereby increasing efficiency in terms of machine utilization) while appointment scheduling will reduce perceived waiting times for the patient (customer experience). Since the customers will probably not always be the patients, but also healthcare professionals and other stakeholders, I imagine that appointment scheduling will be somewhat less relevant to these types of problems than production scheduling. Moreover, integrated processes will be of particular importance considering how easily perishable some of the medical products are. The here-presented hypotheses will be evaluated in chapters 5.9 and 5.10.

2.3 Medical Products with Limited Lifetime

As mentioned in the introduction, the efficient allocation of critical resources is one of the key functions of HCSCM. Medication can be considered a critical resource, and failure to provide the right amount at the right time may result in short- and long-term consequences. Besides the obvious risks of not providing patients with the medicines they need, thus worsening their immediate state of health, lack of treatment may increase their vulnerability to disease: "Medicine stock-outs […] increase the risk of the emergence of drug-resistant strains in the health delivery system, and also result in high levels of morbidity and mortality" (Bvuchete et al. 2020:12).

Perishability means that the lifetime associated with a product is limited. The medication is given a certain shelf life, after which it either cannot or should not be used anymore. In the medical field, the most common reasons for using a best-before-date are to comply with regulations and to warrant optimal medical outcomes. That the product deteriorates creates urgency in transportation, especially if the products are highly perishable and are deemed unusable after a very short time (sometimes just a few hours). Amorim et al. (2013:390) explain: "It is rather difficult to identify or characterize a general perishable supply chain, since perishability is a phenomenon that may happen to occur in a wide variety of situations and it has a rather fuzzy definition." It is generally associated with fresh products, like food, flowers or newspapers whose novelty and, thus, value decrease significantly with time. Time is the most common, but not the only factor in product perishability. Shaabani (2022:143) also mentions transportation issues, temperature conditions, and storage conditions. Moreover, they distinguish four different types of product lifetime: 1) strict fixed lifetime, for "products [that] have a definite maximum usable lifetime. Some examples of this group are newspapers, blood products, and pharmaceuticals" (Shaabani 2022:144), 2) non-strict fixed lifetime, 3) random shelf life and 4) gradual deterioration by time, where the product quality or efficiency reduces with time, examples being alcohol or pesticides or, I would add, biological samples.

As far as I can tell, perishable medical products have never been reviewed on their own, at least not within routing-scheduling problems. In literature reviews on single medical products, like blood or cancer medication, routing-scheduling problems are treated as a category at best, and perishability as one of many constraints. Publications on perishable products have been reviewed several times, but mostly in terms of inventory routing, and none of these surveys focus primarily on medical products: Kergosien et al. (2017:288) reference the survey by Amorim et al. (2013), "where perishability aspects in supply chain management are analyzed comprehensively. A review of the work published on modeling perishability for production and distribution planning is performed, with one part dedicated to integrated approaches." Amorim et al. (2013) mention liquid medicine and the pharmaceutical industry, but only as examples. Similarly, Vahdani et al. (2017) mention blood as an example. More recently, in their Perishable Inventory Routing Problem, Shaabani (2022:151) identify 8 papers on the topic of blood and 3 on healthcare. This makes up about 12,3% of their reference papers, considering that they reviewed 89 papers altogether. However, all 3 papers on healthcare lacked scheduling aspects and were thus excluded from this thesis.

In the reference papers, some authors give an overview of literature on perishable goods. Liu et al. (2020), for example, in their second chapter, provide several tables with overviews on different literatures, like the literature on the scheduling of perishable goods (Liu 2020:6, Table 3). This overview does not uniquely contain medical products, however. To name an example, Devapriya et al. (2017) develop a MIP model for the integrated production and distribution of a generic perishable product, without taking a particular (e.g., healthcare) context into account. That healthcare products have specific characteristics and requirements is indisputable. Lee et al. (2014:463) point out that, compared to the perishable food delivery problem, late delivery is not allowed in their problem on the delivery of nuclear medicine with an extremely short half-life. Moreover, they highlight similarities and differences with the newspaper delivery problem, which also requires strict in-time-delivery but for cancer medication, "production cannot occur in advance and production and delivery must be synchronized." (Ibd.) In another example, Liu et al. (2020:7) point out:

> *"Most perishable products, such as fresh vegetables and fruits, are usually managed by the customers themselves, coordinated among customers, or can be transshipped rather freely in the supply chain network. However, blood products in China can only be supplied and managed by the blood center. This fact causes the existing research in the scheduling of perishable products not applicable."*

All in all, I found that this specific combination of characteristics remains unexplored in the literature. Which medical products are commonly given expiration dates, how long it takes until these products spoil and how OR approaches meet these added challenges is what I aim to find out in the course of this thesis. Perishability will be paid special attention in chapter 5.8.

3. Methodology

In this chapter, I write about literature reviews in general, not just the ways in which they can advance research, but also the problems and dangers that stem from untransparent or incomplete work or even a seemingly haphazard selection of literature. I will then describe the kind of literature review I have chosen for this work, the systematic literature review (SLR), and emphasize why it should find application beyond the medical studies where it is most common. Finally, I present my own approach and elaborate on the keywords I chose, the inclusion criteria for relevant work as well as the limitations I set in terms of publication date, publication language, the publication type, data banks, etc. used for research. The purpose of this is to warrant the replicability of my study and, thus, conform to scientific standards.

3.1 The Systematic Literature Review (SLR)

The main purpose of a literature review is to give researchers a better overview over a certain topic. The reader learns about the current state of art. By summarizing and analysing what has been published previously, the literature survey helps identify gaps in the research and opportunities for further investigation. As Kosztyán et al. (2021:1-2) so eloquently put it:

> *"Conducting effective literature reviews plays a vital role not only for their own knowledge contributions, such as advancing the knowledge and understanding the breadth of the research on a topic of interest, synthesizing knowledge, building theory, aggregating empirical evidence, and becoming oriented in an emerging domain […], but also for their capacity to stimulate subsequent research, which, in turn, validates and extends their contributions."*

Upon looking more closely, the individual expectations one may have when conducting or consulting a review can be mirrored in the different types of surveys: For well-established topics, descriptive reviews can help organize the existing literature, show how questions have developed over time or help identify research gaps; for emergent topics, the ongoing systematization of new publications in scoping reviews is essential for researchers to stay on top of new developments, thus accelerating new discoveries (Kosztyán et al. 2021); for topics relevant to different disciplines, meta-narrative reviews may help synergize the research conducted in these diverse fields, thus bringing to light new opportunities for collaboration or attracting attention to a seemingly new aspect that is, actually, already in discussion in another scientific community (Wong et al. 2013). Surveys can help explain and critically assess, aggregate and integrate data. These are merely some examples of how literature reviews can be classified. Kosztyán et al. (2021:3) describe nine different literature review types and their corresponding strengths and benefits in their typology of literature reviews. Snyder (2019), meanwhile, differentiates three main types of survey methodologies: systematic, semi-systematic or narrative, and integrative literature reviews.

Whatever type of review serves the researcher's purpose, a survey should always provide sufficient information on the literature search and selection. Any confusion as to why authors chose to include a certain paper, but exclude another, similar one casts doubt over the quality of the review and its contribution. If only a random or limited selection of literature is surveyed, the results can be incomplete, distorted or even misleading. To satisfy the academic peer-review process, a scientific work needs to be reproducible. Others need to be able to repeat the search procedure and arrive at the same conclusion, and this requires maximum transparency regarding methodology. Moreover, findings need to be presented in a comprehensible and unambiguous, unbiased and informative, but also a meaningful manner: Snyder (2019:338) points out that one of the most common shortcomings when conducting a review is to only list references and their superficial characteristics without contributing new findings to the discourse.

For these reasons, I strive to conduct a systematic literature review (SLR), which Snyder (2019:334) calls the "gold standard among reviews". Albeit originally developed for the medical domain, SLRs have since entered business research (Snyder 2019:334). Its main characteristic is its rigor: "Systematic review methodology, pioneered and developed by Cochrane, sets out a highly structured, transparent and reproducible methodology" (Lasserson et al. 2019:4). The steps taken for finding literature as well as the reasons for inclusion and exclusion of publications must be documented in as transparent a way as possible. Through its strict methodology, bias is reduced, which increases the findings' reliability (Snyder 2019:334f). One way of ensuring this is using publication standards like PRISMA 2020 (previously PRISMA 2009) or RAMESES (2013).

While reading literature reviews on the topic of OR in HHC in preparation of my own review, it quickly became apparent that few researchers make use of publication standards. Snyder (2019:333) points out that "traditional ways of describing and portraying the literature often lack thoroughness and are not undertaken systematically." Although most authors explain how they proceeded in their review, either in a subchapter dedicated to methodology (Di Mascolo et al. 2021, Grieco et al. 2021, Marynissen and Demeulemeester 2019, Becker et al. 2019, Vieira et al. 2016, Williams et al. 2020) or in their introduction (Abdalkareem et al. 2021, Cissé et al. 2017, Fikar and Hirsch 2017, Ahmadi-Javid et al. 2017), only few decide to follow guidelines such as the 4-stages by Mayring (Dobrzykowski et al. 2014) or make use of reporting tools like PRISMA (Bvuchete et al. 2020). What is more, some of these reviews lack rigor when it comes to describing their methods, using vague wording like "such as" which leaves the reader in doubt as to the whether the lists (e.g., of keywords) are complete: "We […] searched the databases covering several disciplines **such as**, Scopus, Google scholar for relevant papers using combinations of relevant keywords **such as** […]" (Abdalkareem et al. 2021:446, my emphasis). Zhu et al. (2019), despite conducting an extensive review, fail to elaborate on their search method: Unfortunately, there is no detailed information on the way they found their literature beyond the data banks they consulted. In this, I see potential for increasing the transparency and the comparability of literature surveys and, thus, improving the overall quality of research, which is the purpose of PRISMA: "Publication standards are needed to ensure that users of reviews are provided with relevant and necessary information to enable them to assess the quality and rigor of a review." (Wong et al. 2013:2)

Thus, I decided to conduct my systematic literature review with the help of PRISMA 2020. I believe that the field of OR might hugely benefit from this rigorous approach. "This methodology addresses quality issues such as bias, replicability, and credibility. It offers a broader and more accurate level of understanding than a traditional literature review", Bvuchete et al. (2020:15) explain their reasons for choosing PRISMA. It is important to note that publication standards like PRISMA (Page et al. 2021A and B) or RAMESES (Wong et al. 2013) are "not intended to guide systematic review conduct" (Page et al. 2021B:2). Instead, their main aim is "to help authors improve the reporting of systematic reviews and meta-analyses" (Moher et al 2009:2). They ought to be seen as reporting tools that allow "readers to assess the appropriateness of the methods, and therefore the trustworthiness of the findings" (Page et al. 2021B:6). I intend to continuously use the PRISMA 2020 methods included but not limited to their checklist throughout the processes of literature selection and review.

3.2 Detailed Search Process

In line with PRISMA 2020 (Page et al. 2021B:4), I shall now specify my search process and explain the selection of data banks as well as the inclusion and exclusion criteria for the studies. I will describe my preparation, including the first search attempts and my learnings from these efforts, as well as the final process.

Before conducting the literature search, I read 14 literature surveys on OR and HC. The purpose of this was to gain an understanding of the topics covered, of the authors' search and selection process, preferred search criteria, data banks and keywords, and the reasoning behind their classification schemes. The collection of these review papers followed no organized process and underlay no restrictions, other than covering the general topic of OR methods to improve healthcare practices. Table 11: Literature reviews read during preparation (Appendix) gives further detail on which randomly selected literature reviews were consulted in preparation of this thesis, as well as their respective search settings. The full references are included in the bibliography.

The data banks most frequently used were Scopus, Web of Science, Science Direct and Google Scholar. Of these, I chose Scopus and Web of Science for my initial search. Different combinations of keywords were then tested on these data banks.

Ultimately, after a few disappointing attempts wherein the keywords were too restrictive, I followed the lead of Di Mascolo et al. (2021:5) and decided on keywords that were "relatively generic to avoid missing any relevant papers." The search settings are displays in Table 2: Literature search 1.0. Only journal articles published in English were included in the search. To narrow down the search to more relevant results, the settings "Title, Abstract, Keywords" on Scopus and "Topic" on Web of Science were chosen. Other than that, no search limitations were set. During the entire search, I did not impose a time limit because I wanted to trace the emergence of this research topic back to its origins. Purposefully, no category specification was set as it soon became apparent that the relevant publications appeared in various journals and were classified under different categories.

Table 2: Literature search 1.0

Keywords	Search in	Search Platform	Additional Limitations	Last Search Performed	Yield (#)
(routing AND scheduling) + ("health care" OR healthcare)	Topic	Web of Science	Only Journal Articles	18.02.2022, 15:10	234
(routing AND scheduling) + ("health care" OR healthcare)	Title, Abstract, Keywords	Scopus	Only Journal Articles	18.02.2022, 20:02	122

For comparison, Table 3: Literature search 1.1 shows what a difference one additional keyword can make. Notice how the yield number reduces drastically when a keyword as basic as "appointment" is used and again when "appointment scheduling" must be used in combination. If the addition (perish* OR spoil*) is added, only one result remains. This strangely low yield is the reason why I opted for the broader search (Table 2: Literature search 1.0). Both Table 2: Literature search 1.0 and Table 3: Literature search 1.1 display only the yield before duplicates are eliminated and texts are screened.

Table 3: Literature search 1.1

Keywords	Search in	Search Platform	Additional Limitations	Last Search Performed	Yield (#)
(routing AND scheduling) + ("health care" OR healthcare) + appointment	Topic	Web of Science	Only Journal Articles	18.02.2022, 20:45	22
(routing AND scheduling) + ("health care" OR healthcare) + appointment	Title, Abstract, Keywords	Scopus	Only Journal Articles	18.02.2022, 20:10	7
(routing AND scheduling) + ("health care" OR healthcare) + "appointment scheduling"	Topic	Web of Science	Only Journal Articles	18.02.2022, 15:13	6
(routing AND scheduling) + ("health care" OR healthcare) + "appointment scheduling"	Title, Abstract, Keywords	Scopus	Only Journal Articles	18.02.2022, 20:11	3
(routing AND scheduling) + (health) + (perish* OR spoil*)	Topic	Web of Science	Only Journal Articles	19.05.2022, 20:00	1

After the duplicates were removed from the 356 texts (Table 2: Literature search 1.0), 266 remained for closer examination. The records were then screened, first by title and abstract, and at a later stage by reading through the entire article to ensure they fit the inclusion criteria. No automation tools were used during the assessment of the literature. All screening was done manually by a single person, me, which means that some publications may have been overlooked or wrongfully excluded due to human error. How many records were excluded during these steps and for which reasons, was documented in the style of a flow diagram (Figure 1). During a first screening process, the following exclusion criteria were applied to the search results:

- non-journal articles (mainly book chapters) that had accidentally found their way into the original literature list were eliminated,
- publications that were not written in English were eliminated,
- publications that I did not have access to were eliminated,
- publications that, upon a first, quick examination, did not treat routing-scheduling problems in a healthcare context were eliminated. For this, titles, keywords and abstracts were scanned as well as keyword searches within the publication conducted, whenever possible. At this stage, publications were judged rather generously, excluding only what was obviously off-topic, in other words surveys that
    - obviously lacked the scheduling component,
    - obviously lacked the routing component,
    - obviously did not centre on health care problems (or mentioned healthcare only once or twice, as an exemplary application to a general optimization problem),
    - could be considered altogether irrelevant to this study because their focus lay elsewhere (e.g., medical publications wherein “route” refers to the route of administration of medication (oral, intramuscular, etc.).

Please note that some publications fell into more than one category (e.g., conference papers that obviously lacked healthcare aspects). In total, 133 publications were left after the first round of screening, six of which were marked as literature surveys that do not contain algorithms themselves but were considered helpful to this study in other ways.

Among the remaining 133 papers (127 without surveys), different themes emerged around which the papers were clustered (e.g., medical waste management). From my initial areas of interest (appointment scheduling, home healthcare and laboratory services), HHC seemed to be the most popular by far. Research on RSPs for home healthcare included over 100 publications during the first search run alone, including several recent and comprehensive reviews. This may, however, have been caused at least partly by the selection of keywords (see Table 2: Literature search 1.0). Generic though they may have been, they were most fitting for this particular field of research as "home healthcare" includes the term "healthcare", which is not the case for all optimization problems that touch on the medical field. Appointment scheduling in healthcare has been reviewed several times (see chapter 2.2), but hardly anyone seems to have linked it to routing. "Laboratory services" as a search term proved too fuzzy (although a cluster could be formed around it) since its function and role in the publications vary: a laboratory may either be used as a different, problem-specific name for the depot, or it can function as an additional required stop in the route, or it can indeed be linked to new requirements such as a certain timeliness of the medical specimens' delivery. This last point led me to shift the focus to perishable medical products.

The literature on RSPs including perishable medical products seemed neither too broad, nor too narrow for a survey. The inclusion criteria were well-definable and, to the best of my knowledge, the topic has not been reviewed previously. Thus, the final criteria for inclusion were:

1. Combined routing-scheduling problems,
2. in the context of healthcare,
3. featuring the perishability of medical products, not just as a short mention, but as a relevant part of their mathematical model and/or solution approach,
4. published in the English language,
5. in a scientific journal.

Fine-tuning the keywords was not an easy task, since very few papers contain "perishability", "life time", "shelf-life" or similar keywords in their title or abstract. Simply adding the additional keywords (perish* OR spoil*) turned out to be too restrictive (see Table 3: Literature search 1.1). Therefore, all remaining 133 texts from Literature search 1.0 were searched to find all contributions featuring perishable medical products. The prerequisite was that perishability had to be addressed not just in the text, but as part of the mathematical formulation. This was true for 10 articles (including 1 survey) which were then used as a basis for snowballing. Figure 5 (chapter 6.1) shows how each publication was found, and marks the 10 core articles in red and the survey in white.

First, the references of the 10 core articles were searched. If a publication met all the inclusion criteria, it was added to the reference papers. The same backward snowballing procedure was repeated for all reference papers published after 2010. Texts published before this date were included, but their references were not searched again. This time limit was set with the intention of including only the most relevant literature. The idea was that pioneer and key texts would still be referenced after 2010. The focus should be on newer approaches, however, since these would be of more interest to the reader. As Figure 5 shows, the paper by Anaya-Arenas et al. (2021) proved to be the most rewarding during this backward search, with more than twice as many yields as the next best paper. During backward snowballing, a total of 539 references

Table 4: Literature search 2.0

Keywords	Search in	Search Platform	Additional Limitations	Last Search Performed	Yield (#)
((routing OR routeing) AND scheduling) AND (production OR appointment OR transportation OR collection OR delivery) AND (perishab* OR *time OR "cold chain" OR "half-life" OR "shelf life") AND (drugs OR pharmac* OR blood OR platelet OR cancer OR chemo* OR "nuclear medicine" OR specimen OR "bio* sample" OR vacci*)	Topic	Web of Science	Only Journal Articles	05.11.2022, 13:25	68
((routing OR routeing) AND scheduling) AND (production OR appointment OR transportation OR collection OR delivery) AND (perishab* OR *time OR "cold chain" OR "half-life" OR "shelf life") AND (drugs OR pharmac* OR blood OR platelet OR cancer OR chemo* OR "nuclear medicine" OR specimen OR "bio* sample" OR vacci*)	Title, Abstract, Keywords	Scopus	Only Journal Articles	05.11.2022, 13:30	20

were searched,[5] 20 of which were found relevant enough to be added to the literature list. Texts found through backward snowballing are coloured green in Figure 5.

Next, both the initial texts and those found through backward snowballing were used for the forward search. On the pre-selected data bases Scopus and Web of Science, all texts that cited the reference papers were screened and rated based on the same inclusion criteria as before. A total of 377[6] papers was checked. Of these, 17 made it on to the literature list. These publications are coloured yellow in Figure 5. The paper by Ghandforoush and Sen (2010) was the most cited and also one of the most productive during the forward search (6 of 90 total yields made it on to the list of reference papers, and another 6 useful survey papers were identified). However, during the forward search, the discrepancy between the reference papers was not as striking as during the backward search.

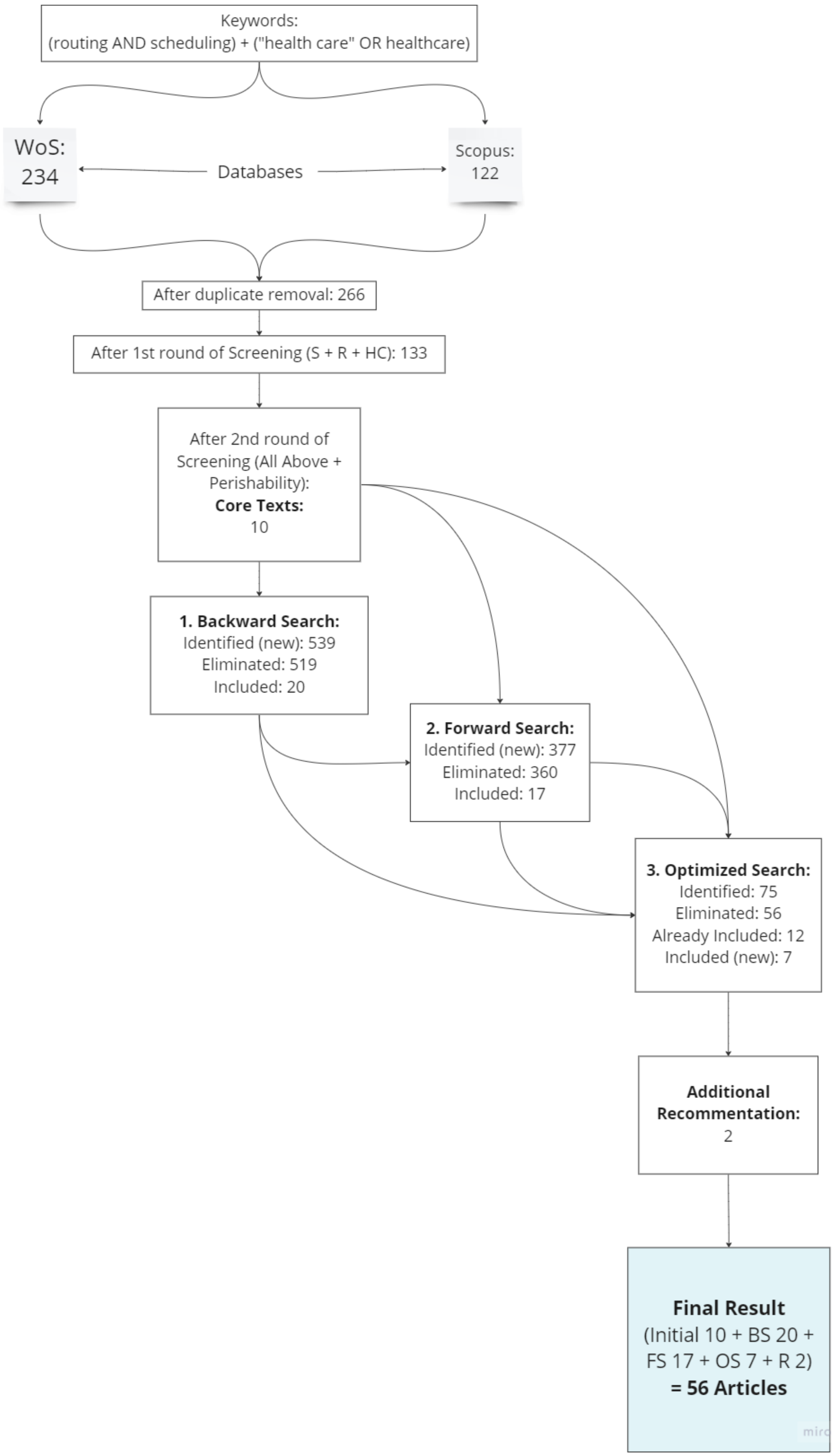
[5] Duplicated have been removed before this count.
[6] Duplicates are removed from this count. Papers that were found through backwards and forwards search were counted towards backwards search.

From all publications on the literature list, the keywords were then extracted and collected. After some more testing and optimizing, a final keyword search was conducted. The search string and settings can be seen in Table 4: Literature search 2.0. This search led to 75 results after duplicates were eliminated, 21 of which are included: 12 had already been on the list and 9[7] more were found. Although this result is not yet optimal, it can still be viewed as a big improvement from the first search (29,33% relevance as compared to 3,76% during the initial search). In this case, the hypothesis that a broader search with more generic keywords would help to avoid missing any relevant publications has been disproved.

Finally, 2 more papers were found through recommendation. These are marked pink in Figure 5 (chapter 6.1). Altogether, without duplicates, 1257 publications were screened, and a total of 56 reference papers were found and will be analysed in the coming sections. For better understanding, the entire search process is outlined in Figure 1. Figure 5 (chapter 6.1) provides a colour-coded visualization of which publication has been found through which technique, and how the texts are connected through snowballing. Documentation for all screened publications, both included and excluded, is available upon request.

[7]Upon closer examination, 2 of these 9 papers (Johannessen 2022 and Park et al. 2022) could not be used for the main analysis but will be found in chapter 6.2.3 on related topics.

Figure 1: Flow diagram inspired by PRISMA 2020 (Page et al. 2021B)



4. Main Clusters

Since this work focuses on perishable medical products, the most obvious distinction is that of product type. In this regard, the publications form clusters around four topics:

1. collection of blood as well as the production and delivery of blood products,
2. collection of medical specimens / samples,
3. pharmaceutical delivery, and
4. production and delivery of chemotherapy medication.

The decision to present the literature as it fits into these four clusters rather than, say, into the collection, processing and delivery phases is purely practical. As a rule, the papers treat only one type of medical product, two at most, whereas they may cover various processes. When it comes to cancer medication, for example, production and distribution are almost always optimized jointly. Of course, there still exist some similarities and cross-references between product types. For example, the blood collection problem resembles the collection and testing of biological samples and specimens in many regards. The blood distribution problem, meanwhile, is comparable to the distribution of pharmaceutical products. Therefore, it is not uncommon for papers in different clusters to mention and build on research relating to a different product. How the reference papers in this thesis cross-reference each other is depicted in Figure 5 (chapter 6.1).

In the subchapters presenting the four product types, the short summaries are listed chronologically to allow the reader an idea of how the research on medical product developed over time. In chapter 5, the reference papers will be analysed in-depth across product types. The here-formed clusters will then once again fade into the background to allow a more wholistic analysis of the literature on routing-scheduling problems featuring perishable medical products.

4.1 Blood and Blood Products

4.1.1 Blood and Blood Products – Background and Relevance

The importance of blood as a resource is indisputable. Citing evidence from the American Red Cross published in 2014, Mobasher et al. (2015:260) show that "[i]n the U.S., every two seconds a patient needs blood or blood products, and more than 41,000 blood donations are needed daily to satisfy the demand." This amounts to a yearly "5 million patients in the U.S. [who] receive blood or blood products such as red blood cells, platelets or plasma via blood transfusions, [and a]round 30 million units of blood products are used in blood transfusion each year" (Özener and Ekici 2018:113, citing the same source from 2014). The need for blood is on the rise, which Özener and Ekici (2018:113) explain through the "advances in the medical procedures that require blood transfusions" as well as the increase in human life expectancy in general. Blood as a medical resource is highly sought after, but the amounts collected cannot keep up with the rise in demand:

> *"According to American Red Cross, total collection of different blood components was 17.3 million units in 2011 which shows a significant decline compared to 2008 (about 9.1 percent). While almost 10.3% of hospitals reported at least one day on which non-surgical blood need could not be fulfilled. […] Although the survey shows distinguished improvement compared to 2008, the results are not satisfactory, since the impact of unmet demand can result in serious health problems or even death." (Rabbani et al. 2017:20)*

Even more severe are the problems in different parts of the world, where the infrastructure for blood supply and management is not as advanced. It should not come as a surprise that “[i]n many countries, people still die because of inadequate supply of blood products.” (Mobasher et al. 2015:260, referencing the World Health Organization, 2014). What makes matters worse is that blood cannot be synthetically produced (El Midaoui et al. 2022:1056). By the time Özener and Ekici (2018) published their text, research on blood substitutes was on the way, but not yet successful. Rabbani et al. (2017:20) confirm that “[b]lood cannot be produced in laboratories and the only source of blood supply is blood donation which makes the blood supply very problematic and critical.” Despite efforts to promote blood donation, not everyone can donate, and not everyone who is able to decides to donate on a regular basis: “[A]round 38% of the population is eligible for blood donation in the U.S., but only 3% of the population donates blood in a year” (Mobasher et al. 2015:260).

The most common type of blood donation is whole blood donation, but platelets mays also be donated separately with a higher possible donation frequency than in the case of whole blood (Özener and Ekici 2018:113). Gunpinar and Centeno (2016:94) write that “[i]n the United States, blood is mostly donated on a voluntary basis although most plasmapheresis donations come from paid donors”. Depending on the recipient, four kinds of donations are distinguished: allogeneic, directed, replacement, and autologous donations. For more information on these different types of blood donations, see Gunpinar and Centeno (2016:94f).

After the collection, donated whole blood is separated into its components through a process called centrifugation (Mobasher et al. 2015:260, Özener and Ekici 2018:113). Another option to derive platelets is the use of a so-called apheresis tool. Rather than separating the platelets from whole blood given by many donors, they are collected from a single donor and the yield is higher. On the downside, this technique requires special equipment, is time consuming and expensive (Ghandforoush and Sen 2010:32).

Blood transfusions and other blood products are used for a variety of purposes: for injuries, medical treatments including anaemia and cancer treatment, orthopaedic and cardiovascular surgeries, open heart surgeries, organ and marrow transplants (Mobasher et al. 2015:260, Rabbani et al. 2017:19, Özener and Ekici 2018:113). The three most referenced blood components in the literature are plasma, red blood cells and platelets. Ghandforoush and Sen (2010:32) also name white blood cells and coagulation factors and point out that “one unit or pint of whole blood can be divided into two to five different component products. Different components prepared from a single unit are then transfused into different patients.” Red blood cells, the most frequently used component, are needed for any patient requiring transfusion. They are needed for surgery, anaemia treatment, treatment of blood disorders and for premature babies. Plasma is necessary for burn and trauma patients as well as clotting disorders. Platelets are used to treat cancer patients during chemo- and radiotherapy, accident and malaria victims, asthma patients and patients with blood clotting problems. They further help control bleeding and are needed during organ transplants, and other surgeries to prevent massive blood loss (Ghandforoush and Sen 2010:32, Mobasher et al. 2015:260, Özener and Ekici 2018:113).

In short, blood products are necessary for both scheduled and emergency procedures. It is wise to always have a buffer for unanticipated medical interventions. However, this type of medical product is characterized by its high perishability: All blood products have limited shelf-lives, with platelets being regarded as the most time-sensitive (Mobasher et al. 2015:260). Their life-span amounts to only five to seven days (Ghandforoush and Sen 2010:32, Rabbani et al. 2017:21, Özener and Ekici 2018:113) or five to nine days (Mobasher et al. 2015:260) after production. Red blood cells expire within 35 (Ghandforoush and Sen 2010:33) to 42 days (Gunpinar and Centeno 2016:95), and frozen plasma and cryoprecipitate deteriorate after one year (Ghandforoush and Sen 2010:33). In addition to being the most unstable, platelets are also the most expensive blood component: “On an [sic!] average platelets derived from whole blood costs $84 per unit and apheresis platelets are considerably more expensive at $538 per unit” (Ghandforoush and Sen 2010:33). The extremely short shelf life of these products in combination with the high costs, high demand and the difficulty of obtaining blood products prompts authors to underline the importance of efficient inventory management, closely matching production to demand (Özener and Ekici 2018:113, Gunpinar and Centeno 2016:95, Ghandforoush and Sen 2010:33).

This is where optimization research comes in. As blood is an incredibly valuable but also perishable resource, optimizing supply chains in the way of reducing blood wastage is one of the main goals. This can be taken even further considering that blood transfusions are of vital importance in the case of a disaster when short response times are of the essence (see Williams et al. 2020:209). Ghandforoush and Sen (2010:32f) demonstrate why healthcare institutions stand to profit from optimizing the platelet production supply chain, their main reasons being the increase of demand, the short shelf life of about five days and the difficulty of producing platelets. A variety of actors stands to benefit from improved blood management practices, “including patients, hospitals or other health providers, blood centers (BCs), blood mobiles, and donors” (Rabbani et al. 2017:20). An interesting point Williams et al. (2020:209) raise with regards to blood collection is that of donor satisfaction: “Due to donors (in most cases) being volunteers and non-remunerated, it is vital to maximise the experience of donors as far as possible [for example through a] convenient location and appointment time[.]” Studies including production (product related) or appointment scheduling (donor related) aspects will be discussed in sections 5.9 and 5.10 of this work.

All stakeholders have “different concerns and priorities which should be considered in [the] blood supply chain to fully manage collection, distribution, and storage operations as well as scarcity and wastage issues” (Rabbani et al. 2017:20). In its entirety, the BSC is much longer and more complex than suggested by the following problem description, “start[ing] from patient needs and end[ing] with transfusion of the needed components to patients” (Rabbani et al. 2017:19), including the collection, the production, the temporary storage and the redistribution of whole blood and processed blood products. Along the entirety of this chain, bottlenecks and optimization issues arise. In this thesis, routing-scheduling problems during the collection and distribution phases are of relevance.

4.1.2 Blood and Blood Products – Collection, Processing and Delivery: Problem Description

In problems arising in the BSC, blood is donated at fixed or mobile collection sites. Donations are then picked up by a bring-back vehicle and delivered to a collection centre. Once they arrive, further processing may be done during which the fresh, whole blood is separated into its components. From these centres, blood and blood products are then distributed to hospitals or clinics (see Gunpinar and Centeno 2016:94; El Midaoui et al. 2022).

This thesis focuses on the routing-scheduling problem encountered during blood collection and distribution. Most papers focus on only one of these two aspects even though in the case of blood, it might be profitable to integrate the collection and delivery stages.[8] Table 5: Papers by supply chain echelon gives an overview of which stage of the supply chain is covered in which paper. The processing of blood (production of blood products) may be addressed in both

[8]Especially when compared to the other products considered in this work: Samples and specimens only need to be collected, cancer medication needs to be produced and then delivered directly to the recipient as it is highly personal, and other types of medication usually only require delivery from one central depot to pharmacies, hospitals or other healthcare facilities. Therefore, considering that blood is the only resource that needs to be collected, processed and then delivered, it is somewhat surprising to see how seldom all three steps are optimized together.

collection and delivery scenarios but is more frequently optimized together with the collection. The reason for this is most likely that blood is required to be fresh (no older than 5 or 6 hours) if it is to be used for platelet production. Extraction then extends the lifespan of the individual blood products. Consequently, time limits during distribution tend to be less strict.

Table 5: Papers by supply chain echelon

Collection	Collection and Delivery	Delivery
Yi and Scheller-Wolf 2003	Ghandforoush and Sen 2010	Hemmelmayr et al. 2009
Dörner et al. 2008	Zahiri et al. 2018	Hemmelmayr et al. 2010
Mobasher et al. 2015	Hamdan and Diabat 2020	Wen et al 2016
Şahinyazan et al. 2015	Eisenhandler and Tzur 2022	Liu et al 2020
Özener and Ekici 2018	Rezaei Kallaj et al. 2022	El Midaoui et al. 2022
	Pirabán-Ramírez et al. 2022	

During collection, the nodes (customers) are collection sites like donation centres or blood mobiles. There is only one depot from which bring-back-vehicles and sometimes blood mobiles[9] depart and where blood must be brought back to. It stands for a blood bank, a central processing centre or a hospital in possession of the necessary equipment to extract blood components. This depot may have a certain demand per planning period, and the nodes may have varying blood potentials, that is, varying amounts of whole blood that can be collected.

Bring-back vehicles are mostly uncapacitated due to the small size of the collected product. If they have capacity constraints, these may refer to a maximum transportation capacity, but also a minimum transportation requirement to keep the costs for vehicles in use low. In some problems, the number of vehicles is fixed. In others, there may be a maximum number of vehicles available for transport, and the optimal number of vehicles in use is sometimes subject to optimization. Similarly, some problems are concerned with the donation centres' (customers') capacity to store blood and even with the number of donation sites to open. In Mobasher et al. (2015), this capacity constraint refers to the maximum number of donations a donation site can handle at the same time, limited in reality through the number of beds or chairs, equipment and staff. The donation sites and processing centres have limited opening times during which appointments may be scheduled. Some problems allow collection of blood after the collection site has closed for the day to ensure that no blood is produced after the last collection. Few

[9]Terminology is not always consistent throughout the various publications. "Vehicle" in the literature mostly refers to the bring-back vehicles, sometimes called "blood shuttles"; at times, the word "vehicle" is also used to allude to blood mobiles. These blood mobiles are, in fact, motorized vehicles like busses or vans, but in the scope of this problem function as mobile collection sites. Therefore, "blood mobiles" will be referred to as nodes or customers (or donation/collection sites), whereas the term "vehicle" will always stand for the bring-back-vehicle or blood shuttle. Also, "production" in the literature may refer to the process of colleting ("producing") blood at a donation site (e.g., Dörner et al. 2008) whereas other authors use the word "production" to refer to the next step in the blood supply chain, the processing of collected blood (the "production" of blood components like platelets, e.g., Ghandforoush and Sen 2010). In this chapter, "production" will refer to the production of blood components while "donation" or "collection" will refer to the production of fresh whole blood.

studies consider the unloading and loading times, the service times at the customers, and some (e.g., Mobasher et al. 2015) consider how much time it takes to complete a donation.

The crucial point in most problems considering highly perishable products is that the blood needs to be brought back to the depot within a certain timeframe after collection so that it may be processed, often called “processing time limit” (Mobasher et al. 2015, Özener and Ekici 2018). This is mostly the case in problems that consider platelet production, since these have the shortened lifespan: in Yi and Scheller-Wolf (2003), Ghandforoush and Sen (2010), Mobasher et al. (2015) and Özener and Ekici (2018), blood has to be returned to the depot within 6 hours, and Dörner et al. (2008) speak of only 5 hours. Additionally, Yi and Scheller-Wolf (2003) and Mobasher et al. (2015) plan another 2 hours for the processing of blood at the depot. In contrast, Şahinyazan et al. (2015), whose focus lies more with the blood mobile extension of the problem, take a much more relaxed approach by assuming a maximum time limit of 24 hours. In other words, their collection sites must be visited once a day.

The daily number of donations may vary or be assumed to be constant. In some cases, to mirror reality more authentically, donations are distributed unevenly throughout the day (e.g., Özener and Ekici 2018). Blood is donated continuously throughout the planning horizon at a rate that, in reality, is not necessarily constant, but for purposes of simplicity is often assumed to be constant during optimization. Another unique feature is that “the blood donations accumulate over time, which forces the collection organizations to schedule more than one pickup from a donation site during a day” (Özener and Ekici 2018:114). However, few problems, either for reasons of simplicity of because the time factors is not as important in their work, limit the visits to customers to one per day.

In more time-sensitive approaches, the number of trips made by the vehicles is often one of the aspects that needs to be optimised. However, there may be certain restrictions imposed on the number of trips through either the blood demand (minimum) or the time limit in relation to the products’ lifespan (maximum), or both. Analogous to classic VRP-TW problems, the sequence and the exact times of the customer visits constitute the output of the problem, but in this case, it is a bit more complex: whether the authors state it explicitly or not, the customer visiting times are extremely dependent on one another and need to be synchronized. Dörner et al. (2008) emphasise these interdependencies between customer visits. As there is a strict time frame within which a donation has to be returned to the depot, the pickup time at one customer site directly affects the possible pickup times at all other customer sites within the same tour. The departure and return times from and to the depot also need to be considered as they are included in the processing time limit.

Typical objectives are the minimization of travelled distance or total driving time, the reduction of cost, or the maximization of output (see chapter 5.3). As for the cost aspect, authors usually consider variable costs for trips and number of vehicles. Additionally, production costs for blood products may be considered (e.g., Ghandforoush and Sen 2010). Some authors impose additional costs on the loss of product, especially as a penalty for late arrival of blood at the depot, but also as costs for units lost due to testing, delays, breakage and contamination (Ghandforoush and Sen 2010). The maximization of output depends on the amount of blood returned to the depot within a certain timeframe. Said timeframe typically relates to the transportation and, sometimes, the waiting and/or processing time at the depot. Some authors allow visiting not all, but only a selection of collection sites. Some sites may be skipped if visiting them means that more blood is lost due to the limited timeframe than can be gained from said collection site (e.g., Yi and Scheller-Wolf 2003, Özener and Ekici 2018).

In its essence, the blood collection problem is a typical routing problem, as Yi and Scheller-Wolf (2003:74) observe: “As a bring-back vehicle must visit a site during the collection hours, this problem naturally falls into the class of vehicle-routing problems with time windows

(VRPTW)." It has been compared to several variations of this problem, including the classic VRP (Özener and Ekici 2018), the periodic VRPTW / periodic traveling salesman problem (Dörner et al. 2008), the Prize Collecting or a Selective Traveling Salesman problem (Şahinyazan et al. 2015). Other OR-problems authors have compared it to, always depending on their own problem characteristics, are the Inventory Routing Problem (Dörner et al. 2008) and the (Team) Orienteering Problem or Maximum Collection Problem (Şahinyazan et al. 2015, Özener and Ekici 2018).

One possible extension relates to the characteristics of bloodmobiles (Şahinyazan et al. 2015, Gunpinar and Centeno 2016, Rabbani et al. 2017),[10] namely their ability to have them move from one location to another, sometimes varying the length of their stay. Blood can be collected either in fixed collection sites, such as collection centres, or by mobiles, typically large motor vehicles like busses or vans, that transport personnel and equipment to different locations. Usually, blood drives involving blood mobiles are held in large public places like colleges or high schools, churches and other places of worship, community centres, companies or military installations, and sometimes even in cooperation with these institutions. As Şahinyazan et al. (2015:22) point out, "[t]hese drives aim to reach at many donors that may not be planning to make a blood donation otherwise", because "mobiles can also reach potential donors who have limited time and limited means of transportation" (Ibd.). As previously mentioned, blood mobiles have the possibility to stay longer in one location depending on the node's blood potential (Şahinyazan 2015). The blood mobiles may be moved several times during the planning horizon.[11]

In the blood delivery problem, the depot is usually a blood bank, whereas the customers may be hospitals or other healthcare facilities. In some scenarios, there is more than one blood bank and customers need to be assigned to depots. Demand can be deterministic (e.g., Hemmelmayr et al. 2009) or stochastic (e.g., Hemmelmayr et al. 2010, El-Midaoui et al. 2022). Still, it can be noted that the nature of the demand is strongly simplified: The need to differentiate between blood products and types (which would translate into various products in the optimization context) is sometimes addressed, but hardly ever featured in the actual solution approach. Other than that, special limitations may be imposed on the transportation mode (e.g., temperature control (Wen et al. 2016) or separate vehicles for unprocessed and processed blood products (Eisenhandler and Tzur 2022)). More than is the case for the collection stage, the delivery-routing is sometimes treated in combination with an inventory routing problem (IRP), and traditionally IRP-related aspects such as safety stock, stockout costs or the capacity of the hospitals are considered. Especially vendor-managed inventory systems, wherein the decision when and how much to deliver to the hospitals is made by the blood banks, seems to be a popular alternative to individual order policies. The benefits of VMI in this context are cost reduction as well as minimization of shortages and product spoilage (Hemmelmayr et al. 2009, 2010; Liu et al 2020).

4.1.3 Blood and Blood Products: Relevant Literature

4.1.3.1 Literature reviews

Among perishable medical products, the most well-researched by far is blood. Consequently, the topic has been reviewed several times before. This chapter shall provide a short

[10]From these three papers, only the one by Şahinyazan et al. (2015) met all the inclusion criteria. The others do not count towards the 56 reference papers. The reasons for their exclusion are given in the chapter 4.1.3.2.

[11]Since the location routing aspect of the problem can affect the output, some authors decide to have a location planning problem precede their vehicle routing and scheduling problem (e.g., Gunpinar and Centeno 2016, Rabbani et al. 2017).

introduction to some of these surveys, even though these do not present their own mathematical models and, thus, do not count towards the reference papers.

The earliest literature survey that fit my search criteria and process was that of Beliën and Forcé (2012). However, Eghtesadifard and Jozan (2022:1175) present another 9 contributions published before that, and some that were printed afterwards. Since Eghtesadifard and Jozan (2022) focus on a broader scope than just RSPs, namely that of the entire BSC, not all of their cited resources might address routing-scheduling problems.

Beliën and Forcé provided a very in-depth literature review on the entire BSC back in 2012, with 98 manuscripts published between 1966 and 2010. They thoroughly examine the texts and present them in eight different classification schemes, ranging from type of blood product over solution methods to performance measures (for a complete list, see Beliën and Forcé 2012:2). Theirs appears to be one of the most detailed and highly cited literature surveys on the blood supply chain to date. One major shortcoming, however, is that their review does not allow the reader to distinguish finely between echelons of the BSC, which makes it rather hard to single out, for example, routing-scheduling problems related to collecting, processing and/or delivery as would be needed in this work.

The review by Osorio et al. (2015) includes quantitative models appertaining either directly to the blood supply chain or to related topics with the explicit application of the BSC (e.g., perishable inventory management) published between 1963 and September 2014. The authors structure their review along four echelons in the supply chain, namely collection, production, inventory and delivery. Integrated models combine two or more stages. Osorio et al. (2015) further classify the papers by the decision level they address (strategic – tactical – operational). Without going into detail regarding this particular type of problem, they mention RSPs in connection with the collection and distribution stage, but not with integrated models. Overall, they lament how few examples of integration they found, which might indicate missed opportunities of optimizing the BSC by linking, for example, vehicle routing and production scheduling.

In their survey, Baş Güre et al. (2018) focus specifically on the appointment scheduling aspect of blood donations, highlighting the lack of research in this field. They present the benefits that may be gained from further exploration of the topic, suggest future opportunities and research direction, and underline the advantages that may be derived from optimizing appointment scheduling for blood collection together with other phases or decisions. Transportation plays a minor role in their review, and the paper by Mobasher et al. (2015) appears to be the only one linking appointment scheduling and vehicle routing.

Seeking to upgrade the works of Beliën and Forcé (2012) and Osorio et al. (2015), Pirabán et al. (2019) search for papers published between 2005 and February 2019 and review a final set of 104 articles, 57.69% of which were published from 2015 onwards (Pirabán et al. 2019:2). This stands to show the increased interest in the topic in the last few years. They present a new taxonomic framework for reviewing and categorizing the literature to best capture the topics covered in it: decision-making and forecasting, issues in the design of the BSC (including echelons and product types, processes and problems/planning decisions, modelling and solution techniques, and data characteristics.

Williams et al. (2020) focus on blood collection. In this review, the authors include 46 publications that appeared between 1996 and February 2019. Within the scope of the collection stage of the blood SCM, they identify four articles featuring appointment scheduling and six texts featuring vehicle routing, with only one overlap (Mobasher et al. 2015). This experience is mirrored in my research, exposing a gap in research at the intersection of these two topics. Moreover, Williams et al. (2020) address the production echelon of the BSC in terms of separating fresh blood into its components. They highlight publications connecting either appointment scheduling or vehicle routing with the production step, but again, the paper of Mobasher et al. (2015) is the only one covering all three topics. AS is identified by the authors as one of the most relevant future research directions. With regards to their emphasis on donor satisfaction, they seem to be suggesting that intra-facility appointment scheduling (in combination with routing) might be a promising research direction.

Eghtesadifard and Jozan (2022) searched WoS for journal articles published between 1990 and August 2021. With the purpose of identifying hot topics and research trends, they analyse 485 contributions by the means of a bibliometric method. Content analysis software is used as well as citation analysis, co-citation analysis, keyword analysis, and co-word analysis. The authors also grant special attention to the topic of red blood cells. Other than literature surveys, publications are not presented or studies in-depth. They identify “vehicle routing” as one of the most frequent keywords in combination with the BSC (Eghtesadifard and Jozan 2022:1184); “scheduling” or even “scheduling routing” or “routing scheduling” are not mentioned at all, however.

Meneses et al. (2022) analyse the strategic and tactical planning levels in the BSC. As such, scheduling of collection, production and transportation are shortly presented, but operational problems relating to the short-term routing and scheduling of problems are not explored in detail. For this, the authors refer to other reviews.

Using a four-stage process, Torrado and Barbosa-Póvoa (2022) identify and review 90 papers published during the last 10 years. They also include a short chapter looking for insights in earlier literature reviews on the BSC. In this, they name the studies by Beliën and Forcé (2012), Osorio et al. (2015) and Pirabán et al. (2019) as the most comprehensive reviews on the topic. Torrado and Barbosa-Póvoa (2022) not only describe BSC phases and planning decisions but appear to be the first to highlight the sustainability dimension in the studies they found.

4.1.3.2 Articles on Blood Collection

Early work on the operational efficiency of blood collection was done in the 1960s and 1970s: “The BSC has been a topical concern since the 1960 s, while a remarkable proportion of the literature in this field took shape during the 1970 and 1980 s”, Eghtesadifard and Jozan (2022:1174) write. Both the paper by Mobasher et al. (2015:261) and Özener and Ekici (2018:116) trace the Blood Collection Problem (BCP) back to Prastacos (1984) who, introducing the problem, writes: “The problem of scheduling collections from n possible collection points of estimated size with K vehicles is a complex combinatoric Vehicle Routing Problem (VRP), which has not yet been examined” (Prastacos 1984:791). However, Prastacos (1984) does not consider a processing time limit or other constraints relating to perishability, which excludes the paper from closer examination in the analysis part of the thesis.

“Yi (2003)[12] was among the first to approach the blood transportation problem as a variant of the VRPTW”, Anaya-Arenas et al. (2021:369) write to confirm the pioneer-status of Yi and Scheller-Wolf (2003). They consider a Vehicle Routing Problem with Time Windows and Time-Dependent Rewards as an extension to the classical VRPTW, adapted to fit the additional restrictions of the product. Blood is collected from donation sites and returned to a central depot to produce blood platelets. To solve the problem optimally, they propose a four-step solution procedure which starts out by generating all feasible solutions. Then, arrival / departure times and the amount of collected blood are optimized. In the third and fourth step, inferior routes are removed, and the best route is selected. The objective is to minimize the total route length, and, by extension, to increase the efficiency and cost-effectiveness of the routes.

[12]Both “Yi (2003)” and “Yi and Scheller-Wolf (2003)” can be found in the literature and refer to the same paper.

Mobasher et al. (2015:262) later call attention to the fact that “each donation site is visited only once which limits the platelet production significantly in practice.”

Dörner et al. (2008) look at the Vehicle Routing Problem with multiple interdependent time windows (VRPmiTW). It is inspired by a real-world problem faced by the Austrian Red Cross blood program. Blood must be transported to the blood bank (central depot) for further processing from various collection sites and within a time span of five hours after collection, lest its quality deteriorates to a point where it cannot be used anymore. In addition to the uneven production rates and time windows for further processing at the central depot, the interdependencies of the time windows at the collection centres pose a particular challenge and distinguish this particular problem. More than 10 years after this paper’s publication, Anaya-Arenas et al. (2021:369) know only of this and one other contribution[13] that consider interdependency in the pickup decisions and the routes’ length limitation.[14] As for the underlying VRP, the authors point out similarities to the periodic VRPTW and the inventory routing problem. They apply three heuristic solution approaches, all based on the savings algorithm by Clark and Wright (1964), and an exact branch-and-bound procedure. The objective is to minimize the total driving distance. While starting with a fixed number of pickups per collection site, they find that increasing this number for some customers unlocks significant potential for cost reduction. As Mobasher et al. (2015:261) point out, however, “[t]he main shortcoming of the study by Dörner et al. (2008) is that even a single donated unit has to be collected. However, in practice not all of the donated units are used for platelet production. Furthermore, they do not consider the availability of the collection vehicles.”

In 2015, Şahinyazan et al. developed a model for the routing of bloodmobiles inspired by the Turkish Red Crescent (TRC), a member of the International Federation of Red Cross and Red Crescent Societies (IFRC). Instead of having the bloodmobiles return the collected blood to the depot, however, the authors introduce an additional vehicle called the shuttle. Every day, the shuttle starts and ends its tour at the depot, gathering the blood collected at the bloodmobiles, so that the mobiles may remain in the field overnight. Because of this extension, the authors call their problem the Selective VRP with Integrated Tours. Their aim is to decide on the tours of the bloodmobiles and the shuttle as well as the length of the stays. Two mathematical models are developed, MinCost-B*-Blood (to collect a pre-determined amount of blood) and MaxBlood (wherein the maximum collection amount is calculated). First, the authors look for exact solutions to the problem and then develop a 2-stage IP based heuristic algorithm to deal more efficiently with larger problems. They perform a Pareto analysis for the two competing objectives of maximizing the collected blood and minimizing the transportation costs. Despite some very interesting extensions, like the possibility for a blood mobile to stay in the same location for up to three days depending on the location’s blood potential or the integration of the shuttle’s route into the blood mobiles’ routes, the authors take a rather relaxed approach to the perishability characteristics of the medical product. Compared to other studies wherein blood deliveries must happen within a very strict timeframe to preserve its platelet production potential, Şahinyazan et al. (2015) content themselves with returning the blood to the central depot at the end of each workday.

The Integrated Collection and Appointment Scheduling Problem (ICASP) presented by Mobasher et al. (2015) take a slightly different approach. It is the only paper on the blood supply chain that addresses appointment and production scheduling aspects. Blood donations and collection must be scheduled first, then blood may be transported to processing sites, where it can finally be processed into various blood products with different shelf lives (5-9

[13]The other contribution is that of Dörner and Hartl (2008). It does not fit the inclusion criteria “article in a scientific journal” it was published as a chapter in a book.

[14] Anaya-Arenas et al. (2021) stress these problem characteristics as they themselves present a similar problem for medical sample transportation. Their paper will be presented in chapter 4.2.3.

days). The authors concentrate on blood platelets, the product with the shortest lifetime that also requires the freshest blood supply. In contrast to other works on the blood supply chain, the authors include the appointment (donation) scheduling aspect into their problem rather than considering fixed times or uniformly distributed donations throughout a day. Thus, they acknowledge the direct impact the donation appointments have on the platelet output due to the perishable nature of the medical product (blood) and the strict time windows that result from it. The objective Mobasher et al. (2015) seek to maximize is the number of platelets produced. They develop a heuristic algorithm called Integer Programming Based Algorithm (IPBA) and test it on 30 instances generated from real data. For a short discussion of Yi and Scheller-Wolf (2003), Dörner et al. (2008) and Ghandforoush and Sen (2010; presented in chapter 4.1.3.4) in relation to their own work, see Mobasher et al. (2015:261). All of these works are also mentioned by Anaya-Arenas et al. (2021:369).

In 2018, Özener and Ekici published their study on the Maximum Blood Collection Problem (MBCP). Their goal is to schedule blood collections in such a way that the production of platelets is maximized while a 6-hour processing time limit is respected. To this end, they propose an integrated clustering and routing framework. An arbitrary (rather than a uniform) donation pattern is assumed to make the problem more realistic. They then solve the problem heuristically. Four different heuristic methods (2 take a greedy approach, 2 use a set of pre-processed routes) are applied and tested on a set of generated data. More than others, Özener and Ekici (2018) build on earlier publications, in particular on the texts by Yi and Scheller-Wolf (2003) and Dörner et al. (2008). This repeated referencing and comparing allows for a better understanding of the evolution of the blood collection problem.

Two papers that did not make it onto the list of reference papers deserve to be highlighted, since they met many of the inclusion criteria, provided valuable insight to the BSC and were used during the background research on the BSC (chapter 4.1.1) and bloodmobiles in particular (chapter 4.1.2): The paper by Rabbani et al. (2017) was ultimately excluded because the solution representation (Rabbani et al. 2017:31) includes only the customer sequence, but no transportation schedule. The paper by Gunpinar and Centeno (2016) was excluded for similar reasons.

4.1.3.3 Articles on Blood Delivery

In response to a problem brought forward by the largest Austrian blood bank, that of the Austrian Red Cross (ARC), Hemmelmayr et al. (2009) formulate a vendor-managed inventory routing problem (VMIRP). They describe and demonstrate the advantages of a centralized distribution system, wherein the blood bank rather than the hospitals decides on the quantities and delivery dates. Trying to balance flexibility with regularity (e.g., fixed routes, repeating delivery patterns), they design a two-week delivery schedule. With the goal of cost reduction, they develop and test two alternative approaches: one integer programming approach and one Variable Neighbourhood Search (VNS). The mathematical model aims to minimize the travel time and contains constraints relating to product spoilage, safety stock and inventory capacity. The methods are then tested using nine test sets derived from data provided by the ARC, wherein eight test sets represent eight months and a ninth set an average month in the year 2003. During this first paper, they use a deterministic problem setting, all the while acknowledging that this is, in practice, not very realistic. A year later, they published an extension to their study that allows for stochastic product usage.

Once year later, Hemmelmayr et al. (2010) extended both of their original approaches to address the stochastic demand. To this end, they introduce a two-stage stochastic program with recourse: “The set of first stage decisions concern the regular deliveries to demand nodes and the second stage decisions (or recourse decisions) consist of adjustments to the quantities based on emergency situations”, Meneses et al. (2022:12) summarize in their review. A variety of recourse strategies is presented to address emergency demand, and the original objective function from Hemmelmayr et al. (2009) is adapted. Finally, extensive computational experiments are conducted on the real-life data provided by the Austrian Red Cross, even accounting for different blood type.

Wen et al. (2016) took a somewhat different approach in their UAV-based Capacitated Vehicle Routing Problem (UCVRP). First, due to the nature of their selected vehicle, capacity plays an integral role: using drones (or Unmanned Aerial Vehicles, UAVs for short) strongly reduces the vehicles’ capacity as compared to the trucks or shuttles most used in these types of problems. Second, the blood’s perishability is not related to time, but to temperature. The authors want to keep the temperature of the blood between 2°C and 10°C, which means that depending on the environment, it must be either warmed or cooled. The weight of the hot water or ice (summed up under the term appendage) adds additional weight to the UAV. Aside from the transportation distance and time, the temperature of the blood during and after delivery depends on the initial temperature and amount (weight) of the appendage in relation to the amount of transported blood. They propose “an optimal method for calculating the mixing proportion between blood and appendage in different circumstance” (Wen et al. 2016:19). Finally, the UCVRP is one of the few multi-objective problems included in this thesis. The authors aim at simultaneously minimizing the total milage and the total number of UAVs used. In their setting, these are two conflicting objectives, although the authors concede that “they are not completely antagonistic” (Wen et al. 2016:16). Their solution space therefore contains a Pareto optimal set with trade-offs between their solutions. For their proposed algorithm, MOEA/D-N-UVRP, they apply a local search to the decomposition-based MOEA (multi-objective evolutionary algorithm). Their method is compared to two other algorithms, NSGAII-CUVRP and MOEA/D-CUVRP, and tested through experiments on a public dataset.

Liu et al. (2020) take an VMI approach to the problem. To tackle the massive problem of blood products shortages in China, a blood collection centre monitors the demand of several hospitals and distributes the blood accordingly. The perishable nature of blood products is addressed, and penalty costs are imposed should blood shortages or wastages occur. These costs are present in the objective function, which minimizes the total cost, more specifically the sum over the inventory holding cost at the blood centre and hospitals, wastage cost, shortage cost and transportation cost. The authors consider multiple periods during their planning horizon, and the amount of expired product needs to be calculated at the beginning of each period. As for the solution method, an adaptive large neighbourhood search algorithm and an integrated algorithm are designed based on the decomposition method. Experiments are conducted on the real-world example of platelet distribution in Nanjing, China.

El Midaoui et al. (2022) focus on the distribution of blood and blood products from blood centres to hospitals. To preserve the quality of the products and, consequently, save lives and costs, they pay attention to special storage and transportation conditions, such as vibration avoidance, temperature maintenance, and timely delivery – at least in theory, as these aspects unfortunately are not featured in their mathematical models. Instead, their focus is set on demand uncertainty: Due to the fluctuations of demand, especially in times of a crises or a pandemic, the authors use machine learning to predict future demand. First, they fuzzify historical data while preserving the priority of newer data. After training their model, a defuzzification process is used to predict the demand for each blood product of each hospital. Afterwards, they apply a genetic algorithm to solve the vehicle routing and scheduling problem. Since they consider a multi-depot scenario, grouping (of customer/hospitals) plays a role next to routing and scheduling. They compare their transfer learning and fuzzy logic approach to ANN and ARIMA models.

4.1.3.4 Articles on Integrated Models

Ghandforoush and Sen (2010) develop a decision support system (DSS) to improve the platelet production supply chain, the same blood product treated by Mobasher et al. (2015) and Özener and Ekici (2018). Ghandforoush and Sen (2010) take a more wholistic view, from scheduling blood collections at the donor sites to production, distribution and redistribution of the finished product, the platelets, to and between hospitals (see Fig. 1. Platelet production supply chain, Ghandforoush and Sen 2010:33). Their user interface resembles that of Zabinsky et al. (2021). Information in their interface is not automated but needs to be keyed in manually. The paper centres on scheduling transportation of blood from donor sites to the production centre for each day of the week, all the while keeping the demand in mind. The ILP solver solves a nonlinear integer model with the objective of minimizing the daily cost of platelet production. Said costs are the combination of the production, the transportation, and the yield loss (through production or testing) costs. The authors uncover potential for cost and staff time savings by reducing the number of underutilized blood mobiles.

Zahiri et al. (2018) present a complex integrated multi-product optimization problem comprising various stages of the BSC. Accordingly, they call their problem the blood collection, production, distribution and routing planning (BCPDRP). To avoid congestion during transfusions at hospitals, they develop a multi-priority queuing system based on the urgency level of the recipients. The dynamic nature of the supply and demand is accounted for and transshipments are allowed. They also consider the perishability of their various blood products. Their proposed mathematical model simultaneously minimized the network costs and maximized the remaining shelf life of products delivered to the hospital. A possible trade-off between these two objectives is analysed. To efficiently solve the large size instances, they present a novel hybrid meta-heuristic algorithm. Their method, the MSDV algorithm, is based on a self-adaptive differential evolution (SDE) algorithm and a variable neighbourhood search (VNS). To demonstrate its relevance, they compare the performance of their approach with other current methods (MOICA and NSGA-II) on a set of generated medium- and large-sized instances and on a case study.

Hamdan and Diabat (2020) design a multi-objective BSC model, from blood donations to blood usage in hospitals, to improve blood supply in the aftermath of a disaster such as earthquakes, floods or wars. Since the occurrence and the effects of disasters are subject to high uncertainty, the authors use both robust optimization techniques and two-stage stochastic optimization. The first stage involves pre-disaster planning (location planning for donation centres, allocation of donors to centres, as well as collection and transportation) and their second stage post-disaster planning. The likelihood of different disaster scenarios is taken into account and routes are specified accordingly. A bi-objective framework is assumed and solved by the means of a Lagrangian relaxation algorithm. Their first objective, the minimization of delivery time, is the combination of transportation time(s) from the collection centres to the blood banks and from there to the hospitals. As their second objective, they minimize the total system cost. A real case study using 15 different disaster scenarios is used to test their method.

Eisenhandler and Tzur (2022) consider collection, processing and distribution activities in a multi-period setting. They characterize their type of problem as Multi-Period Collection and Distribution Problems (MPCDPs), of which they present two real life examples: albeit the motivation to their study comes from a food rescuing scenario (gleaning), they describe how blood donation and collection can also be modelled as a MPCDP. In both scenarios, the product has a short shelf-life and must abide to safety regulations that dictate, in this case, that processed blood (tested and separated into its components) cannot travel in the same vehicle as blood that has not yet undergone screening. Moreover, it needs to be processed in a central facility before being distributed to its various destinations (medical centres), where transfusions to end-customers can be performed. The complete problem is decomposed into separate collection and distribution sub-problems that are linked to each other. The expiration dates are fixed. The authors' special humanitarian objective function balances the effectiveness and the equity of the product allocation. In an optimized version of the collection subproblem, it also maximizes the earliest day when the demand cannot be fully supplied. Their approach is tested over real-life and generated instances. Since gleaning is the authors primary application example, the real-life examples are based on the 2017 operations of the Israeli food bank "Leket Israel".

Pirabán-Ramírez et al. (2022) introduce the multi-trip vehicle routing problem with increasing profits (MT-VRPIP). Blood donation, transportation and processing are considered in this integrated model. Donations at the collection sites follow a linear increasing function. The authors address the perishability of blood through a processing time limit (whole blood must be processed within 8 hours of donation to allow for the production of blood platelets and cryoprecipitate) and an arrival time limit (blood must arrive early enough at the blood centre before its closing time to allow testing and processing). This makes production of all blood products, even the more time-sensitive ones, possible. The objective function minimizes the total cost comprising the transportation, delay, and shortage costs. For their solution method, the authors develop a hybrid iterated local search metaheuristic. It is tested over 103 instances based on the blood collection system in Bogota, Colombia. Real information is gathered, and the missing information is generated.

Since time is of the essence in a post-disaster setting, Rezaei Kallaj et al. (2022:9) combine blood collection via bloodmobiles and blood delivery via drones in an emergency. In a trade-off between the time of blood collection and the number of blood units collected, the staying time of bloodmobiles is subject to optimization. They do not have to interrupt their tours and return to the depot thanks to drones: "To prevent blood from expiring, and to deliver it to the hospitals and medical centres on time, drones visit bloodmobiles to take the collected blood units and deliver them to the disaster area" (Rezaei Kallaj et al. 2022:2). In this, the drones' function resembles that of the blood shuttle in the paper by Şahinyazan et al. (2015), except that blood is delivered right to where it is needed. Rezaei Kallaj et al. (2022) take four different blood groups into account. The authors present a bi-objective mathematical model wherein their first objective is to maximize the number of collected blood units and the second is to minimize the maximum arrival time of bloodmobiles and drones at the affected zone. Due to the uncertainty in demands and the number of donors, they chose a two-stage stochastic programming approach. In the first stage deterministic model, the routes for the vehicles are decided. The second stage variables, the arrival and staying times of the vehicles, are scenario dependent. The authors apply a Particle Swarm Optimization algorithm, MOPSO, and test it over small, medium, and large instances on real-life data. Rezaei Kallaj et al. (2022) arrive at the conclusion that drones are useful to support the blood mobiles during such crisis situations (see also: chapters 6.2.2 Emergency Setting and 6.2.3 Drone Usage).

4.2 Biological Samples and Specimens

4.2.1 Biological Samples and Specimens: Background and Relevance

Laboratory testing finds numerous applications in healthcare, including "the detection, diagnosis, monitoring and treatment of diseases and other medical conditions" (Yücel et al. 2013A:503). Primarily, bodily fluids such as salvia, urine or blood are tested. In recent years, the testing of nasal swabs has gained world-wide importance due to the COVID-19 pandemic. Wolfinger et al. (2023) demonstrate how efficient testing has been a key strategy in combating the spread of the virus. As such, one might argue that public interest in quick and effective medical tests has risen over the last years, even though its importance has been indisputably high for a long time. "It is estimated that lab testing has an impact on over 70% of medical decisions," Yücel et al. (2013A:503) write, citing a source from 2008. Clinics and hospitals, but also physicians' offices and other healthcare providers need test results to accurately diagnose and treat their patients. Even though some larger hospitals have proper laboratories, it is very common for these services to be outsourced to clinical testing companies with specialized personnel and equipment (see Yücel et al. 2013A:503, Zabinsky et al. 2020:537, Anaya-Arenas et al. 2016:602). Anaya-Arenas et al. (2021:367) argue that this centralization yields advantages in terms of quality control as well as cost reduction (technical equipment, economies of scale). To fully exploit the potential of centralized testing, operations need to be optimized: "An important determinant of the operational costs is the effective utilization of the high-tech processing equipment and skilled labor, which in turn is affected by the way the specimens are transported from the sites to the laboratory", Yücel et al. (2013A:503f) write, pointing out one such possibility for reducing bottlenecks and, thus, costs: "In particular, the arrival rate of specimens to the laboratory has to match (or exceed) the processing rate so that starvation of the processing resources can be avoided." (Ibd.) There is lots of room for optimization if these operations are to run smoothly, considering that the objectives are conflicting: Since laboratories are still economic actors striving for profitability, decisions must be made based on the priorities of (1) cost reduction, (2) fast turn-around times, yet (3) reliable / accurate results, high quality testing services. As multiple authors point out, centralized medical testing requires an adequate transportation plan, not just for reasons of cost-effectiveness, but also to prevent the biological samples' deterioration (Anaya-Arenas et al. 2016:602, Anaya-Arenas et al. 2021:367, Zabinsky et al. 2020:538, Yücel et al. 2013A:503). A compromise has to be found since prioritizing only the fast transportation of specimens may cause transportation costs to skyrocket.

To illustrate the immense potential for supply chain optimization, consider the following example. Anaya-Arenas et al. (2016) describe the transportation system (or rather the lack thereof) in Quebec at the time of their publication:

> *"[E]ach laboratory and SCC [sample collection centre] is responsible for selecting the transportation services they use and how they use them. In most cases (around 70%), SCCs have signed blanked transportation contracts with local carriers, so SCC employees order a transportation service whenever they feel it is necessary. In the rest of the cases, SCCs simply calls a taxi service. These multiple and uncontrolled transportation modes result in two negative consequences related to the tracking and control of (1) the costs of specimen transportation and (2) the quality of the transportation done by the transportation providers." (Anaya-Arenas et al. 2016:602)*

In general, the transportation of biological samples is less regulated and less centralized than the collection and transportation of blood donations, which is usually organized by large organizations such as the Red Cross or the Red Crescent and subject to strict regulations. Instead, in the literature it appears that specimen logistics (aside from official testing sites during the COVID-19 pandemic, perhaps) are up to individual laboratories and, as the abovementioned example showcases, sometimes even less organized than that. This poses many problems considering how carefully biological samples ought to be handled.

The quality of transportation plays an important role for a variety of reasons. Firstly, contamination must be avoided. Secondly, traceability concerns need to be addressed. As biological samples are used for diagnostic purposes, they are highly personal. Thirdly, medical specimens have a very short lifetime, "varying from 5 to 24 hours or more depending on the type of sample" (Anaya-Arenas et al. 2021:367). If they are not processed within a certain timeframe, the quality of the samples can drop considerably, or they can spoil completely (Zabinsky et al. 2020:538). The freshness of the sample has a direct effect on the quality of the result. Therefore, it is essential that the samples arrive at the laboratory within a certain timeframe. Yücel et al. (2013A:503) point out that "[m]ost clinical testing companies have strict agreements on turnaround time, which is generally required to be less than one business day, and sometimes as short as a few hours for urgent requisitions." Customer satisfaction (the customers being the healthcare professionals that request the testing, and sometimes the patients themselves) depends on timely processing of samples. For more details on the internal process of clinical testing companies, the reader may refer to Yücel et al. (2013A:503f).

4.2.2 Biological Samples and Specimens – Collection and Processing: Problem Description

In the eyes of Anaya-Arenas et al. (2021:369), there are "two characteristics that make [the sample collection] problem more than a straightforward VRP: (1) the interdependency between successive visits to customers (SCCs), and (2) the lifetime of the products (samples) that limits the time available to return to the depot (the laboratory)." They then compare the visit interdependency to problems encountered in the home care planning context, where different care activities need to follow a certain order within pre-specified timeframes. They compare the maximum time constraint to return a sample to the depot to the blood management problem (Anaya-Arenas et al. 2021:369). Yücel et al. (2013A:504) also draw comparisons to the blood collection problem, particularly because "(i) units to be collected accumulate over time and (ii) there is a deadline for the completion of processing." However, in contrast to blood products, the lifetime of biological samples varies even more greatly and is much shorter than that of processed blood products. Another aspect that weighs more heavily in the specimen supply chain is that of traceability. In comparison to blood, which (past a certain point in processing) does not need to be traced back to the original donor, biological samples are highly personalized. They serve the main purpose of diagnosing diseases in patients. Thus, documentation needs to be more thorough and always up to date, so that samples can always be traced back to their origin. In addition, patients need the option of enquiring about the testing status of their specimen. At the same time, increased information availability creates the need for sufficient discretion and data security, but these problems would lead far beyond the scope of this thesis.

As the lifetime of the goods is limited, the problem is most frequently compared to the vehicle routing problem with time windows. Zabinsky et al. (2020:538f) liken it to the transportation of perishable goods and point out that the HHC-RSP "shares many characteristics with our problem; it is necessary to combine routing and scheduling, there are many side-constraints (temporal, geographic, and assignment type constraints), and often multiple objectives." Although taking samples at patients' homes has been a potential task of nurses in HHC scenarios for a long time (e.g., Haitam et al. 2021, Liu et al. 2013), it has received more widespread attention since the outbreak of the COVID-19 pandemic (Tlili et al. 2022). Therefore, collection and transportation of biological samples does not only share characteristics with HHC problems but is frequently included in them (see also: chapter 6.2.1).

Outside the context of healthcare, Yücel et al. (2013A:504) highlight the differences and similarities of the biological sample collection problem to the Inventory Routing Problem (IRP) and the Team Orienteering Problem (TOP), the latter of which also serves as foundation for the work of Tlili et al. (2022). Zangeneh-Khamooshi et al. (2013:1215) mention courier routing and scheduling.

Despite slight variations between the reference papers, the basic characteristics reduce to the following: a number of locations, generally collection centres, testing stations or hospitals (customers), need to be visited by one or more vehicles. The specimens, samples or testing swabs (goods) then need to be brought back to a central laboratory (depot) for testing. A time limit is set on this process, albeit the subtleties might vary: The timer on the transportation either starts the moments the samples are collected from the patient or the moment they are picked up by the vehicle. This is because some authors argue that the collection sites possess special storage units with optimal conditions, like perfect temperature, that preserve the samples' lifetime until pickup (see chapter 5.8). Still, storing the specimens indefinitely is counterproductive since they need to be processed sooner rather than later. Some authors consider the samples' lifetime and the maximum transportation time as two different measures (e.g., Anaya-Arenas 2016). The transportation timer then ends either upon arrival at the laboratory, once processing starts or once processing ends. These limits on the transportation time are generally tackled in the mathematical models either through the main function (minimization of total travel time, total tardiness, etc.) or via penalties (see chapter XX). If the timespan is exceeded, the sample deteriorates or spoils. Then, the mathematical model might simply apply a penalty; the real-life consequences, however, are a bit more complex. A patient might need to return to the collection site for a second sample to be taken, which would result not just in increased costs, but also in a lot of additional planning effort. Furthermore, patient satisfaction suffers from a return visit, as might the health status of patients and even others, for example if a contagious disease is detected too late.

In order to reduce the risk of sample deterioration, balancing the workload is important at various stages of the process. En-route drop-off of specimens at the laboratory, realized through multiple trips for vehicles, are common. Moreover, due to the short time windows, it is also customary to allow multiple visits to the customers collection sites. In some cases, a minimum number of visits to a collection centre is imposed. If, for example, the opening hours of a collection site stretch from 9am to 3pm, it might be advisable to visit not only when it closes, but also around 12pm, or, alternatively, at 11am, 1pm and again at 3pm. Meanwhile, visiting it at 2pm and again at 3pm would be rather counterproductive, which is why some authors consider spacing out the visits. The last pickup from the collection site should be made shortly after it closes (see Anaya-Arenas 2016, Anaya-Arenas 2021). Sometimes, the working hours of the staff and/or the opening times of the collection site are taken into account.

Capacity constraints are sometimes considered, either in the vehicles (even though some authors note that samples themselves are usually of negligible size, they may still require special transportation conditions, such as cooling boxes) or at the laboratory (typically in terms of bottlenecks for the processing of samples). As mentioned above, the processing stage at the laboratory might be included in the samples' lifetime. Even after optimal collection and transportation, delays at the laboratory may cause the specimens to spoil at the last minute. Naji-Azimi et al. (2016:58) are among those who include the laboratory resources in their models:

> *"The boxes are opened at the Lab, and each sample is manually registered in the system and bar-coded for tracking purposes during the analysis process. These manual tasks are time consuming and […] constitute a bottleneck of the samples'*

supply chain. In fact, if too many boxes arrive in a short period of time, samples are queued and may suffer long wait, which might exceed their remaining lifetime making them unsuitable to be analyzed. Our observations on the ground confirmed that some days or periods are more popular for sample collection. Thereby, reducing the maximum number of samples boxes arriving within a time period is desirable in order to normalize the Lab workload and minimize sample losses."

They tackle this bottleneck by setting a limit on the number of boxes that may arrive during certain time intervals. Loading and unloading times at the laboratory are considered (Anaya-Arenas 2016, Naji-Azimi 2016), but practically set to zero in some problems (Anaya-Arenas 2021). Others (Zabinsky 2020) do not take them into account at all. The possibility of waiting times is acknowledged in all problems, but rarely addressed explicitly in the mathematical model. Routes typically start and end at the depot. Transportation requests may be known in advance or arrive dynamically (see chapter 5.6).

4.2.3 Biological Samples and Specimens: Presentation of the Literature

This chapter introduces the most reference papers (23 out of 56). Subdividing them into smaller clusters for better read- and comparability is not easily done. Unlike blood, the specimens SC cannot be sensibly split into various echelons. Some papers specifically speak of blood samples, but in their handling within OR contexts, blood samples do not differ from other, undefined samples. Thematically, two group could be formed: Papers that feature an emergency setting and papers that include HHC topics (see chapter 6.2). Apart from these two groups, the papers will be presented chronologically and/or in research strands wherein authors directly build on the predecessors' or their own earlier work(s).

Pioneer work in the field of specimen collection was done by McDonald in 1972. In fact, neither I nor the authors referencing McDonald (Yücel et al. 2013A, Anaya-Arenas 2021) seem to be aware of any earlier work on this topic. In the vehicle routing and scheduling problem by McDonald (1972), a small fleet of vehicles collects specimens from collection points like doctors' offices and hospitals before taking them to laboratories. The author acknowledges that "the transfer of a specimen from its point of origin to the appropriate laboratory should be accomplished with the minimum delay since the amount of information provided by a specimen diminishes rapidly with the age of the specimen" (McDonald 1972:434). As for the main objective, McDonald mentions patient service levels and costs, but ultimately decides on minimizing the total time required to make all collections. The model is formulated as a VRP with only four constraints and for the heuristic solving method, the author chooses Gaskell's modified savings criterion and the three-optimal tour method to look for possible improvements. Two test problems are solved, a real-life one and a hypothetical one, although the author does not provide much input data or information on data provenance. Finally, a "formal solution procedure" is presented to allow decision makers to implement the method in real life hospitals and laboratories.

Back in 2004, Revere and Roberts set out to improve the laboratory courier system of a large multihospital system in a Texas metropolis. They purposefully stick to easily implementable solutions with readily available software such as Excel so that their approach may be used by hospital organizers. Data from 8 acute care hospitals as well as 11 healthcare clinics goes into the study, with a planning horizon of two weeks including weekends. The process involves four stages: assessment, mathematical modelling, system optimization, and staffing solutions. During the second stage, travel routes from the hospitals to the laboratory are determined using the traveling salesman model from QSB. Travel times are estimated with the help of MapQuest. The objective is to minimize the traveling time considering returns to the laboratory and a two-hour-limit on the transportation of specimens. Gantt Charts are them built in Microsoft Project to adjust start- and end times as well as employee shifts. Revere and Roberts (2004A) achieve a 16.4% cost reduction in addition to numerous other advantages (easily adaptable schedules, outsourcing avoided, etc.).

Revere published two articles that year. The title and the publication environment of Revere (2004B) differ from Revere and Roberts (2004A). In form and content, however, there is negligibly little difference between the two texts. In order not to distort the outcome, both articles will be counted as one (Revere 2004) for most of the analysis part of this thesis. The reasons for this as well as the publication of this second article this will be explored in chapter 5.1.

Ren et al. (2010) present a multi-shift VRP with overtime, inspired by a large HC organization in southern California. The company transports medical samples and lab-specimens, but also documents, mail and X-rays from medical buildings and a central laboratory. The authors acknowledge that "most medical samples are perishable and must be processed within a certain period, so the demands have time windows" (Ren et al. 2010:1987), but that is the extent to which perishability is featured in this work. The focus lies on overtime and shifts. Vehicles can work overtime to cover demand close to the beginning or end of their shift, as long as the overtime limit is not reached. Unmet demand is outsourced to taxi companies. Although demand uncertainty is addressed in theory, for the purpose of the MIP, demand is assumed to be known. The objective is to minimize the overall transportation costs, composed of four cost factors (travel, overtime, regular driver usage, and taxi). The authors create an initial solution with the help of an insertion-based heuristic and improve it using tabu search. Around these approaches, they build a shift independent and a shift dependent algorithm. The planning horizon stretches over multiple days, and each 24-hour-period is separated into three shifts. These three shifts are consecutive, which is one of the main differences to the work of Zangeneh-Khamooshi et al. (2013), who allow shifts with variable schedules.

Zangeneh-Khamooshi et al., in 2013, first presented VeRSA (Vehicle Routing and Scheduling Algorithm), which was then expanded in later problems (Zabinsky et al. 2020, 2021; Petronaiu et al. 2021). The research by Zangeneh-Khamooshi et al. (2013) is inspired by the University of Washington Medical Center (UWMC), Department of Laboratory Medicine. They call their new problem the VRPWCT (vehicle routing problem with windows and cycle times) and strive to minimize the turn-around-time of the samples, that is "the difference between the time that the specimen is available and the time that the test result is ready" (Zangeneh-Khamooshi et al. 2013:1215). Their objective is to minimize the time needed to produce test results. Shifts are variable; they can begin during any time of the day to allow for more flexibility but are associated with a maximum duration. For their solution method, the authors combine an indexing rule, which helps prioritization among samples, with a branch-and-bound algorithm. As mentioned previously, they later built on this research to improve VeRSA.

Zabinsky et al. (2020) aim to minimize the completion time of the collection of medical samples, which they liken to minimizing the make span in classic scheduling problems. Drivers may drop off specimens at the laboratory during their routes and start their shifts at any moment within a 24-hour-period. They build of VeRSA, describing their extension as follows: "The approach used in Zangeneh-Khamooshi et al. (2013) combines the indexing rule with a standard LP relaxation to generate bounds and provide a *feasible* solution to a *single*-trip, multi-shift vehicle routing problem, whereas here, in this paper, we obtain the *optimal* solution to a *multi*-trip, multi-shift vehicle routing problem" (Zabinsky et al. 2020:540). The efficiency of the algorithm in tested over 3 small and 3 large sample problems with up to 57 clinics and 12 vehicles, based on real data from the University of Washington Medical Center. They also compare their approach to other methods. Although VeRSA is not per se dynamic, it finds good solutions very quickly. This allows for the algorithm to run several times a day, whenever new information (cancellations, additional pickups) is made available.

A rather untypical approach is presented by Yücel et al. (2013A), who respond to the urgency of sample analysis not through minimization of travel or cycle time, but by increasing the efficiency of the entire collection and processing stages. In contrast to similar problems, they include the laboratory's processing rate and balance collection times accordingly, so that the samples do not all arrive at once and bottlenecks during analysis are avoided. The resulting problem is called the Collection for Processing Problem (CfPP). The authors sum up their special problem characteristics as follows: "CfPP is a routing problem with multiple tours, accumulation over time, a finite processing capacity, a processing deadline, and multiple prioritized objectives" (Yücel et al. 2013A:504). Their two hierarchical objectives are: (1) maximizing the number of specimens processed, which depends on both the accumulation and the processing rate, and (2) reducing transportation costs. The first objective outweighs the second in terms of importance as the consequences of unprocessed specimens may be serious (Yücel et al. 2013A:504; see also chapter 4.2.2). Upper and lower bounds as well as heuristic solution methods are used to solve the problem. Despite or due to their problem's complexity, their solutions are limited to one vehicle and 10-18 testing nodes.

Later, Yücel et al. (2013B) extended their problem to a multi-vehicle version, which they called mCfPP. Their focus shifts to a make span objective, as they find that "minimizing the makespan is sufficient to optimize the other objectives as well" (Yücel et al. 2013B:1629), the other objectives being the minimization of idle time and the maximization of the processed amount by a certain due date. To gain insights into the minimum fleet size and optimal make span under different workload settings, the authors analyse two special cases of the problem (single site, multi-vehicle and single site, single vehicle). Based on these experiments, they develop a heuristic called cluster-schedule (CS) based on a polynomial-time, constant-factor approximation algorithm in two phases (clustering and scheduling).

Grasas et al. (2014) define their Blood Sample Collection Problem (BSCP) as a Capacitated Time-Constrained Open Vehicle Routing Problem (CTCOVRP), with both the capacity and the timing-constraint relating to the blood samples: The capacity is limited to the number of thermal containers that a vehicle can transport, and the maximum route duration is set to two hours, which the authors name as the time that "blood samples can last without deterioration" (Grasas et al. 2014:2). Inspired by a real problem faced by the laboratory Catlab, located in the Vallès Occidental region in Spain, the goal is to minimize the number of vehicles. Grasas et a. (2014) solve the problem heuristically using a Biased Random Key Genetic Algorithm (BRKGA), and run experiments for up to 43 centres. At the time of publication, the authors only knew of one similar paper, which was excluded from this review for language reasons.[15]

In 2016, Anaya-Arenas et al. first presented their biomedical sample transportation problem (BSTP). Their research is prompted by the supply chain optimization project *Optilab*, the Quebec government's attempt at reengineering of the health supply chain. This first stage of the *Optilab* project lays the groundwork for future publications (Naji-Azimi et al. 2016; Anaya-Arenas et al. 2021). Biological samples need to be transported from the sample collection centres (SCCs; clients) to a central laboratory (depot). The BSTP is based on the multi-trip vehicle routing problem with time windows, but they consider particular constraints due to the perishable nature of the samples, most prominently the samples' maximum transportation time. The authors point out that compared to the related blood collection problem, specifically citing Dörner et al. (2008), their samples' deterioration process does not begin right after they are obtained, but when the samples are collected by the vehicle; in other words, they assume that samples can be stored under relatively stable conditions in the SCCs (Anaya-Arenas 2016:603). To solve the problem, they present two alternative mathematical formulations: "The

[15]Belles-Sampera B, Ventura-Pedretb S, Gomis-Castellvi M, March-Amengualc JM: Rutas de recogida de muestras y error en el proceso analítico. Revista del Laboratorio Clínico 2012, 5:10–17. (Citation left unchanged.)

first one deals explicitly with the multiple transportation requests at each SCC, while the second one duplicates the SCC, such as each node only has one transportation request" (Anaya-Arenas 2016:605). They use a two-stage heuristic approach with two construction and one improvement procedure. Since the transportation is done by external carriers, the distance travelled corresponds directly to the costs. Their objective is the minimization of travelling distance, which in later publications is changed to the minimization of travelling time (Naji-Azimi et al. 2016; Anaya-Arenas et al. 2021).

Naji-Azimi et al. (2016) tackle what they call vehicle routing problem with desynchronized arrivals at the depot (VRP-DA). This research is prompted by the *Optilab* project, same as Anaya-Arenas et al. (2016), whose paper they build on. After their predecessors centralized and better coordinated the transportation network to reduce costs, Naji-Azimi et al. (2016) concentrate on the bottleneck that is the arrival of samples at the laboratory: Upon arrival at the laboratory, the biomedical samples need to be registered for tracking purposes. As this process takes time, they limit the maximum number of samples to arrive at the lab within a time period. Having the samples queue for too long between arriving at the lab and processing might exceed their limited lifespan. The objective shifts from minimizing the travel distance (Anaya Arenas et al. 2016) to minimizing the routes' total duration, with an added penalty factor when the maximum number of boxes per period is exceeded. Interestingly, they split the workday into different time periods, which neither of the papers by Anaya-Arenas et al. (2016, 2021) did. This is probably done to better spread the arrival of samples throughout the day.

Anaya-Arenas et al. (2021), building on their research from 2016, add flexibility and complexity to their biomedical sample transportation problem (BSTP): First, they include precedence constraints between the customer visits. Second, they consider flexible opening hours of the SCCs (tactical decision). Third, taking the limited lifetime of the samples into account, the most urgent sample in each route dictates the maximum transportation time. They develop an iterated local search (ILS) heuristic that is able to efficiently solve large instances. After an initialization stage, the ILS iterates between a "soft" adaptive diversification and a hard diversification stage. Small- and medium-sized instances can be solved to optimality within a short computational time. In total, they consider 38 instances based on real data from Quebec's laboratory network.

Over a series of publications, Elalouf et al. (2015, 2018, 2021) improve the structure of a three-echelon blood sample collection chain, including clinics, centrifuge centres and a centralized testing laboratory. Their efforts contribute to "an extensive research project supported by the Israel National Institute for Health Policy Research, and involving Israel's two largest Health Maintenance Organizations (HMOs)" (Elalouf et al. 2021:217). Since this blood is not meant for processing and redistribution, but rather for testing and diagnosing illnesses in patients, it is discarded after the test results have been obtained: "In contrast to the case of blood donations, there is no inventory planning process; samples are disposed of after testing" (Elalouf et al. 2018:196).

The first contribution to this project was published in 2015 by Elalouf et al. It is a facility location problem with the aim of determining how many centrifuge centres are needed to optimally support the blood sample collection chain. "The results showed that the number of centrifugation centers could be reduced from 29 to 26, and that doing so would yield annual savings of about $100 K" Elalouf et al. 2021:218). This paper is mentioned here for reasons of completeness, but not considered during the main analysis due to its lack of routing-scheduling aspects.

The paper Elalouf et al. published in 2018 is most similar to the others in this chapter. The aim of this classic routing-scheduling problem is to "determine the number of vehicles that should be used for sample delivery and to identify the optimal schedule for the pickup process" (Elalouf 2018:192). All samples must be delivered to the laboratory within a certain time after collection, which is limited by the laboratory's utilization rate. The objective function minimizes costs and includes a penalty for late delivery. As their solution technique, the authors develop an “advanced heuristic”, which is a combination of three algorithms, and compare it to a genetic algorithm. The heuristic’s main output are the vehicle fleet size and the quality of service, the later referring to the number of samples that arrive at the laboratory on time. Unpredictable circumstances that affect transportation time, such as traffic jams, are addressed in terms of a probability that deliveries might be late.

Later, Elalouf et al. (2021) added more complexity to their problem. They explain the main difference between their 2021 and their 2018 problem setting in the following quotation:

> *“Clalit’s blood sample supply chain, which is the system investigated here, is more complicated than that of Meuhedet. Specifically, in Meuhedet’s system, blood samples are centrifuged at the clinics where they are collected and are then sent to a centralized testing laboratory. Clalit’s blood sample supply chain includes an additional echelon: namely, centrifugation centers. Therefore, the task we address here (i.e., obtaining optimal (or near-optimal) vehicle fleet size while maintaining adequate service quality) is more complex than that investigated in [Elalouf et al. 2018].” (Elalouf et al. 2021:218f)*

Thus, different time limits are imposed on the resource: “Since blood coagulates, the samples must be centrifuged within a predefined time span (expiration time), usually no more than 2 h after the sample has been obtained” (Elalouf et al. 2021:218). In Elalouf et al. (2018), this constraint is relaxed because the centrifugation can be performed in the clinics where the blood is collected. Instead, in this earlier version of the problem, the testing “only” needs to be performed on the same day as the blood collection. The more complex problem from their 2021 paper is solved through a simulation-based approach.

The goal of Benini et al. (2022:1) is to “find a transportation plan minimizing the total traveled distance, in such a way that all samples are delivered within their lifetimes.” Each of the blood and biological samples has a specific lifetime, but in contrast to other publications, Benini et al. (2022) allow stabilization to prolong the samples’ lifetime. This operation is performed at centres called “spokes”. They can be visited several times, but each sample can be stabilized at most once. Extending the lifetime takes a certain service time, and samples that have been brought to the spokes can be picked up by a different vehicle. These transfers are only permitted for samples at the spoke centres, however. The authors present three versions of a MILP, all of which aim at minimizing the travelled distance. The main difference is that $MILP_1$ and $MILP_2$ use time indexed variables to deal with multiple visits ($MILP_2$ being smaller in size), while $MILP_3$ “employs standard routing variables and uses multiple copies of each spoke so that each copy can be visited at most once” (Benini et al. 2022:3). The first two versions prove more successful. Their solution technique, the Hybrid Adaptive Large Neighbourhood Search (H-ALNS), allows exploring infeasible solutions, too, and combines 13 different heuristics. It is tested over small and large instances based on real data from the Local Healthcare Authority of Bologna, Italy. They also evaluate batching policies to group the (sometimes more than 1000 daily) samples based on their lifetimes.

Malladi et al. (2022) address biological sample collection for Region Hovedstaden in Denmark as one of their two case studies. The aim of their Stochastic Fleet Size and Mix Problem (SFSMP) is to optimize the vehicle fleet mix using electric vehicles (pick up vans and bicycles). The strategic objective is cost minimization: To the operational cost over the entire planning horizon of 10.6 years (see chapter 5.1), the authors add the acquisition costs. Operational costs, in this case study, include minimizing costs for missed doctor visits as well as energy costs. The samples’ perishability is addressed through shift limitations (150 minutes) due to the assumption that the specimens degrade 3 hours after extraction. The vehicles also use climate control (vans) and climate boxes (bikes), and the authors study the effect of temperature on planning the fleet operations, both of which may affect the energy costs. Uncertainty relates to customer requests and ambient temperature. They propose a two-stage stochastic program. Their solution techniques consist in a heuristic variation of the Sample Average Approximation (SAA) and a state-of-the-art Adaptive Large Neighbourhood Search (ALNS) algorithm.

4.2.3.1 Specimen Collection in an Emergency Setting

Wang et al. (2015) wonder how to integrate random urgent demands into a delivery schedule, taking the medical specimens as an example. They model this Courier Delivery Problem (CDP) as a variant of the Multi-trip Vehicle Routing Problem (MVRP) with time windows, "with uncertainty in customer occurrence and urgency in customer demands" (Wang et al. 2015:38). The urgency is expressed through a drop-off deadline, which for normal requests is 2 hours and for urgent requests 1 hour after the earliest pick-up time.[16] This makes the problem by Wang et al. (2015) the most time-restricted of all papers analysed in this thesis. The uncertainty, meanwhile, is modelled through scenario-based stochastic programming with recourse. The authors present a MIP formulation with the objective of cost minimization, which is composed of the traveling cost, outsourcing cost, and route dissimilarity cost. Outsourcing costs occur if demand is unmet and therefore assumed to be outsourced to an external carrier (taxi). The dissimilarity refers to "the dissimilarity between the first stage solution and the recourse actions taken in each scenario, which aims to improve the service quality" (Wang et al. 2015:27). To solve the problem, they develop a heuristic based on insertion and tabu search. Experiments are then conducted on both generated and real data from a healthcare provider in Southern California.

In light of the recent COVID-19 pandemic, interest in the timely collection and testing of medical samples has risen. Tlili et al. (2022) take a look at the early response to the pandemic in Tunisia, when demand for medical personnel to perform at-home tests was high and resources were extremely scarce. They describe the protocol and triage phase used to schedule visits to patients in order of priority: Since it is impossible to test all suspected cases, each patient is given a score, and scores above a certain threshold are added to the ambulances' wait list. The objective of this problem is to maximize the scores of the patients visited during the one-day planning horizon. Additionally, hospitals where samples are tested have limited capacities in terms of available testing kits and staff working hours. These capacity constraints somewhat resemble the strategy of avoiding laboratory congestion (see Yücel et al. 2013, Ziya-Gorabi et al. 2022). Finally, a maximum time limit is set on the individual routes. This is presumably done to preserve the quality of the samples, although the authors do not mention their reasons behind their maximum route duration explicitly.[17] The entire collection process is depicted in Figure 2 (Tlili et al. 2022:4). This problem is based on the Multi-Origin–Destination Team Orienteering Problem (MODTOP) and solved using two variants of genetic algorithms: a Hybrid Genetic Algorithm combining the k-means along with the evolutionary operators and a Memetic Algorithm considering a local search. Several computational experiments are conducted, both on benchmark and real-case instances from the city of Tunis. The efficiency of the approach is further established by comparing it to five state-of-the-art methods, four of which are outperformed.

In their contagious disease testing problem (CDTP), Wolfinger et al (2023) tackle the problem of clarifying potential COVID-19 cases with a SARS-CoV-2 polymerase chain reaction (PCR)

[16] During experimentation on real data, the drop-off time limits are raised to 4 hours and 2 hours respectively.
[17] Only towards the end, the authors mention the daily working time of the ambulance driver (Tlili 2022:13), which may be another possible reason for setting a maximum route duration.

test. The swabs are collected and analysed in a laboratory. Somewhat like the blood (mobile) collection problem, specimens can be collected either in fixed test centres or by mobile test teams. However, they assume that the test centres are already built and the decision whether to open a centre can be made on a daily basis. In their literature review, Wolfinger et al. (2023:170f) focus mostly on the location routing aspect of their problem. They consider their own problem similar to the novel location-or-routing problem (LoRP), which is itself closely related to the location routing problem (LRP) and the covering location problem (CLP). Another related problem is the vehicle routing problem with intra-route facilities (VRP-IF). No literature related to the perishability aspects is cited. Perishability is expressed through the time-to-test and time-to-result limits:

"The time-to-test limit can be expressed in the form of a time window for each suspected case, within which the IDT [infection detection test] must take place. Suspected cases that are tested in test-centres must be scheduled accordingly and vehicles must adhere to these time windows when visiting a suspected case. Likewise, the time-to-result limit requires a scheduling of cases in laboratories." (Wolfinger et al. 2023:171)

Their objective is the minimization of the total cost, composed of opening test-centres and routing mobile test-teams (including fixed and variable costs). They propose a large neighbourhood search metaheuristic, wherein a good solution (first the initial solution, then the current best-known solution) is iteratively destroyed and repaired in different ways until a stopping criterion is reached. Two scenarios, one urban and one rural, were used for the computational study. In total, 200 problem instances in 3 size-categories were generated based on real data provided by the Austrian Red Cross.

4.2.3.2 Specimen Collection in Home Health Care

A seminal paper introducing specimen collection to home health care is that of Liu et al. (2013). Since it lacks the perishability aspect, it had to be excluded from the main analysis, but will be presented in chapter 6.2.1.

Haitam et al. (2021) work on a vehicle routing problem with time windows, synchronization, and priority. They receive data from the BioGuich laboratory in Témara, Morocco, which has added the service of taking and collecting samples from patients in their homes to limit their mobility since the outbreak of the COVID-19 pandemic. Blood and urine samples are collected from the patients' homes by mobile nurses. The priority of the sample depends on the nature of the requests. Ranked from lowest to highest, least priority is given to flexible times requests, followed fixed times requests and finally critical requests. About 30% of the total samples collected are considered critical, which means that they have a turnaround time of only 90 minutes. The laboratory tasks a specialized team with collecting these samples. The authors address topics of HHC, like nurse-to-patient assignments and continuity of care, or compliance with the work schedule of the nurses. Moreover, they provide a small overview of recent papers published on the VRP in HHC, categorized by their objectives (Tables I and II). Their own problem, meanwhile, is broken down into a daily routing problem and solved using a taboo search algorithm and a variable neighbourhood search algorithm. For testing, they form two groups of instances, one small and simple, the other based on real data provided by the BioGuich laboratory. Since only the second group considers critical samples, this is the one I will be focusing on for this thesis. Detailed information on the size and composition of the instances as well as the numerical results is provided in Tables IV through VII (Haitam et al. 2021:349f). Their real instance size is among the largest encountered in this thesis, with instances including up to 200 patients, 20 nurses and 5 collection points for samples. Their results helped the BioGuich laboratory to save "considerable time and increase the traceability of the samples collected, which improves the quality of the tests carried out" (Haitam 2021:350).

Entezari and Mahootchi (2021) study the home health care scheduling routing problem HHCSRP with numerous extensions: time windows for both patients and staff, including break-times; caregiver requirements with regards to patients' preferences (based, for example, on gender or language skills) as well as qualification level; continuity of care, but within a single day (instead of a multiperiod problem) for reasons of patient experience and information transfer; interdependence of services (simultaneous and precedence); and, finally, specific limitations related to blood sampling. Constraints 17-19 ensure that blood samples are brought to a virtual[18] blood node within a certain time window. The (single-)objective function is composed of five weighted performance measures: (1) total time travelled, (2) total tardiness of services provided to the patients, (3) total overtime of staff members, (4) continuity of care violations, and (5) violations of staff time windows. The solution method is based on a genetic algorithm that produces near-optimal solutions. For lack of real or benchmark examples, the method is tested over small- to large-sized generated instances.

Synchronization and precedence, continuity of care and (two types of) caregiver qualifications are also part of the HHCRSP by Shahnejat-Bushehri et al. (2021). One type of caregiver performs primary tasks, including the collection of biological samples. These caregivers start their tour at the depot, collect samples at the patients' houses and bring them to a laboratory within a specific time window, and return to the depot. The other category of caregiver, the auxiliary nurse, also starts their tour at the depot, where they may collect medication for patients or receive updates on their status. After visiting the patients, they return directly to said depot, without going to the lab. A day is divided into four periods, and patients can be visited at most twice per period. Shahnejat-Bushehri et al. (2021) cope with uncertainty by choosing a robust optimization approach. Stochastic programming is ruled out due to a lack of historical data that would permit them to estimate the distribution of the parameters. They apply 3 meta-heuristic algorithms: simulated annealing, genetic algorithm, and memetic algorithm, the last of which is shown to outperform the others for large problem instances. Generated instances in three problem sizes (small, medium, large; up to 56 instances with a size of 100 patients) are used for testing. Finally, the authors also propose a dynamic extension to the problem.

A recent, relevant work in the context of HHC is that of Ziya-Gorabi et al. (2022). The authors present a tri-objective location-allocation-routing model. Their three objectives are: 1. cost minimization, including location, transportation, allocation, and human resource costs; 2. minimization of CO_2 emissions; 3. minimization of mean waiting time in the formed queue. This last objective function is of most interest to this thesis not just because of its novelty, but because it aims at minimizing the congestion in HHC centres that would delay the analysis of laboratory samples. In this, the works of Ziya-Gorabi et al. (2022) somewhat resemble the papers by Yücel (2013A, B) and Naji-Azimi (2016) who also consider the arrival rate of specimens in the laboratory a bottleneck. Ziya-Gorabi et al. (2022) follow the M/M/C queue model to tackle this problem. Other than that, patients receive medicines and medical supplies from HHC centres and send return medicines, medical waste and laboratory samples back. Therefore, and because of their environmental objective, the authors also reference the green pharmaceutical supply chain (PSC). Still, there seem to be no particular timing constraints associated with medication, other than the general time windows to serve patients. The allocation-aspect refers to assigning patients to HHC centres regarding their disease type and licenses to serve that disease. The authors apply LP-metric and goal attainment (GA) methods to balance their three objective functions, and they rank the proposed methods by simple additive weighting (SAW) method. For testing, three randomly generated test problems with different sized (small,

[18]In this work, the authors consider four so-called virtual nodes that are not related to patients: the starting- and the end-node, a blood-node where samples need to be dropped off, and a break node for staff.

medium) were used. Overall, the LP-metric method performed better. A fuzzy model is presented to address uncertainty.

4.3. Drugs and Pharmaceuticals

4.3.1 Drugs and Pharmaceuticals: Background and Relevance

The importance of timely and safe delivery of medication is indisputable (e.g., Aydınalp and Özgen 2022:1, Chen et al. 2021:3, Wu et al. 2022:654). Demand for drugs is on the rise, and so pharmaceutics is one of the fastest growing sectors (Bouziyane et al. 2020:299). This growth is fuelled by the surge of the world population in general, including and partly due to the aging of the population which, as a consequence, sees an upsurge of chronic diseases, "such as diabetes, heart failure, Alzheimer's disease, depression, cancer, etc." (Wu et al. 2022:654). Simultaneously, the pressure on pharmaceutical enterprises and distributors is increasing, accelerated by fierce competition and ever higher customer expectations (Ibd.). Drug manufacturers and logistics companies struggle with balancing low delivery costs and quick response to customer needs (Wu et al. 2022:680). Among the features that differentiate the pharmaceutical supply chain from a typical one, Aydınalp and Özgen (2022:1-2, my emphasis) write: "One of the most significant aspects of this supply chain is the delivery of medicines **in a reasonable time, in the right amount and to the right location**. In this situation, proper vehicle routing for the transportation of products becomes very critical." In the following, I would like to explore each of these three aspects.

1. In a reasonable time: Some medications have an extremely short shelf life (e.g., cancer medication, see chapter 4.4), others are less perishable. The speed at which a medicine deteriorates should be one of the factors that influence the urgency of its delivery. Apart from the expiration date, other reasons for the timely delivery of medication are the medical urgency of patients waiting for the drug (Chen et al. 2021:4), but also competitive pressure among pharmaceutical companies (see above), and special delivery requirements such as cold chains, which will be explored later in this chapter. Moreover, as will be shown through aspects 2 and 3, pharmacies frequently require dynamic ordering policies as well as just in time delivery, so that patients may pick up their medication on the same or by the next day (Bouziyane et al. 2020:305, De Magalhães and De Sousa 2006:178).

2. In the right amount: The reason why pharmacies place several orders during the working day is a combination of the aforementioned high demand and small storage spaces: "In densely populated urban areas, the shop area of pharmacies is getting smaller and smaller, the number of items is increasing" (De Magalhães and De Sousa 2006:178). Bouziyane et al. (2020:299f) described the same situation as recently as 2020. As pharmacies do not have a large surface area for storing large quantities of drugs, they push the stocking activity to the distributors. Other factors in this decision are "diversified and fluctuations in drug demand [and] keeping low inventory to avoid drug expiration" (Wu et al. 2022:654). All of this contributes to the practice of placing multiple orders during a single day, some of them in small quantities.

3. To the right location: Geography and infrastructure issues feature more in these types of problems than others. The examples mentioned in argument 2 concern urban areas with sufficiently reliable infrastructure to permit a just in time ordering policy. The issue is much larger than this, however. El Midaoui et al. (2020, 2021) tackle the problem of supplying hospitals in Morocco with drugs, while Petronaiu et al. (2021) and Zabinsky et al. (2021) are concerned with pharmaceutical (mostly vaccine) distribution in Mozambique. In their cases, locality is hugely important since the accessibility of healthcare institutions, especially in rural regions of these two countries, takes a toll on logistics operations. El Midaoui et al. (2020:1143;1145)

point out how infrastructural issues, like pharmacies being too few and/or located too far apart, can negatively affect distribution practices. They argue that in Morocco, due to political reasons, pharmacies (warehouses) and healthcare institutions were built in some regions rather than others, which leads to an imbalance between demand and supply. In those cases, planning practices may profit immensely from allowing other pharmacies to step in and supply healthcare institutions further apart when their local pharmacy cannot accommodate urgent demand. This is the reason why their routing-scheduling problem is preceded by a location routing problem, where locations for new pharmacies are proposed. Among the challenges identified by Petronaiu et al. (2021:2334) are, in particular, "inadequate vehicles, limited cold storage, road availability, and variable weather conditions." All of these are also true in other localities, one might argue, but in their context of hurricane-struck Mozambique, damaged streets and bridges liable to collapse pose an enormous threat not just to the delivery vehicles and their supply, but also to healthcare personnel driving said vehicle. It seems that the transportation of the medication itself is less of a challenge than the post-disaster setting. Moreover, they mention political and administrative complications like increased demand uncertainty "in poor neighborhoods and low- and middle-income countries […] due to lack of accurate population estimates" (Petronaiu et al. 2021: 2336). This is primarily a problem faced by humanitarian logistics rather than the private sector, where information about supply and demand may not be perfect, but much more accurate (Petronaiu et al. 2021:2337). For more information on the emergency setting and humanitarian logistics, see chapter 6.2.2. Meanwhile, De Magalhães and De Sousa (2006) as well as Wu et al. (2022) take a more neutral approach to locality (apart from the challenges presented in argument 2). While they test their method on data from Portugal and China respectively, the local infrastructure does not greatly affect their model. However, Wu et al. (2022:656f, my emphasis) also mention location aspects: "Pharmaceutical distribution has the characteristics of **large and scattered distribution points**, small volume and light weight of medical goods." Borumand and Beheshtinia (2018:1402) coordinate orders across a set of suppliers scattered over different geographical zones.

Until this point, I have largely used the terms "drugs", "pharmaceuticals" and "medicines", which are very generic terms for all kinds of medication. The reason I chose not to be more specific is because neither are the reference papers: On rare occasions, authors specifically mention that different types of products are featured in their approach (Borumand and Beheshtinia 2018:1412), but generally, they use these three terms to describe their products. There is one exception, however. A small cluster containing 4 papers formed around vaccines (see chapter 4.3.3.2), two of which focus specifically on the COVID-19 vaccine (Andoh and Yu 2022, Secundo et al. 2022).

Without a doubt, the recent pandemic has stimulated the development of new vaccines. Once a drug is available, the production, distribution and administration processes play an integral role on increasing the vaccination coverage rate as fast as possible, and therefore, these research topics have also seen a surge in popularity recently (Secundo 2022:11, Zabinsky et al. 2021:3). Efficient vaccine distribution was considered an important measure to slow down the spread of the pandemic (Lin et al. 2022:14). Right after the COVID-19 vaccine was developed, the number of available vaccines was scarce, and high supply uncertainty was one of the biggest challenges for planners:

> *"This uncertainty yields bullwhip effects and delays the downstream distribution to the local vaccination centers. Because of this reason, the planning and scheduling of the local vaccination are drastically affected […] and a large number of vaccines are wasted due to ineffective vaccination planning. A recent report by Mahase (2020) shows that many GPs in the UK are frustrated with the logistics problem and*

delayed delivery of the Pfizer-BioNTech'sCOVID-19 vaccines, which result in a large number of booking cancellations and rescheduling of the vaccination." (Andoh and Yu 2022:2)

Once out of the refrigerator, vaccines must be injected within a certain time limit, lest the dosage be wasted (Secundo 2022:11). Temperature management is more crucial in the case of vaccines than for any other medical product presented in this thesis: "[H]ealth products, especially vaccines, are most at risk of temperature excursions during transit; having products packed well and delivered efficiently to health facilities reduces risk to vaccines and maintains their potency" (Zabinsky et al 2021:3). Heat exposure must be avoided, but at the same time, vaccines are at the risk of freezing. In fact, the World Health Organization as well as vaccine manufacturers recommend that vaccines, save the oral polio vaccination, are stored and transported at a constant temperature between 2° and 8° Celsius to maintain their potency (Yauba et al. 2017:1). As demonstrated by Yauba et al. (2017), this recommendation is hardly ever complied with in reality. Temperature requirements are "important for all vaccines, but especially so for COVID-19 vaccines due to limited supply, high demand, and the special ultra-cold chain requirements for some COVID-19 vaccines" (Zabinsky et al 2021:3). By this they mean that Pfizer-BioNTech's COVID-19 vaccine must be kept at −70°C (Andoh and Yu 2022:2), which requires specialized equipment. Andoh and Yu (2022:2) bring forth another point which is rarely raised, namely the "large energy consumption and environmental impacts to maintain the temperature requirement during transportation and storage." They consider the balancing of economic, environmental, and societal[19] sustainability the most significant challenge for vaccine distribution (Ibd.).

One paper differs considerably from the rest, for several reasons. Chen et al. (2021) introduce two concepts no other publications in this chapter address: automated medicine delivery (AMD) and intra-hospital transportation. The Telelift AMD system they describe can "deliver medicines and other materials to patients. This system can mitigate the scarcity of medical staff, allow the staff to focus on core patient care tasks, and reduce disease contamination in hospitals" (Chen et al. 2021:1). These are invaluable benefits that make further exploration of this delivery method worthwhile, even though it comes with new and different logistical challenges. Moreover, they claim that "internal transportation in the hospitals has not received much attention" (Chen et al. 2021:3), which is true at least for the reference papers I found. Overall, their medicine production and delivery processes closely resemble that of cancer medication (compare: Chen et al. 2021:5f and chapter 4.4 of this thesis). I will elaborate on this observation in chapter 6.1.2.

4.3.2 Drugs and Pharmaceuticals – Production and Delivery: Problem Description

There is not "one" routing-scheduling problem for the pharmaceutical supply chain. The problem framework varies more than for the other product types. From humanitarian actions in disaster-struck regions to highly competitive urban settings, the situational challenges appear more relevant than the product-related ones except for two specific, very fragile product types which are vaccines and cancer medication. Especially the emergency setting (supply uncertainty, risk penalties, urgent requests) and competitive requirements (dynamic demands) are featured more in drug transportation problems than in other clusters.

[19]Societal sustainability in this case refers to responsible distribution and fair allocation of vaccines (Andoh and Yu 2022:2).

Like other clusters, all problems aim at optimizing the transportation and, sometimes, production or administration of medical products, in this case drugs. Apart from a single paper, authors define their problems as a VRP of some sort, with varying extensions and priorities: Andoh and Yu (2022) as well as Petronaiu et al. (2021) speak of a capacitated vehicle routing problem (CVRP), Aydınalp and Özgen (2022) formulate their problem as a VRPTW and Bouziyane et al. (2020) as a VRPSTW (vehicle routing problem with soft time windows), El Midaoui (2020, 2021) present a MDVRP (multi depot), Wu et al. (2022) a heterogeneous fleet VRP (HFVRP) and De Magalhães and De Sousa (2006) a dynamic VRP. The one exception to this rule is the publication by Chen et al. (2021), who develop a nested queuing network for their processing and delivery subsystems, thus awarding equal importance to optimizing production and transportation. As mentioned previously, their approach resembles those on cancer medication and will not be granted much attention in this current chapter.

As these VRP-varieties suggest, the cluster on pharmaceutical delivery can be subdivided into four categories: While most papers focus on just the delivery of the medicines (e.g., Aydınalp and Özgen 2022, Petronaiu et al. 2021, Wu et al. 2022, etc.), some take the production stage into account (Borumand and Beheshtinia 2018, Chen 2021), one combines delivery and administration (Secundo et al. 2022), and others address a location routing problem before they form routes (El Midaoui 2020, 2021). The papers considering production or administration are similar in that all three consider the minimization of make span (or tardiness), which are usually associated with production scheduling problems. Other popular objectives are the minimization of costs (e.g., Andoh and Yu 2022, Aydınalp and Özgen 2022, etc.) or delivery time (Bouziyane et al. 2020, Petronaiu et al. 2021).

In the VRPs, the depot is usually a pharmaceutical producer or distributor, and the clients are mostly healthcare institutions (hospitals, vaccination centres) rather than individual patients. Among the exceptions is the paper of Secundo et al. (2022), where, similar to the HHCP, patients are visited in their homes to receive their vaccinations. They mention a depot, but do not clarify which type of facility dispatches the vehicles. In the following citation, Wu et al. (2022:654) describe the particularities of this particular problem type, including the constraints that derive from these characteristics:

> *"Due to the unique features of the pharmaceutical logistics, the VRP for Pharmaceuticals Delivery is different from regular vehicle routing problems in several aspects (Kramer et al., 2019): First, medical products have the characteristics of small* ***size, light weight, and high value*** *in terms of physical form. The candidate vehicles need to have different size with varying carry capacity. Secondly, in terms of market chain, some medicines have* ***short shelf life, fast expiry dates, and tight time requirements*** *for user supplies. Thus, delivery time window become a critical constraint. Thirdly, in terms of circulation, the physical characteristics of some products demand special requirements for* ***storage, packaging, and delivery****, thus, the condition to deliver products with similar characteristics need to be considered. All these conditions put forward restricted requirements on the pharmaceutical logistics." (Wu et al. 2022:654, my emphasis)*

With regards to the first observation, all reference papers featured constraints on the vehicle capacity. The one exception, again, are Secundo et al. (2022), who remain unclear in this regard and, thus, probably assume unlimited capacity. The vehicles appear to be homogenous in most problems, and El Midaoui et al. (2020) even specify that all of their vehicles are identical in terms of capacity and shape. The exceptions are Borumand and Beheshtinia (2018) and De Magalhães and De Sousa (2006), whose vehicles have different capacities; Zabinsky et al. (2021) and Petronaiu et al. (2021), who consider vehicle conditions in terms of risk; Andoh and Yu (2022) who use heterogeneous vehicles in their simulation and base their fleet composition on the vehicles' capacities and maximum travel distances within the time window; and Wu et al. (2022:654) who write: "[B]ecause the demand for pharmaceutical products fluctuates greatly, fleet vehicles are not always entirety [sic!] used in their delivery. There is a problem of vehicle selection in scheduling plans," since they have heterogeneous vehicles in their fleet and need to choose which ones to dispatch.

Another way of dealing with fluctuating demands and orders that arrive during the planning horizon is dynamic planning. Bouziyane et al. (2020:300) ascribe the need for this approach to the characteristics of the sector: "In view of the growing demand for pharmaceutical products, and to respond to repetitive daily orders from pharmacies, this research addresses the need to propose a method for dynamic planning, which takes the characteristic of this crucial sector [into account]". Dynamic approaches will be discussed in chapter 5.6.

Second, all papers either minimize transportation time or include time windows, except El Midaoui (2020, 2021)[20] and Andoh and Yu (2022), who consider timing restrictions in their simulation, but not the mathematical model. Their papers take an indirect approach to product perishability, as will be explained in chapter 5.8. All other papers feature objectives or constraints with timing requirements usually associated with the products' shelf lives.

Third, perishability is less straightforward than for other products: in addition to the limited lifetime, product fragility is sometimes expressed through very careful, temperature-regulated, risk-avoiding transportation methods. Therefore, several papers address the need for special storage or transportation. De Magalhães and De Sousa (2006) mention storage in cold or psychotropic areas. Andoh and Yu (2022) elaborate on cold chain requirements. Petronaiu et al. (2021) differentiate between products requiring cold storage/transportation and "dry" products without special requirement. Secundo et al. (2022) address the cold supply chain by stating that their vaccines may not stay out of the refrigerator for too long before being administered, which limits their transportation and administration ("processing") times. Borumand and Beheshtinia (2018) consider 50 different product types, whereas Wu et al. (2022) assume that all products can be transported together, which acknowledges the differences between the products while simultaneously stating that they are not significant enough to justify special transportation. Another way to tackle special transportation needs is through considering the risk of vial breakage associated with the condition of the roads and the vehicles:

> *"Different factors can lead to vial wastage in vaccine distribution. In addition to refrigeration or cold boxes keeping the vaccines within a proper temperature range, closed vial wastage may be due to breakage of vials (Hanson et al., 2017). We include the risk of breakage of vials due to poor road condition or poor vehicle condition with a penalty parameter." Petronaiu et al (2021:2339)*

Risk penalties are repeatedly featured among the objectives in vaccine distribution problems (Secundo et al. 2022, Petronaiu et al. 2021). In the work of Secundo et al. (2022), however, it refers to the vaccine expiration risk. Moreover, they also include uncertainty and address the pandemic. The tendency to tackle uncertainty in the pharmaceutical supply chain, at least in the appropriate settings, has been mentioned at the beginning of this chapter. In the following section, the papers will be presented individually.

[20] The authors are unclear in their terminology. Their objective is the minimization of distance, which is equal to the minimization of cost, but at one point, they write: "the main function in MDVRP is to optimize the delivery time and decrease spending cost" (El Midaoui et al. 2020:1150).

4.3.3 Drugs and Pharmaceuticals: Presentation of the Literature

4.3.3.1 Drugs (General)

De Magalhães and De Sousa (2006) are among the earliest works on the pharmaceutical distribution problem. Based on the case study of a distributor of pharmaceutical goods in Portugal, the authors start out by describing the company's ordering, picking and delivery process. They point out product-specific characteristics like storage in cold or psychotropic areas that are, unfortunately, not accounted for in their solution approach. They model their problem as a dynamic VRP, wherein pharmacies within a certain area receive several small deliveries from a central depot, and orders arrive during the day. The authors deal with dynamic demand by designing an algorithm that can be run several times during the planning period. A 4-step heuristic is proposed: first, pharmacies are clustered, second, routes are constructed, third, a route is chosen, and forth, the route is improved. Operators may decide to postpone some deliveries to wait for more orders to arrive. The goal is to reduce lead-times without increasing the costs. The algorithm is then evaluated by simulating a week's worth of operations. In comparison to the manual procedure used at that time by the real-world distributor, the authors observe improvements with regards to delivery times as well as non-tangible benefits, such as better information availability and increased flexibility for the operators.

In their integrated vehicle routing and production scheduling problem, Borumand and Beheshtinia (2018) consider five objectives function, including the minimization of (1) the total delivery tardiness, (2) the production cost, (3) the emission by suppliers and (4) the emission by vehicles as well as (5) the maximization of the production quality. In their solution method, called GA-VIKOR, they combine a genetic algorithm (GA) with the multi-criteria decision making (MCDM) technique VIKOR. Numerical experiments are conducted on real and generated data: The data for the real-life case study is collected over three weeks from an Iranian pharmaceutical distribution company. One main company receives 50 different types of medication in a total of 122 orders from 12 suppliers and 6 vehicles with different capacities to collect them. The goal is to find the best production and delivery sequence. In several generated problems with different sizes, the method is then compared to similar algorithms and exact solutions to prove its efficiency.

Bouziyane et al. (2020) also present a multi-objective optimization problem (MOP). Their *Disrupted Vehicle Routing Problem with Soft Time Windows* aims at simultaneously minimizing the total travel time and the total time delay considering both scheduled and unexpected customers. For their solution method, the authors combine a genetic algorithm to improve the initial population (step 1) with methods of neighbourhood search (VNS; step 2) and, finally, an improved multiobjective local search (IMOLS) procedure (objectivewise local search) for each objective (step 3). They use the Pareto approach to find solutions along the Pareto front. This approach is then tested on a small set of randomly generated instances. What makes this problem interesting is that the authors account for disruptions caused by new orders that pharmacies place during the working day. "Given the specificity of the pharmaceutical sector, re-optimization is not practical for this case," Bouziyane et al. (2020:305) argue, "so, in this work we propose an effective method to find the original optimal solution and we use information of this plan to insert new requests by a local search method, in order to ensure rapid response to pharmacies." The authors observe that, since these dynamic customers are served as soon as possible, their delays are smaller than those of static customers.

El Midaoui et al. (2020) examine the drug-supply situation of Moroccan hospitals. First, they elaborate on the importance of medication logistics in hospitals, especially in terms of costs, patient satisfaction and service quality. In their paper, healthcare facilities receive their pharmaceutical deliveries from either regional pharmacies or directly from the central depot. This multi-depot aspect adds complexity to their problem, which is why they concentrate on clustering first. In this step, they take the hospital bed capacity (HBC) per region into consideration. Second, a genetic algorithm (GA) is used to generate the routes, consisting of a sequence of hospitals with the option to revisit the depot for refills. Healthcare facilities may only be visited once by the vehicles. The objective of this MDVRP is the minimization of cost and distance (El Midaoui et al. 2020:1146) or delivery time (El Midaoui et al. 2020:1150).

In 2021, El Midaoui et al. published a second paper wherein the information from the 2020 paper is presented in a more condensed way. However, no new characteristics or data sets were added, and the problem was not expanded.

The paper by Chen et al. (2021) uses a Telelift-based automated medicine delivery (AMD) system to improve intra-hospital medicine transportation. Their model combines medicine preparation and delivery: medication is first produced in a hospital's own pharmacy and the distributed to the different departments. To solve the model, the authors propose "[t]wo nested queuing models [that] captur[e] the stochastic interactions among demand, the pharmacy and transport," and they "adopt the two-moment approximation method to solve the nested queuing model" (Chen et al. 2021:18). Simulation is used to validate these approaches. Compared to the other texts in this chapter, this one most resembles the problems on cancer medication. The paper by Lee et al. (2014) is even mentioned in the literature review. The authors analyse how the number of vehicles and of pharmacists impact the throughput time. Moreover, they consider both normal and peak demand and compare two different vehicle assignment policies (shared and dedicated).

The problem by Aydınalp and Özgen (2022) most resembles the standard routing-scheduling problem. Although they acknowledge that pharmaceutical products have limited shelf lives, they address them in their problem formulation only indirectly. Their objective function minimizes costs, but they do impose time windows and limit the maximum route length. Small problems are solved optimally with GUROBI® solver, while larger problems are tackled through simulated annealing (SA) and an adaptive large neighbourhood search (ALNS). These methods are then tested on a case study, the real-life data for which was provided by a pharmaceutical company in Turkey. As for their contribution, they state that "to the best of our knowledge, for the first time, the ALNS algorithm used for VRPTW in pharmaceutical supply chain network design" (Aydınalp and Özgen 2022:13), and indeed, among my reference papers, there is no other paper on the PSC published before 2022 that uses an ALNS (see also: chapter 5.4).

In their multi-type vehicle assignment and route optimization model, Wu et al. (2022:655) consider what they call "the unique characteristics of pharmaceutical logistics": While they also address special storage- and delivery-requirements like temperature and humidity control, for their model, they take a distribution time limit and the vehicles' carrying capacity into account. Their objective is to minimize the (variable and fixed) vehicle costs, and they address the perishability of the medical product by imposing a maximum delivery time constraint. The authors develop a Hybrid Particle Swarm Intelligence Algorithm that makes use of mutation and crossover operators as well as 2-opt local search strategy to deliver near-optimal solution in a short time. A vehicle assignment principle based on cost network and Dijkstra's algorithm is also proposed to better balance the distribution time limit and the high loading rate. To prove their method's efficiency, they conduct extensive experiments, first by comparing their method to two intelligence-based heuristics; then by comparing their results to benchmark problems from the literature; and finally on a real-world case-study. The data for the real-world problem is provided by a pharmaceutical logistics company in Tianjin, China, with 363 customers, 3 different types of vehicles and different drug needs for customers.

4.3.3.2 Vaccines

VeRSA, the algorithm developed by Zabinsky et al. (2020) for the purpose of specimen collection (see chapter 4.2.3), was later adapted by Petronaiu et al. (2021) and Zabinsky et al. (2021): “Instead of using a commercial solver, a new solver, called vehicle routing and scheduling algorithm (VeRSA) (Zabinsky et al., 2020), was tailored to fit the considerations of vaccine distribution” (Petronaiu et al. 2021:2336). Both papers by Zabinsky et al. (2021) and Petronaiu et al. (2021) centre on the same Route Optimization Tool (RoOT) for the delivery of temperature-sensitive healthcare products like vaccines. The goal is to provide an easy-to-use planning tool for emergency situations, particularly in low- and middle-income countries: It was developed in cooperation with the government of Mozambique and tested with information from Mozambican provinces. Within 2 minutes, good solutions for up to 50 healthcare facilities and 5 vehicles are produced, which allows for fast re-calculating in case of disasters. The algorithm accounts for road conditions that could pose transportation and storage risks to medication requiring cold chain distribution, and vehicles or facilities may quickly be disqualified if damaged. Many different medications can be transported. For reasons of simplicity, however, they are classified as refrigerated or non-refrigerated products. The two objectives, (1) the minimization of transit time and (2) the risk penalties for using vehicles or roads that are not in good condition, can be balanced using a weight. Alternatively, users are free to optimize only one of both objectives. Costs do not feature in their main function and are only calculated after the routes have been built. The input- and output-data are written in Microsoft Excel files, which allows logisticians with little training to quickly adapt to new circumstances, with the added benefits of (typing) error reduction and data harmonization through drop-down menus. Yet, this simple mode of input offers some downsides as well: Data needs to be complete, distances between healthcare facilities must be entered manually by the personnel, and routes cannot be visualized via a mapping tool. At this point in time, the tool is limited to single day trips which does not correspond to the real-life situation, but a workaround exists. RoOT is open-access and readily available via GitHub.

The main difference between the texts by Petronaiu (2021) and Zabinsky (2021), who both worked on the same project, is this: The paper by Petronaiu et al. (2021) focuses more on the mathematics behind the problem, that is the vehicle routing and scheduling problem, the mathematical model, the solution approach and the numerical results from testing. Zabinsky et al. (2021) are more concerned with the software faced by the user, that is, the Excel sheets and their various input and output values.

Prompted by the COVID-19 pandemic, Andoh and Yu (2022) look at sustainable last-mile cold chain logistics operations of COVID-19 vaccines in Norway. Due to the high supply uncertainties during the early stages of vaccination, cold chain requirements and other practical challenges such as timeliness of vaccine delivery, they consider theirs a very complex short-term planning problem. They develop a two-stage decision-support approach, composed of route optimization and advanced simulation (combining discrete event simulation and Monte Carlo simulation), which is then tested on a real-world case study. The data represents Inland County, Norway, and was collected during December 2020 and March 2021 by the Norwegian Institute of Public Health (NIPH). Additionally, the authors include sustainability considerations into their problem because they found environmental concerns missing in existing research: Andoh and Yu (2022:5f) conducted a keyword co-occurrence analysis for vaccine supply chains and cold chain logistics. Besides uncovering research gaps, it proved very helpful in identifying why it might have been so hard for me to find literature on this topic of pharmaceuticals and vaccines, and what might be done better in the future. This will be part of the discussion in chapter 6.1.2.

Secundo et al. (2022) take a slightly different approach to vaccine distribution. In light of the recent COVID-19 pandemic, their routing-scheduling problem tackles homebound vaccination.

Their approach is based on a VRP, and vaccinations are seen as jobs with associated processing times. Vaccines need to be administered within a certain timeframe because they cannot stay out of the refrigerator for too long. Different kinds of patients are categorized to either receive their first or second vaccination dose, which is associated with different working times (more paperwork for first time patients). Ultimately, the authors want to optimize workforce management for home vaccine delivery with a schedule that maximizes the vaccine delivery rate. Driving and working times are subject to uncertainty. They propose a fuzzy Artificial Immune Algorithm as their metaheuristic solution approach. The Pareto optimal set of solutions balances the minimisation of make span and vaccine expiration risk. A case study with 22 patients in the city of Lecce, Italy, is developed based on real data.

4.4 Cancer Medication

4.4.1 Cancer Medication: Background and Relevance

One area that may benefit significantly from improved routing and scheduling techniques is cancer treatment. Hadid et al. (2022:2) show how tackling challenges in cancer care has been identified as a major development goal by the United Nations and the World Health Organization, thus prompting, among others, research on improving the day-to-day operations in cancer care:

> *"Cancer is the second most frequent cause of death worldwide. More than 16% of the current global population deaths are from cancer [1]. According to the most recent world cancer report [2], the total global cancer expenditures were approximately $1.16 trillion in 2010. This number is expected to increase by 50% as the number of cancer cases diagnosed annually is expected to double by 2040. Cancer treatments include surgery, radiotherapy, chemotherapy, or a combination of the above. Nevertheless, more than half of the global cancer patients required chemotherapy in 2018 [3]. Wilson et al. [4] have predicted a major health crisis driven by unmet chemotherapy demand over the next two decades." (Hadid et al 2022:1)*

Before going any further, one important restriction ought to be pointed out: Most of the literature I found on this topic, namely the papers by Chahed et al. (2009), Kergosien et al. (2017) and Robbes et al. (2022) (in addition to papers that were ruled out due to their lack of routing aspects, such as Garaix et al. (2020), Kergosien et al. (2011), or Mazier (2010)) portray the French healthcare system. The only exception to this is the paper by Lee et al. (2014) which was published by an international, mostly South Korean team. It is obvious that there is a concentration of research on this topic in France, but the rules and regulations imposed on by the French healthcare system might not be universally applied. Therefore, the treatment process outlined here portrays the French system, but may not necessarily reflect the practices in other parts in the world.

Chahed et al. (2009:182), who focus on the chemotherapy at home problem, confirm the French interest in this field of research. They trace the problem back to the anti-cancer drug unit of the European Hospital George Pompidou, where it was first defined according to these authors. A change in French healthcare regulations required the drugs to be prepared in a "specific unit with an insulator or flow hood" (Chahed 2009:180), moving the preparation from the patients' homes where it was previously performed to specialized institutions. The risk for error and toxicity at the homes was thus reduced, but a transportation dimension was added to the problem, and production was centralized which comes with a whole new set of planning challenges. Before addressing these, however, I would like to outline the treatment process, to make it clear to the reader how and why the production and delivery of cancer medication deserves its own chapter rather than a sidenote in the previous one.

According to both Robbes et al. (2022) and Garaix et al. (2020), who collaborate with different medical facilities[21] and thus describe slight variations in the treatment process, chemotherapy treatments are preceded by an individual consultation with an oncologist, wherein patients receive their personalized treatment plan "based on different factors including cancer type, health condition, age, gender, etc." (Garaix et al. 2020:134). Garaix et al. (Ibd.) mention the collection of bio samples, more specifically a blood test, the day before this appointment. Said test is supposed to reveal whether the patient is able to receive the treatment, or whether the injection must be postponed due to their state of health. The final decision to go ahead with the treatment is made during the consultation and the prescription[22] is sent to the pharmacy, all on the day of the injection appointment. The prescription contains information on "the type of medical chemotherapy preparation that will be administered to the patient, the exact dosage and the time schedule of administration" (Kergosien et al. 2017:289). In comparison, in Robbes et al. (2022) the (first) consultation takes place a few days before the treatment. The production order or prescription is designed then. The final health check that leads up to the decision to proceed with the treatment (and, thus, the drug production) is made during a second consultation just before the patient is set to receive the medication. In both cases, the patient waits on-site for the drugs to be prepared and then injected. Kergosien et al. (2017:289) point out that, "[d]epending on the date of administration prescribed by the doctor, the drug must be stored in a refrigerator at a recommended temperature or be immediately delivered." Robbes et al. (2022:791f) provide further detail on the three-step drug production process, including a graph that helps visualize the chemotherapy process (Figure 3, Robbes et al. 2022:792). For more detailed information on the entire production process, please consult Kergosien et al. (2011). Garaix et al. (2020:134-135) mention that the next appointment is set up before the patient leaves.

Whether the patient is set to receive the injection in a healthcare facility or at home, the production of the drugs takes place in a different location from the subsequent treatment. Savelli et al. (2018; see Robbes et al. (2022:791)) confirm that, with the objective to "enhance the quality and security of the chemotherapy treatment," a series of measures are in place to safeguard the preparation process, including a regularly cleaned, sterile environment and specialized personnel. "A production line is composed of a sterilizer and an isolator, where a pharmacy technician realizes the chemotherapy preparations for injection. Once the product is processed, a control is performed (a sample of the preparation is tested)", Kergosien et al. (2017:289) write. Since the medication is produced in such a special facility rather than where the injection takes place, the production process ought to be coupled with a transportation problem. This may encompass the delivery of drugs and/or the transportation of outpatients to a hospital or a treatment centre using an ambulance service. In this thesis, I will solely concentrate on the transportation of the medical products.

As previously mentioned, Lee et al. (2014) published the only non-French contribution that passed the literature selection criteria. Moreover, they focus on nuclear medicine rather than on chemotherapy, in particular on the isotope F-18, which has an extremely short half-life.[23] Keeping this in mind, production quantities need to be carefully planned so that the patients receive exactly the right radiation level at the time of treatment. Therefore, the production quantity is calculated "based on the production time and the usage time accounting for F-18's

[21]Robbes et al. (2022): Clinical Oncology Biopharmaceutical Unit (UBCO) at the regional hospital in Tours, France; Garaix et al. (2020): Institut de Cancérologie Lucien Neuwirth (ICL), in Saint-Étienne, France.

[22]An example of such a treatment plan in provided by Garaix et al. (2020:134).

[23]"F-18's half-life, 110 minutes, is the elapsed time until the number of atoms reduces to the half of its initial state." (Lee et a. 2014:461)

half-life" (Lee et al. 2014:461). In their scenario, the medication manufacturer receives the orders a day before the treatment is scheduled and may then pool multiple orders from the same hospital. He then schedules the delivery vehicles' visits to these healthcare facilities, carefully balancing the production time and the end of usage (end of treatment) time (Lee et al. 2014:461).

Whatever the steps that precede the treatment, what it comes down to is this: Drugs are always prepared on demand, in highly specific and individual dosages, with little to no lead time. As Robbes et al. (2022:791) explain: "The goal of this procedure is to avoid loss of medication when the patient's health precludes receiving the medication." They further elaborate on the importance of timely delivery and administration of the drugs in order to adhere to strict quality standards. Consequently, they consider total tardiness a key performance indicator, and emphasize its relative importance as compared to production or delivery costs (Robbes et al. 2022:792). The same, if not more, attention to product perishability is required in the problem by Lee et al. (2014), and both chemotherapy and nuclear medicine require a high degree of coordination between production and delivery.

Chahed et al. (2009:182) very compactly summarize how the characteristics of cancer medication add to the complexity of the production and delivery problem:

> *"The sterile, personal, perishable and dangerous aspects of anti-cancer drugs make the problem particularly challenging. Drugs are sterile because of the hygiene and quality standard imposed on their production and transportation. They are personal since the necessary doses to their production depend on the creatinine, weight and height of the patient [13]. Thus, a drug produced for one particular patient can not be administered to another one. Each drug has a specific shelf life time beyond which it becomes obsolete, and therefore, it cannot be used. The shelf life time varies from 2 hs to a few days. Drugs are dangerous to people handling them without particular precautions [14]. These drugs can be presented in varied forms (syringe, diffuser and pocket) and can differ by their volumes, their stabilities, their costs and their administration durations. In addition, due to their personal character, these drugs have a very strong diversity." (Chahed 2009:182)*

In connection to the danger associated with these drugs, Lee et al. (2014:462) mention that the toxicity demands special packaging. Besides protecting healthcare workers, patients and the general public from radiation, this packaging serves the added purpose of maintaining product integrity. According to Robbes et al. (2022:810), "each vial has a stability time (i.e., lifetime after opening) and a cost that can amount to thousands of euros". Lee et al. (2014:463), who put special emphasis on the short lifespan of their product, argue that their problem's "novelty comes from the half-life of the nuclear medicine, which requires that production quantity be adjusted to meet the order quantity and that the timing of production be determined considering both production and delivery." In comparison to the other medical products discussed in this paper, perishability may well be the most crucial in this scenario. Add to this the cancer medication's personal nature and the fact that doctors might find patients unfit to receive treatment shortly before their scheduled injection, and the problem becomes vastly more complex than the delivery of other medical products as discussed in the previous chapters. How these aspects find their way into the actual optimization problems is explored in the following section.

4.4.2 Cancer Medication – Production and Delivery: Problem Description

More so than for the other products, the integration of production and distribution problems is common for cancer medication. This has to do with the nature of the drugs, as has been explained at the end of the previous subchapter. Due to the fast deterioration of product value, Lee et al. (2014:463) compare their Nuclear Medicine Production and Delivery Problem (NMPDP) to the perishable food delivery problem and to newspaper delivery. However, they also emphasize that in their case, late delivery is prohibited altogether (rather than just penalized) and the production quantity and timing need to be calculated with the medicine's half-life in mind, both of which adds complexity to the problem. As the paper by Chahed et al. (2009) shows, the transportation aspects of the problem can also be combined with a HHC / nurse routing setting. Chahed et al. (2009:182) differentiate "three stages of the anti-cancer drug supply chain [that] have to be considered (Fig. 1): the production of anti-cancer drugs, their distribution and their administration to patients", all of which are inter-related. The previous subchapter outlined the treatment process as the actors perceive it; this subchapter will address the optimization aspects of these processes.

The production subproblem has been likened to a single machine scheduling problem (Chahed et al. 2009) or a classic uniform parallel machines scheduling problem (Kergosien et al. 2017), a three-stage hybrid flow shop scheduling problem (Robbes et al. 2022) and a special case of the variable-sized bin packing problem (Lee et al. 2014). The transportation subproblem, meanwhile, is mostly reduced to a traveling salesman problem (Chahed et al. 2009; multi-trip traveling salesman problem with a single salesman in the case of Kergosien et al. 2017) or described as a vehicle routing problem: a vehicle routing problem with time windows in the case of Lee et al. (2014), a multi-trip vehicle routing problem with a single vehicle of unlimited capacity by Kergosien et al. (2017) and a multi-trip vehicle routing problem with due dates by Robbes et al. (2022). The production and transportation sub-problems are usually linked through a precedence relation, since the production of the drugs must be finished before they can be delivered. Moreover, as some of the drugs are so very fragile, the time of administration should be kept in mind during production planning.

In a real-life scenario, demand for cancer medication is highly uncertain. Chahed et al. (2009:182f) differentiate between elective and emergency demand and acknowledge that due to the necessary demand validation (i.e., a doctor validating the order before production), planning production is very difficult. In some cases, orders can be cancelled at very short notice due to poor patient health, a change in or the end of treatment, and sometimes even a patient's death. Although the reality is much more complex, Chahed et al. (2009) assume a deterministic demand case. In contrast to chemotherapy drugs, nuclear medicine also requires the optimization of the production quantity. Production amounts (if the production amount is not equal to the demand, as is the case in Lee et al. (2014) due to the nature of nuclear medicine) and starting times are usually subject to optimization. Kergosien et al. (2017) and Robbes et al. (2022) do not speak of demand or drugs, but of jobs that need to be assigned to machines and delivered to the customers: "Each chemotherapy drug intended for a single patient is called a job" (Robbes 2022:792f). In all cases, due to the individual nature of the medication, one specific drug / job corresponds to one patient.

Most authors take into account that the processing needs to be followed by a control step (Kergosien et al. 2017, Robbes et al. 2022). This screening is typically perceived as an automated task with a fixed rate, despite variation between the drugs themselves. Kergosien et al. (2017:289) even mention that they assume there is no waiting time between the processing and the control.

The number of machines available to the manufacturer is sometimes restricted to one for reasons of simplification (Chahed et al. 2009); generally, however, the manufacturer has a certain number of machines at his disposal, not all of which have to be in constant use. If the machine is used, a certain fixed cost may be associated with the production run (Lee et al. 2014). The machines are usually associated with a certain production capacity and/or rate.[24] In the case of Robbes et al. (2022), a certain number of workers is assigned to each machine.

The batching of orders is common in these types of problems: Lee et al. (2014) batch customer orders before production. Chahed et al. (2009:183) list the option of batching drugs for delivery, but the actual assumptions of their simplified problem dispense with this need altogether (see below). Kergosien et al. (2017) batch the order before delivery whereas Robbes et al. (2022) batch their jobs both for sterilization (the first step of processing) and again for delivery.

Once the production step is completed, the orders need to be delivered. As for the transportation subproblem, it appears like a standard TSP at first sight: Routes start and end at the depot. Delivery persons visit a sequence of customers and deliver the products. The limits on the number and the capacity of the delivery vehicles vary: Only Lee et al. (2014) impose capacity limits on their heterogeneous delivery vehicles, while Robbes et al. (2022) consider multiple delivery persons and Chahed et al. (2009) and Kergosien et al. (2017) each have a single delivery person, all with unlimited capacity. These problems usually allow multiple trips; only the oldest paper (by Chahed et al. 2009) allows one single trip. Split deliveries are only addressed in one paper (Lee et al. 2014) where they are explicitly forbidden.

Different from a standard VRP-TW, however, the orders are associated with several times. Kergosien et al. (2017:289) mention:

- a release date, that is the time when a doctor validates the treatment, after an examination of the patient. Production cannot start before the release date,
- a processing time which depends both on the type of drug and the production rate of the machine,
- a stability time if the administration of a certain drug is subject to a stability constraint. It ticks down from the start of production. The drug needs to be delivered before it runs out,
- a due date or delivery due date which corresponds to the desired starting time of the treatment.

Robbes et al. (2022:793f) mention all but the third, and Chahed et al. (2009:186) write about the duration of production, of administration, of the loading at the production station, and, finally, a shelf life time, which is similar to the stability time in that "[t]he delivery and the administration of the drug have to be carried out within the drug shelf life time period". Lee et al. (2014), who include standard time windows for vehicle availability and for servicing a customer in their model, also include a medicine usage time, which corresponds to the end of the customer's time window and influences the start and amount of production. Through these times, production and transportation are interrelated.

The solutions to these types of problems usually assign jobs/orders to machines (if there are several machines available) and then sequence them on the machine(s). The solution to the transportation subproblem contains the customer sequence and the arrival times at the customer locations, which in these problems is equivalent to the beginning of the treatment.

Another characteristic that distinguishes this type of problem is the importance of other objectives than cost. In fact, only the objective function of Lee et al. (2014) centres on costs. The

[24]Lee et al. (2014:462) mention that "[t]he manufacturer has K different machines (cyclotrons) with different capacity", each capable of multiple production runs in a day. Robbes et al. (2022:793) further differentiate between the "sterilizer capacity Qi (i.e., the maximum number of jobs that can be sterilized at a time) [and the] constant sterilization processing time."

other three papers focus on time: Chahed et al. (2009) minimize the total travel time whereas both Kergosien et al. (2017) and Robbes et al. (2022) seek to reduce the tardiness of the delivery, and, thus, the total time delay for chemotherapy treatment. In this setting where timely delivery of fragile drugs is of the essence, these objective functions allow the decision makers to better comply with quality requirements (patients), minimize overtime (staff) and optimally utilize expensive equipment.

In addition to classical features of appointment scheduling problems, the high amount of uncertainty creates the need for a dynamic scheduling policy (see Gupta and Denton 2008:805) – at least in theory, since the research is not sufficiently advanced to properly address the problem's dynamic nature. Kergosien et al. (2017) mention this among their recommendation for future research directions.

4.4.3 Cancer Medication: Presentation of the Literature

4.4.3.1 Literature Reviews

My search process yielded three literature reviews related to cancer medication. The main focus of the survey by Sahin and Matta (2015) is home health care, with a special focus on chemotherapy in HHC. Saville et al. (2019) dedicate themselves to OR techniques throughout cancer care services.

Hadid et al. (2022) approach the outpatient chemotherapy process from an OR direction. They found 45 relevant papers on which they perform a bibliometric and a content analysis. Only few of these publications include transportation problems, and in fact, one of the authors' main findings is the lack of holistic solution that go beyond narrow, idealized problem formulations.

4.4.3.2 Articles

In their pioneer work,[25] Chahed et al. (2009) lay the cognitive groundwork for a series of future studies on cancer medication production and delivery. It came at a time when France introduced new legislation on the conditions under which the preparation of these chemicals must be done, in a special location. Therefore, the transportation problem has to be combined with production scheduling. Despite thinking far ahead and analysing a variety of problem variations, Chahed et al. (2009) limit themselves to a rather simple version of the chemotherapy-at-home-scenario: The model they develop is a traveling salesman problem coupled with production scheduling. They determine the production and delivery starting times but limit themselves to a single machine and a single nurse who visits all patients in one tour. Their purpose, however, is not to solve a real-life problem but rather to introduce this new problem and study the effect of the anti-cancer medication's particular characteristics (shelf-life, production, and administration time) on the solution.

In a second article, Chahed et al. (2011) slightly modify their mathematical model with respect to constraints 9 and 10. In the 2009 paper, they only mention the loading time, whereas in the 2011 publication, they include it in the mathematical formulation. In the later paper, they also include a discussion on their algorithm's properties. Despite slight variations, their problem and solution methods largely remain the same. Due to these strong similarities, and to not distort

[25]Gutiérrez et al. (2013:177) confirm that "the work presented by Chahed et al. [20], is the first published paper that tackles the inventory problem in a HCC network." Chahed et al. (2009, 2011) mention that they are not aware of any previous texts on "coupled production-distribution problems related to personal perishable products" (Chahed et al. 2011:24) and I was not able to find any earlier publications.

the results, the papers will be treated as one during the analysis part (summarised under Chahed et al. (2009), which is the more prominent of the two).

Chahed et al. (2009, 2011) consider the transportation problem on the same level as the production scheduling, as a separate problem of equal importance. In this, they differ from other works which treat the drug delivery merely as an interim stage between production and administration. For example, Mazier et al. (2010) present a study on optimizing production scheduling of cancer medication without paying and attention to the delivery: Although they considered a similar scenario, they assume that the treatment takes place very close to the production site, which leads to negligible transportation times. A year later, Kergosien et al. (2011) presented software that allows for better traceability during the cancer medication production and administration process, thus further reducing delays. Again, the focus lays on scheduling the drug preparation, whereas routing as a part of the treatment process is monitored, but not included in the optimization. Both papers resulted from the cooperation with UBCO in Tours, same as Robbes et al. (2022). According to Robbes et al. (2022:790), the publication by Mazier et al. (2010) marked the beginning of said cooperation, whereas the software developed by Kergosien et al. (2011) was still in use ten years later. Due to their lack of routing, both the paper by Mazier et al. (2010) and Kergosien et al. (2011) were excluded from the main analysis.

Lee et al. (2014) study the nuclear medicine production and delivery problem (NMPDP). The extremely short half-life of the drug they base their work around needs to be considered at the time of production planning: „F-18's half-life, 110 minutes, is the elapsed time until the number of atoms reduces to the half of its initial state", the authors explain (Lee et al 2014:461) and follow up with the formula used to calculate production quantities. However, the production amount is calculated right at the beginning of their algorithm and does not figure in their mathematical model. Instead, the rapid deterioration of the drug finds its way into the MIP through strict customer service time windows that must not be violated. Their production scheduling problem is a special case of the variable-sized bin packing problem whereas the delivery part is modelled as a pickup and delivery problem with time windows (PDPTW).

Interestingly, Lee et al. (2014) do not build on any of the earlier research on cancer medication RSPs. Despite considering many of the same problem specifications, it appears that the authors were unaware of the existence of the French studies: "To our knowledge, no previous work has considered the nuclear medicine production and delivery problems (NMPDP) posed by F-18, an isotope that requires scrupulous determination of manufacturing levels as well as accounting for its rapid deterioration" (Lee et al. 2014:461). Or perhaps their approach to production planning simply reminded them more of other perishable products that also require calculating the production amount: Instead of citing the aforementioned earlier works by the French research teams, Lee et al. (2014:462f) in their literature review focus on the delivery of perishable food items and newspapers. They also dedicate a paragraph to integrated production scheduling and distribution problems, but for a newer, more thorough review on this type of problem, the reader is referred to Robbes et al. (2022): Building on the research done by Moons et al (2017), who studied integrated production and distribution problems before 2017, Robbes et al. (2022:789) created a Venn diagram displaying the contributions made to this project from 2017 to 2020.

Kergosien et al. (2017) combine the chemotherapy production with a delivery problem in the forms of a uniform parallel machines scheduling problem and a multi-trip traveling salesman problem with only one salesman, respectively. Further, they add product-specific lifetime constraints to account for the particularly short half-life of cancer medication. In their objective function, the authors seek to minimize the maximum tardiness of delivery. They opt for a Benders decomposition and a Tabu Search heuristic. The effectiveness of their chosen method is tested over 18 sets of generated instances inspired by the real-life situation of the Oncology Clinic of the Hospital Center of Tours (France). What they do not account for, however, is the dynamic setting wherein cancellations occur if a patient is deemed unfit to receive his treatment. This is pointed out in the future research directions.

Building on their earlier work from 2019,[26] Robbes et al. (2022) dive deeper into the chemotherapy production and delivery problem, which integrates the hybrid flow shop scheduling and the multi-trip vehicle routing problem. Their study is motivated by real-life processes in an oncology unit, where expensive cancer medication is only produced *after* a patient has been deemed fit for treatment by a physician. After outlining the process, they present their model, wherein they minimize the total tardiness (total time delay) of the chemotherapy delivery. As an extension of their conference paper from 2019, they add two new solving methods that produce better results: a bilevel gradient descent (BGD) and a greedy randomized adaptive search procedure (GRASP). The altogether four heuristics presented in the 2021 paper (reference algorithm, multilevel heuristic algorithm, bilevel gradient descent and greedy randomized adaptive search procedure (GRASP)) are tested over 480 real and generated instances. These experiments prove that the GRASP with 5 or 10 iterations yield the best results, and the runtime is so short (on average under one minute) that the method may be used in a dynamic problem setting. Overall, the authors note that methods that calculate the expected delivery batches before scheduling the production outperform those that start with the production schedule.

[26]In 2019, Robbes et al. published a conference paper on the same problem, which was excluded from this analysis because of the publication type.

5. Analysis of the Literature

The purpose of this chapter is to analyse the papers in a cross-product framework. I want to highlight patterns in research, regardless of the order in which the papers were presented. This may require unravelling the cluster-structure I have built in the previous chapter. Unless specifically stated otherwise, 53 papers are used as the basis for analysis. In order not to distort the results, publications that appear in different journals or years but treat the same topic without relevant extension or variation are excluded from most sections. This leads to the elimination of 3 papers from all chapters but 5.1 *Publication Medium and Date*. Thus, for information on Revere (2004B), please refer to Revere and Roberts (2004A); on Chahed et al. (2011) to Chahed et al. (2009); and on El Midaoui et al. (2021) to El Midaoui et al. (2020).

A word of caution: Chances are that my search method did not reveal all publications that are available on this topic, and even if it did, 53 publications is not much. Especially in as small a cluster as cancer medication, 50% reduces to just two papers. Therefore, I have tried to always provide absolute numbers alongside percentage data. Still, the here-presented analysis may be incomplete and under- or overrepresented in certain cases. Another aspect is that not all papers provide the same kind or depth of information. During this entire chapter, an asterisk (*) in a graph or table means that this claim was not explicitly stated by the authors but derived from interpretation of the material. Other reservations are pointed out at the end of chapter 5.8, alongside relevant examples, and during the *Discussion* part of this thesis (chapter 6).

5.1 Publication Medium and Date

The following chapter sheds light on when and where the reference papers were published. This chapter includes all 56 reference papers, because even though some papers might show little variation in content (Revere 2004A / B, Chahed 2009 / 2011, El Midaoui 2020 / 2021), it is nonetheless interesting to see which journals they appeared in.

While Revere and Roberts (2004A) appeared in the *Journal of Healthcare Management*, Revere (2004B) was published in the *Business Process Management Journal* and, thus, has a stronger business-focus. Revere (2004B) contains more detail on the healthcare institutions, on the process and on the numbers (less rounding up or down). Still, the two articles treat the same case study, describe the same approach and yield the same results. Interestingly, only Revere and Roberts (2004A) showed up during the key word search in the data banks, whereas Revere (2004B) was found during the snowballing search in the references used by Yücel et al. (2013A). Similarly, Chahed et al. (2009) published their first article in a medical journal (*Health Care Management Science*) while the second article appeared in *Supply Chain Forum: An International Journal*. The adaptations for the OR-publishing environment were discussed in chapter 4.4.3. Again, only one of the two articles showed up during the keyword search (Chahed et al. 2009). In contrast, the same keyword search produced both texts by El Midaoui (2020, 2021). I found this all the more surprising since neither of the journals they were published in (*Advances in Science, Technology and Engineering Systems* and *International Journal of Web-Based Learning and Teaching Technologies,* respectively) falls under the healthcare or SCM/OR-categories.

Since the inclusion criteria stipulated that only journal articles would be included, there is no need to evaluate different publication types. Books, book chapters, conference papers, etc. showed up during the search process, but were eliminated immediately. Instead, I want to take a closer look at the journals themselves. The 56 contributions were published across 34 different journals, 10 of which included at least 2 relevant articles. These journals are displayed in Table 6: Publication journals. A list of the remaining 24 journals with less than 2 relevant contributions is available upon demand. Alternatively, and in order to know which article appeared in which journal, please refer to the full citations of all articles in the references.

20 of the 34 journals appear on the list of scientific journals by VHB-JOURQUAL3.[27] Of these, 17 journals cover topics related to OR and/or logistics or production. The remaining 3 belong to the discipline of healthcare management. Moreover, 17 journals had received a rating: 4 journals are rated A, 8 are rated B, and 5 are rated C. Most articles (7) used in this thesis were published in the *European Journal of Operational Research*, which is an A-rated journal. 3 journals rank second with 4 publications each*: Annals of Operations Research, Computers and Operations Research* and *Transportation Research Part E.*

When looking at the 10 journals listed in Table 6: Publication journals, and again when taking all 34 journals into account, it is very clear that this type of problem might feature a medical topic but is located primarily in the field of SCM/OR: Of the 40 articles published in journals that were assigned a category, only 4 were published in journals from the field of health care. Of these 4, 3 centred on medical specimens.

Looking at when the articles were published reveals a growing trend in this area of research. The earliest paper that meets all including criteria was published in 1972, and it is the only one that appeared in the last millennium. 7 papers were published between 2000 and 2009, another 20 from 2010 to 2019, and 28 papers (exactly half of all contributions) from 2020 onwards. The year 2021 and 2022 present the largest number of contributions, with 9 and 13 articles respectively. This is particularly impressive considering that the year 2022 was not considered in full: The last, updated literature search was conducted on the 5th of November 2022. The distribution of articles in terms of publication date from 2000 onwards[28] is shown in Figure 2.

The upsurge in research from 2020 onwards is likely related to the recent COVID-19 pandemic, as will be explained in chapter 6.2.2. I did not find a relevant correlation between the publication date and the kind of medical product. The earliest paper from 1972 centred on medical specimens, the second-earliest from 2003 on blood collection. Drug delivery was first addressed in 2006 and cancer medication in 2009.

Table 6: Publication journals

Journal Name	Count	Rating	Category[1]
European Journal of Operational Research	7	A	OR, PROD
Transportation Research Part E	4	B	LOG
Computers and Operations Research	4	B	OR, WI
Annals of Operations Research	4	B	OR
Computers & Industrial Engineering	3	B	PROD
Health Care Management Science	2	A	Health Care
Journal of the Operational Research Society	2	B	OR
INTERNATIONAL TRANSACTIONS IN OPERATIONAL RESEARCH	2	no rating	OR
Optim Lett	2	no rating	no rating
Expert Systems With Applications	2	no rating	no rating

[27] Liste der Fachzeitschriften in VHB-JOURQUAL3, online via https://vhbonline.org/vhb4you/vhb-jourqual/vhb-jourqual-3/gesamtliste. Last access: 21.11.2022, 21:00.
[28] The one outlier from 1972 was excluded from the graphical representation.

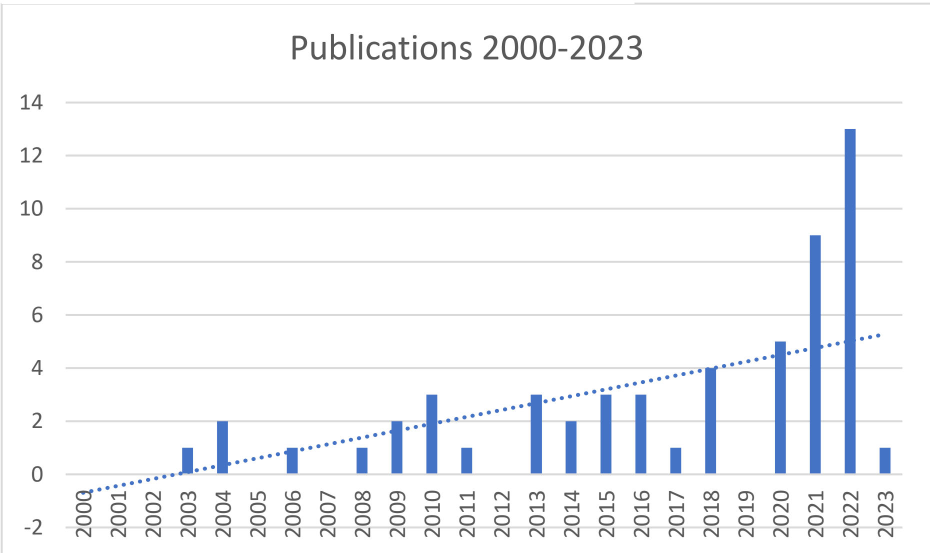
In the blood supply chain, a slight shift from a focus on blood collection to distribution and, finally, integrated or wholistic models considering several stages can be observed: In 2018, the last of the 6 papers on blood collection and the first of the 5 integrated models was published. As for the drug SC, all papers expect for one outlier from 2006 were published from 2018 onwards, and all 4 papers on vaccine distribution have been published in the last two years (2021, 2022).

5.2 Planning Horizon

As the general framework of this thesis requires microlevel planning (decisions regarding routing and scheduling), it should not come as a surprise that all publications focus on the operational planning level. Some include tactical decisions in their works, like Anaya-Arenas et al. (2021), who make tactical decisions for the opening hours of each collection centre, or Şahinyazan et al. (2015), who consider the blood potential of their blood mobiles' location. Meanwhile, the paper by Malladi et al. (2022) features one of the few strategic decisions, in their case regarding the optimization of the fleet mix.

A more relevant distinction for RSPs, however, is that between single and multiple time periods. Lahyani et al. (2015:4) explain the difference as follows: "The distribution plan may be computed over a single period or over several periods. In the Periodic Vehicle Routing problem (PVRP), […] [a]t each period, one has to decide which customers are served in this period and which orders are postponed to the next periods." Meanwhile, Fikar and Hirsch (2017:88) define single-period optimization problems as "settings where a single working day is assumed as the planning horizon." In line with this definition, in the analysed literature, a day was most often seen as a single period and not divided further. Since the included problems are of mostly operational nature, days are the most relevant time unit: Out of 53 papers, more than half (28 papers) limited their time horizon to a (work)day. In 6 cases, however, a single workday was split into several periods. Due to their periodic structure, these 6 papers were counted towards multi-period problems. Unless a time horizon was explicitly or implicitly split into different periods, it was assumed that a single planning period was used. No publication specifically mentioned applying a single planning unit shorter or longer than a day. As always, interpretations

Figure 2: Articles by year of publication, from 2000 onwards



and assumptions in Table 8: Planning environment are marked with an asterisk.

A total of 32 publications were classified as single- and 21 as multi-period problems. In a multi-period model, not all service requests arise in the same planning period (Fikar and Hirsch

2017:91). In the context of the SR-problems at hand, this might mean that blood mobiles stay in one location overnight; blood banks in VMI-systems may have to plan when and how they supply the hospitals over the duration of a week; or a laboratory may design its drivers' working schedules and routine routes for the next month.

From the multi-period problems that named a specific planning horizon, all but one remained within the scope of two weeks. Ren et al. (2010) split several days into 3 shifts each. Eisenhandler and Tzur (2022) also mention several days and explore a rolling horizon framework in their Online Appendix. Weekly or bi-weekly schedules are developed by several authors, some of which (e.g. Revere and Roberts 2004A) differentiate between weekdays and weekends. A 12-day rolling horizon based on the shelf life of the blood product (7 days) is chosen by Liu et al. (2020).

As for the exception of the two-week-scope, the longest planning horizon by far is that of Malladi et al. (2022) with 10.6 years, based on the average lifetime of vehicles. Including seasonal fluctuations,[29] they calculate with "227 working days per year and two work shifts per day" (Malladi et al. (2022:11). This exceptionally large horizon is caused by their objective of optimizing the vehicle fleet mix based on costs for acquisition and operations.

No relevant differences between the product types could be found. Sorted chronologically by date of publication, no significant shift in research interest or approach could be noted.

[29] Malladi et al. (2022:11) find that demands are distributed differently during summer and non-summer parts of the year.

Table 7: Objectives

			# Objectives		Cost-related Objectives		Time-related Objectives			Other Objectives					
Authors	Year	Product	Single	Multi	Cost (transp.)	Cost (other)	Travel time	Cycle / Compl. time	Tardiness	Travel Distance	Risk Penalty	Product Output	# Staff / Vehicles	Environmental	Other
Anaya-Arenas et al.	2016	Specimen	x							x					
Anaya-Arenas et al.	2021	Specimen	x				x								
Andoh and Yu	2022	Drugs / Vaccines	x		x										
Aydınalp and Özgen	2022	Drugs	x		x										
Benini et al.	2022	Specimen	x							x					
Borumand and Beheshtinia	2018	Drugs		x (5)		x			x					2	1
Bouziyane et al.	2020	Drugs		x (2)			x		x						
Chahed et al.	2009	Cancer	x				x								
Chen et al.	2021	Drugs	x												1
De Magalhães and De Sousa	2006	Drugs		x (2)	x			x							
Dörner et al.	2008	Blood	x				ext.			x					
Eisenhandler and Tzur	2022	Blood		x (2)											2
El Midaoui et al.	2020	Drugs	x		ext.		ext.			x					

El Midaoui et al.	2022	Blood	x		x					x				
Elalouf et al.	2018	Specimen	x		incl.	x								
Elalouf et al.	2021	Specimen	x										x	
Entezari and Mahootchi	2021	Specimen		x (5)			x		x					3
Ghandforoush and Sen	2010	Blood	x		incl.	x								
Grasas et al.	2014	Specimen	x										x	
Haitam et al.	2021	Specimen	x						x	x				
Hamdan and Diabat	2020	Blood		x (2)		x	x							
Hemmelmayr et al.	2009	Blood	x		ext.		x			ext.				
Hemmelmayr et al.	2010	Blood	x		x		x			ext.				
Kergosien et al.	2017	Cancer	x						x					
Lee et al.	2014	Cancer	x		incl.	x								
Liu et al.	2020	Blood	x		incl.	x								
Malladi et al.	2022	Specimen	x		x									
McDonald	1972	Specimen	x					x						
Mobasher et al.	2015	Blood	x									x		
Naji-Azimi et al.	2016	Specimen	x					x			x			
Özener and Ekici	2018	Blood	x									x		
Petronaiu et al.	2021	Drugs / Vaccines		x (2)			x				x			
Pirabán-Ramírez et al.	2022	Blood	x		incl.	x								

Ren et al.	2010	Specimen	x		x										
Revere and Roberts	2004	Specimen		x (2)		ext.	x						x		
Rezaei Kallaj et al.	2022	Blood		x (2)			x					x			
Robbes et al.	2022	Cancer	x						x						
Şahinyazan et al.	2015	Blood		x (2)	x							x			
Secundo et al.	2022	Drugs / Vaccines		x (2)	ext.			x			x				
Shahnejat-Bushehri et al.	2021	Specimen	x		incl.	x									
Tlili et al.	2022	Specimen	x												1
Wang et al.	2015	Specimen	x		incl.	x									
Wen et al.	2016	Blood		x (2)						x			x		
Wolfinger et al.	2023	Specimen	x		incl.	x									
Wu et al.	2022	Drugs	x		x										
Yi and Scheller-Wolf	2003	Blood	x							x					
Yücel et al.	2013A	Specimen		x (2)	x							x			
Yücel et al.	2013B	Specimen	x					x				ext.			ext.
Zabinsky et al.	2020	Specimen	x					x							
Zahiri et al.	2018	Blood		x (2)	incl.	x									1
Zangeneh-Khamooshi et al.	2013	Specimen	x					x							
Ziya-Gorabi et al.	2022	Specimen / Drugs		x (3)	incl.	x			x					1	

incl. = included   ext. = by extension

5.3 Objectives

This chapter looks at whether a problem optimizes a single or multiple objectives, how many objectives there are, and the category under which these objectives could be summarized. In Table 7: Objectives, a single x signifies that a statement is true; numerical values are used instead of x in the last two columns, where more than one objective per paper falls into the respective category. The addition "by extension" can mean two things: either the authors make it explicit that different goals relate to each other linearly, for example if the total distance is minimized, but can be multiplied by a cost factor to determine the routing costs; or the authors were unclear in their terminology and mention different goals that may or may not be linearly related. This was most often the case for travel time and travel distance. In such cases, the paper is counted towards that goal that is optimized through the objective function in the mathematical model.

Some authors only consider the objective functions of papers that apply exact solution methods (e.g., Pirabán et al. 2019). In the following evaluation, I opted to include all papers, even those without mathematical models. Some still make their objective(s) unequivocally clear, like Elalouf et al. (2021:226) in the following excerpt: "The objective of the current study was to use our simulation model to identify the optimal vehicle fleet size for transporting blood samples from Clalit's clinics to their corresponding centrifugation centers." Others, however, were not clear without ambiguity. De Magalhães and De Sousa (2006:182) write that "the main objective of the company is to improve the quality of the service to customers, i.e. to decrease the delivery time, without significantly changing the current costs that are roughly related to the driving distances." I first counted them towards single-objective problems with the objective of maximising service quality. Only after noting that Bouziyane et al. (2020:302) describe this paper as a MO-problem, I revised my first assessment.

Out of 52 publications, 37 papers optimize a single objective problem (SOP) while 15 balance multiple objectives. For multi-objective problems (MOPs), the number in parentheses specifies how many objectives each publication includes (Table 7: Objectives). Most multi-objective problems focus on balancing 2 different objectives. One paper considers 3 objectives (Ziya-Gorabi et al. 2022) and two papers consider 5 objectives (Borumand and Beheshtinia 2018; Entezari and Mahootchi 2021).

If a paper features two or more objectives, conflicts between the different objectives may arise, and trade-offs must be found (Lahyani et al. 2015:7). Several options are available to find a balance between the objectives. Ziya-Gorabi et al. (2022:11) present the most important multi-objective decision-making (MODM) approaches. Among my reference papers, some authors use the Pareto approach to find a set of non-dominated solutions (Şahinyazan et al. 2015; Wen et al. 2016; Bouziyane et al. 2020; Secundo et al. 2022). Hamdan and Diabat (2020) use the Epsilon-constraint method to transform the MOP into a SOP. Others choose to transform multiple objectives into a single objective problem by allocating weights to each objective (Entezari and Mahootchi 2021; Petronaiu et al. 2021; Borumand and Beheshtinia 2018). For example, Zabinsky et al. (2021) and Petronaiu et al. (2021)[30] seek a trade-off between risk and travel time. Therefore, the objective function is a weighted sum of total transit time and sum of all penalties for chosen vehicles and roads during transit. They allow the user of their software to assign weights between 0 and 10 to each of their objectives, which makes it possible to concentrate on just one of these two goals (weighting one with 10 and the other with 0). Wen et al. (2016) chose to decompose their MOP into single-objective subproblems. Eisenhandler

[30] Since these two publications have the same, weighted objectives, were published by (largely) the same group of authors and concentrate on the same problem, they were counted as one in this evaluation so as not to distort the results.

and Tzur (2022) do the same and differentiate between an optimization subproblem and a feasibility subproblem, thereby imposing a hierarchic structure on the different objectives. Similarly, Yücel et al. (2013A) considered two hierarchical objectives, namely maximizing the amount of specimens processed by the next morning and minimizing the daily transportation cost. Since the first objective is given more importance, it is optimized first. The solution then serves as an additional constraint while the transportation costs are minimized. Interestingly, in their other paper, they change their objective function: Yücel et al. (2013B) focus on minimizing the make span since, they argue, "the makespan is sufficient to optimize the other objectives as well" (Yücel et al. 2013B:1629), the other objectives being the minimization of the total idle time of the processor, and the maximization of the processed amount by a due date such as the next morning. The higher-level objective from Yücel et al. 2013A is thus kept, but only as a side-effect of optimizing the make span, whereas the lower-level objective of cost-minimization is not at all included in Yücel et al. 2013B. De Magalhães and De Sousa (2006) calculate several parameters, including both objective values, for the possible routes and leave it to the decision makers to choose the route that best fits their expectations.

Some authors whose papers were counted towards SOPs present variations of their mathematical models, like El Midaoui et al. (2022). Technically, their paper would not be considered a multi-objective model because only one objective is optimized at a time. The authors propose two MIP formulations, one for the (single depot) VRP and one for the MDVRP. They only consider a "matrix of costs or distances" (c_{ij} in the first model and D_{ij} in the second model), so variable routing costs and distances are used interchangeably. However, in the first model, they also consider a fixed cost / cost of vehicles and describe their objective as cost minimization, whereas in the second model, they speak of "minimiz[ing] the total delivery distance and cost of each vehicle within a blood bank" (El Midaoui et al. 2022:1063). In the evaluation, they were counted towards SOPs, but towards both cost and distance minimization.

Another special case that needs to be mentioned is that of Hemmelmayr et al. (2010), who first minimize the total travel distance during the planning period and then present four recourse actions, the second, third and fourth of which introduce objective functions that aim at cost minimization. Since there is a clear distinction between the initial optimization and the recourse, this paper, too, was classified as a SOP.

In contrast, Revere and Roberts (2004A) tackle two different objectives in two subproblems: During the routing subproblem, transportation time is minimized. This objective, the authors argue, has many positive side effects: "minimizing on transport time would be effective (specimen travel time) and efficient (employee hours)" (Revere 2004B:406) because employee hours are considered the largest cost of transportation. For the same reason, in the staff scheduling subproblem, the objective is to minimize the number of employees during a two-week shift. Total costs are minimized by extension, but transportation time and the number of employees are counted as two separate objectives and, thus, the paper is classified as a MOP.

Cost reduction is among the most frequent objectives for these types of problems (Pirabán et al. (2019:14). Other common objectives include "the total traveled distance, the total time, […] the fleet size, and/or maximizing the service quality, the collected profit" (Lahyani et al. 2015:7). Altogether, 22 papers[31] addressed costs in at least one of their objectives: 10 papers optimized only the routing costs in their objective function, while 12 focused on a larger or different understanding of costs. These "other costs", as I chose to call them, are usually composed of various cost aspects: They may encompass routing costs, but also production costs, the cost of opening and/or maintaining blood collection or testing sites, outsourcing costs, etc. I decided to single out "routing cost" because it was the one cost aspect most often optimized on its own, and it seemed interesting to see how often just the routing costs were considered as compared

[31]Not counting papers optimizing costs (by extension).

to a larger cost focus. Table 7: Objectives shows, moreover, that only 2 papers that had the goal of cost reduction granted no attention to routing costs at all. Those that did, focused solely on production cost (Borumand and Beheshtinia 2018), and “the total system cost”, defined as “the cost of equipping fixed blood collection centers and the cost of establishing new mobile blood collection centers” (Hamdan and Diabat 2020).

It should not come as a surprise that timely delivery also plays a major role: “The blood delivery time objective is vital as it prioritizes the delivery of blood products that are fresher, which has been medically proven to yield benefits to patients,” Hamdan and Diabat (2020:5) explain why they choose to include a time-related goal in their bi-objective problem. There are multiple ways to minimize delivery time. I identified three main groups: travel time (10), cycle or completion time (7), and tardiness (7). The numbers in parentheses specify how many objectives were identified in each of these groups, although the terminology in the papers is not always as straight-forward. The group “cycle/completion time”, for example, encompasses everything that goes beyond pure travel time, such as the total time required to make all collections (McDonald 1972), the make span (Yücel et al. 2013B; Secundo et al. 2022) and the time from when the specimen is available for pickup until it is delivered to the central laboratory (Zangeneh-Khamooshi et al. 2013, Zabinsky et al. 2020). Zangeneh-Khamooshi et al. (2013:1220) call the minimization of cycle time “a traditional objective function in a scheduling problem” and go on to highlight similarities between their VRPWCT and a typical scheduling problem. Between them, these objectives account for 24 time-related objectives. One could also add the maximization of the remaining product shelf life, which was classified under “other” objectives since it fit none of the three aforementioned categories. Then, with a total 25 out of 78 objectives, timely delivery accounts for around a third of all goals.

Minimization of travel distance is another common objective in these types of problems. This also proved to be true in this thesis, where 8 papers feature the minimization of travel distance (route length, total milage) as their objective. In some cases, authors seem not to differentiate between travel distance and travel time or cost (see above, El Midaoui et al. 2022).

Risk of expiration and/or damage during transportation is addressed in 3 papers, 2 of which focus on drugs or, more specifically, vaccines. The third paper adds a penalty to when specimens arrive at the laboratory in order to balance out the arrivals throughout the day to avoid congestion and expiration (Naji-Azimi et al. 2016). Each of these three papers includes time-related aspects among their objectives. Meanwhile, the maximization of output is addressed in 5 papers, 4 of which focus on blood as a resource and 1 on the processing of biological samples. Another 4 papers optimize the number of vehicles/UAVs/employees.

2 papers addressed a total of 3 environmental objectives. I found this surprising as I had anticipated that this topic would have received more attention. Green objectives are only ever considered in MOPs, alongside other goals, and never as the sole objective. Borumand and Beheshtinia (2018) minimize both the emissions of the suppliers and the emissions of the vehicles. Ziya-Gorabi et al. (2022) minimize the total emitted greenhouse gases (i.e., CO2) by all considered ambulances.

Outside of these categories, 6 papers also optimize 9 “other” objectives. 3 of these are included in the paper by Entezari and Mahootchi (2021), who address the total violation of CoC (Continuity of Care), the total overtime of the staff members and the violation of staff time windows; and 2 are included in the paper by Eisenhandler and Tzur (2022), who seek to balance the effectiveness and the equity of food/blood distribution in the delivery subproblem and maximize the earliest day whose demand cannot be supplied in full in the collection subproblem. Fairness is also the objective addressed by Chen et al. (2021). The remaining objectives include: maximizing the order quality (Borumand and Beheshtinia 2018), maximizing the of scores of visited patients depending on their urgency/importance (Tlili et al. 2022), maximizing the remaining product shelf life (Zahiri et al. 2018).

5.4 Solution Method

85% of all papers present a mathematical model, even if one or more approximate methods are then proposed to solve the problem. The remaining 8 papers include only fragmented problem formulations (Grasas et al. 2014), IP-like formulations in the form of written text (McDonald 1972, Zabinsky et al. 2021), or none at all. Revere and Roberts (2004) and Secundo et al. (2022) mention a mathematical model but do not include it in their paper. With the exceptions of Elalouf et al. (2021), Zabinsky et al. (2021) and Secundo et al. (2022), all papers without a (M)IP-model were published before 2015. Some papers present a mixed integer non-linear program (MINLP) which is then linearized (Ghandforoush and Sen 2010, Mobasher et al. 2015).

With respect to the solution methods, 9 papers use exact methods (15%), 20 use heuristics (34%) and 23 (39%) use metaheuristics. Simulation is applied in 3 papers (5%). Another 3 are counted towards “other” (5%) and 1 paper self-identifies as matheuristic (2%). This amounts to a total sum of 59 for only 53 papers, because 6 publications feature solution methods from 2 different categories and are counted twice. The reason an overwhelming majority of publications chooses approximate methods is that the presented problems are NP-hard combinatorial optimization problems, and exact methods are unable to optimally solve such increasingly large and complex problems within reasonable computing time. Meanwhile, approximate methods find near-optimal solutions fairly quickly (Wen et al. 2016:2, Lahyani 2015:8, Pirabán et al. 2019:18f).

Among the exact methods, branch-and-bound is by far the most popular. It is, however, important to stress that the exact algorithms VeRSA (Zangeneh-Khamooshi et al. 2013, Zabinsky et al. 2020) and RoOT (Zabinsky et al. 2021, Petronaiu et al. 2021) all use the same BnB and indexing rule framework as they build on each other’s work. The earliest paper using an exact method generates all possible routes in order to then optimize them and select the best one(s) (Yi and Scheller-Wolf 2003). Such an approach is, of course, only possible for problems of a certain size. True to type, the instance sizes solved with exact algorithms are on the smaller side. The largest problem solved by an exact method contains 57 clinics and 12 vehicles (Zabinsky et al. 2020). Meanwhile, in the newest papers applying exact methods, Petronaiu et al. (2021) and Zabinsky et al. (2021) explicitly recommend using their algorithms to plan routes for 50 health facilities or less.

Heuristic methods have always been used, from the first reference paper in 1972 to some of the newest papers published in 2022. The earliest paper by McDonald (1972) applies a simple savings algorithm. The newer papers, meanwhile, experiment with more complex heuristics, like a hybrid particle swarm intelligence algorithm (Wu et al. 2022). Heuristics are often applied together with other solution types, like exact methods (Dörner et al. 2008, Yücel et al. 2013A) or metaheuristics (Hemmelmayr et al. 2009, Malladi et al. 2022). Other than simple heuristics and construction and improvement methods, authors often take a clustering and routing approach (De Magalhães and De Souse 2006, Mobasher et al. 2015): Typically, authors chose to cluster first, route (or schedule, Yücel et al. 2013B) second; one paper, however, makes it very clear that it presents an integrated clustering and routing approach (Özener and Ekici 2018).

Pirabán et al. (2019:19) explain: “Metaheuristics are high-level concepts for exploring search spaces by using different strategies. They are often successful alternatives to solve optimization problems under uncertainty.” Indeed, none of the papers including uncertainty use exact methods, and more than half (8 out of 14) papers use metaheuristic approaches. Genetic algorithms (9) either in its pure or hybrid forms are the most popular metaheuristic. Different variants of neighbourhood searches are also frequently used: LNS (3), ALNS (4), Variable neighbourhood (6).

Hybrid methods often find application. Shaabani et al. (2022:155) explain hybrid methods as a combination of "two or more heuristic and metaheuristic methods to take advantage of different algorithms simultaneously since each solution approach has its own capabilities." A total of 9 papers (17%) applies hybrid methods, and preferably hybrid genetic algorithms (Borumand and Beheshtinia 2018, Tlili et al. 2022) as well as hybrid local searches (Bouziyane et al. 2020, Pirabán-Ramírez et al. 2022).

The types of simulation used in the reference papers are discrete event simulation (2), Monte Carlo simulation (1) and Gamma distribution (1). Pirabán et al. (2019:19) emphasize that simulation is primarily a method to deal with uncertainty: "[s]imulation is widely used to manage uncertainty in the supply chain design […] Simulation models are ideally suited for representing complex stochastic systems, although there is no guarantee of finding an optimal solution." While this is true for two of the three reference papers that apply simulation, the third by Elalouf et al. (2021) does not give priority to uncertainty. At one point, the authors even elaborate on their reasons for modelling their travel times on a deterministic basis rather than stochastically (Elalouf et al. 2021:222).

According to Fikar and Hirsch (2017:88), "the term matheuristic is used for hybrid methods combining exact solution procedures with heuristics or metaheuristics." Among all 53 papers, Eisenhandler and Tzur (2022) were the only ones to choose a matheuristic approach. Only when describing the future perspectives, Anaya-Arenas et al. (2021:378) mentioned that their "research is now shifting to the use of a matheuristic approach merging the exact formulation and approximated solution techniques."

Looking at the timeline, one can notice a shift from exact methods to heuristics and on to metaheuristics. Exact methods, with the exception of recent publications around VeRSA/RoOT, were mostly used for smaller-sized problems until about 2010. Heuristics, meanwhile, have been popular throughout the entirety of the analysed time, but saw a decline in favour of metaheuristics after 2018. From 2020 onwards, metaheuristics and simulations, but also alternative methods have received particular attention. As for single- and multi-objective problems, no significant correlation could be found between the number of objectives and the solution approach. Providing an assessment on which method(s) perform the best would be a difficult if not impossible task since, as chapter 5.7 will show, the test instances and scenarios are very diverse and sometimes incomplete information does not allow an adequate comparison at all. Moreover, many of these methods are tailored to the specific problem settings.

5.5 Stochastic vs. Deterministic

Problems can be classified as deterministic or stochastic depending on whether there is uncertainty. In a deterministic setting, the decision-making environment is certain, and problem parameters are known to the decision maker. By no means does this imply that the problem is simple or easily solved: Pirabán et al. (2019:3) write that "[t]he complexity of this environment arises principally because of the large number of possible outcomes, which may need to be identified and compared […] However, several parameters such as supply and demand have inherent uncertainties in the BSC." This is also true for other medical products, not just blood. In this sense, assuming a deterministic setting is a simplification of a much more complex reality and "not entirely suited to real-life unpredictabilities" (Di Mascolo et al. 2021:33). In optimization research, however, it is the norm rather than the exception because including uncertainty in a problem adds complexity. In my analysis, a problem is classified as deterministic if it does not specifically address uncertainty. As such, 39 out of 53 problems assume a deterministic problem setting, while the remaining 14 feature uncertainty.

When it comes to uncertainty, Pirabán et al. (2019:3) consider three main categories: "stochastic, unknown, and fuzzy. In the stochastic group, the probability distributions of uncertain parameters are known and described by either continuous or discrete functions. In the unknown environment, the decision maker has no information about the probability distributions of random parameters. The fuzzy environment considers random parameters as fuzzy numbers." In a slight variation, Shahnejat-Bushehri et al. (2021) distinguish three methods of addressing uncertainty: 1) Fuzzy chance-constraint programming, 2) Stochastic programming, and 3) Robust optimization. These three categories are also mentioned in Torrado and Barbosa-Póvoa (2022) and they will be used in the subsequent analysis of uncertainty in the literature.

Stochastic approaches are the most well-known way of dealing with uncertainty and have been applied to a wide range of VRP variants (Shahnejat-Bushehri et al. 2021:2). They require uncertain parameters with known probability distributions. De Magalhães and De Sousa (2006:181) point out that this uncertainty can be "related with several aspects of the problem, namely the moment of ordering, the size of orders, travel times and distances, among others." In line with the claim by Shahnejat-Bushehri et al. (2021), in my research, stochastic programming is also the most popular way to cope with uncertainty. 9 out of 14 papers including uncertainty use stochastic approaches:

Andoh and Yu (2022:17) use several stochastic parameters in their simulation to mirror "the real-world environment and to estimate the impacts of uncertainty[.]" They name examples, but do not specify which parameters remain stochastic in their approach. Chen et al. (2021:18) capture "the stochastic interactions among demand, the pharmacy and transport" by proposing two nested queuing models, one for regular and one for peak demand, as would be the case during accidents, virus outbreaks and catastrophes (Chen et al. 2021:3). Hemmelmayr et al. (2010) extend their 2009 paper by considering stochastic product usage, which creates the need for recourse policies. They then use "external sampling to convert the two-stage stochastic optimization problem into a deterministic optimization problem" (Hemmelmayr et al. 2010:686). In their *Stochastic Fleet Size and Mix Problem* (SFSMP), Malladi et al. (2022:2) "assume customer requests and temperature are stochastic at the strategic planning stage and are only revealed prior to operations every day." Rezaei Kallaj et al. (2022) present both a deterministic and a stochastic version of their problem. Potential uncertainty concerns the number of blood donors and demands. Wang et al. (2015) also address demand uncertainty in the form of urgent random demands. In response to the inherent uncertainty of input data, specifically in donation and demand sizes, Zahiri et al. (2018) propose a multi-stage stochastic programming approach with a combined scenario tree. De Magalhães and De Sousa (2006) and Bouziyane et al. (2020) tackle dynamic problems, which are presented in the next chapter of this thesis.

If the probability of uncertain parameters cannot be determined, alternatives to stochastic methods are needed. Among the literature analysed here, 3 papers choose to use fuzzy parameters, and 2 publications apply robust approaches.

Triangular fuzzy numbers are used in two publications to express uncertain parameters: Secundo et al. (2022:7) use them to express the uncertainty on travel and processing times. Ziya-Gorabi et al. (2022), who present their mathematical models in the definite and fuzzy states, fuzzify four parameters, namely the CO_2 emission rate, the travel time between two nodes, the duration of the nurse service, and the patient pickup demand. The last paper by El-

Midaoui et al. (2022) uses fuzzy logic on their data in four stages (a fuzzifier, a defuzzifier, an inference engine, and a rule base fuzzification).

Robust optimization allows for efficient solutions in all possible scenarios. This is of particular interest if too little is known about the probability distribution to sensibly predict future outcomes (e.g., if insufficient historic data is available to derive distributions from). 2 publications apply robust optimization: Shahnejat-Bushehri et al. (2021:2) choose a robust strategy “due to the lack of enough data to estimate these distributions”. Hamdan and Diabat (2020:2) propose a “robust counterpart model that allows the user to select the level of robustness required[.]”

Interestingly, until 2021, all papers featuring uncertainty were stochastic or not closer defined. All papers featuring fuzzy or robust approaches were published from 2021 onwards. Table 8: Planning environment provides an overview on the planning environment in terms of uncertainty and dynamism.

Table 8: Planning environment

Authors	Year	Product	Planning Le-vel	Single-Period	Multi-Period	Uncertain	Deterministic	Dynamic	Static
Anaya-Arenas et al.	2016	Specimen	Operational	x (day)			x*		x*
Anaya-Arenas et al.	2021	Specimen	Tactical &Operatio-nal	x (day)			x		x*
Andoh and Yu	2022	Drugs / Vaccines	Operational		x (week)	x		x	
Aydınalp and Özgen	2022	Drugs	Operational	x (day)			x		x
Benini et al.	2022	Specimen	Operational		x*		x*		x*
Borumand and Beheshtinia	2018	Drugs	Operational	x*			x*		x*
Bouziyane et al.	2020	Drugs	Operational	x (day)		x*		x	
Chahed et al.	2009	Cancer	Operational	x (day)			x		x
Chen et al.	2021	Drugs	Operational	x*		x			x*
De Magalhães and De Sousa	2006	Drugs	Operational		x (week)	x		x	
Dörner et al.	2008	Blood	Operational		x (day)		x*		x*
Eisenhandler and Tzur	2022	Blood	Operational		x (days)		x		x*
El Midaoui et al.	2020	Drugs	Strategic* (LR) &Ope-rational	x*			x		x
El Midaoui et al.	2022	Blood	Operational		x (week)	fuzzy			x*

Elalouf et al.	2018	Specimen	Operational	x (day)			x		x*
Elalouf et al.	2021	Specimen	Operational	x (day)			x		x*
Entezari and Mahootchi	2021	Specimen	Operational	x			x		x*
Ghandforoush and Sen	2010	Blood	Operational		x (5 days)		x		x
Grasas et al.	2014	Specimen	Operational	x*			x		x*
Haitam et al.	2021	Specimen	Operational	x (day)			x*		x*
Hamdan and Diabat	2020	Blood	Operational		x (day)	ro-bust			x*
Hemmelmayr et al.	2009	Blood	Strategic* &Operatio-nal		x (2-weeks)		x		x
Hemmelmayr et al.	2010	Blood	Strategic* &Operatio-nal		x (2-weeks)	x	x		x*
Kergosien et al.	2017	Cancer	Operational		x		x*		x
Lee et al.	2014	Cancer	Operational	x (day)*			x		x*
Liu et al.	2020	Blood	Operational		x (12 days)		x		x*
Malladi et al.	2022	Specimen	Strategic &Operatio-nal		x (10.6 years)	x			x*
McDonald	1972	Specimen	Operational		x (1 day, multiple periods)		x		x
Mobasher et al.	2015	Blood	Operational	x (day)			x		x*
Naji-Azimi et al.	2016	Specimen	Operational		x (1 day, multiple periods)		x*		x*
Özener and E-kici	2018	Blood	Operational	x (day)			x		x*
Petroianu et al.	2021	Drugs / Vaccines	Operational	x (day)			x	recalcula-tion	
Pirabán-Ramírez et al.	2022	Blood	Operational	x (day)*			x*		x*
Ren et al.	2010	Specimen	Operational		x (several days, 3 shifts)		x*		x*

Revere and Roberts	2004A	Specimen	Operational		x (2-week-period, week-days and weekend)		x	recalculation	
Rezaei Kallaj et al.	2022	Blood	Operational	x*		x	x		x
Robbes et al.	2022	Cancer	Operational	x (day)			x	recalculation	
Sahinyazan et al.	2015	Blood	Tactical &Operational		x (week)		x		x
Secundo et al.	2022	Drugs / Vaccines	Operational	x*		fuzzy			x*
Shahnejat-Bushehri et al.	2021	Specimen	Operational		x (1 day, multiple periods)	robust	x	x	x
Tlili et al.	2022	Specimen	Operational	x (day)			x*		x
Wang et al.	2015	Specimen	Operational	x (day)		x			x
Wen et al.	2016	Blood	Operational	x*			x*		x*
Wolfinger et al.	2023	Specimen	Strategic* (LR) &Operational		x (1 day, multiple periods)		x		x
Wu et al.	2022	Drugs	Operational	x*			x*		x*
Yi and Scheller-Wolf	2003	Blood	Operational	x (day)*			x*		x*
Yücel et al.	2013A	Specimen	Operational	x (day)			x		x*
Yücel et al.	2013B	Specimen	Operational	x (day)			x*		x*
Zabinsky et al.	2020	Specimen	Operational	x (day)			x	recalculation	
Zabinsky et al.	2021	Drugs / Vaccines	Operational	x (day)			x*	recalculation	
Zahiri et al.	2018	Blood	Tactical &Operational		x	x		x	
Zangeneh-Khamooshi et al.	2013	Specimen	Operational	x (day)			x*		x*
Ziya-Gorabi et al.	2022	Specimen / Drugs	Strategic* &Operational	x		fuzzy	x		x*

5.6 Dynamic vs. Static

A problem can be static or dynamic, depending on when information becomes available. If all information is known in advance, the problem can be considered static. Its result, then, is a "set of predefined routes which will not be reoptimized nor recalculated if data change along time" (De Magalhães and De Sousa 2006:181). If, however, some information is revealed during the planning horizon, e.g., if a new request arrives as the vehicle is already performing the tour, the problem is dynamic (Shahnejat-Bushehri et al. 2021:2). The new information then needs to be incorporated into the model and the "scheduling plan established at the beginning of the planning period may be adjusted" (Lahyani et al. 2015:2). Bouziyane et al. (2020:300) point out that pharmacies frequently encounter such unexpected, short-notice orders while the workday is already in progress. In their model, they speak of "disruptions, which are unanticipated event occurring during the execution of the routes, and the disruption management is destined for revising an operational plan in real time in order to provide quickly good solutions for the disrupted VRP" (Ibd.). Thus, they consider their problem a special case of the dynamic VRP. Theirs is among the few papers to choose a dynamic approach.

Only 10 out of 53 analysed papers propose solutions for incorporating unplanned requests, half of which do not develop an inherently dynamic approach. Instead, their efficient solution methods allow for quick re-calculation as new information becomes available. This is the case in the work of Zabinsky et al. (2020:538), for example, whose solution approach VeRSA allows that "the schedule and route can be quickly updated in real-time. This provides flexibility to add a new pickup in case a new specimen becomes available and to adjust for cancellations." Similarly, Revere (2004B:407) writes that "the dynamic travel time database provides updated information as needed", but in their other publication (Revere and Roberts 2004A:333), their approach to dynamism sounds a little more labour-intensive: "Service changes can be easily entered into the software by a nontechnical manager, resulting in a new, quickly available, optimal solution."

Meanwhile, in the dynamic stochastic VRP presented by De Magalhães and De Sousa (2006), orders arrive during the day which leads to the partial postponement of decisions. Andoh and Yu (2022:12) mention dynamic demands among the "practical requirements related to the logistics operations for COVID-19 vaccine delivery [that] can be properly modeled in the simulation stage." They mention that their "vaccine logistics system is tested under dynamic and realistic conditions" (Andoh and Yu 2022:11), but do not explore dynamic scenarios in greater detail. Shahnejat-Bushehri et al. (2021:2) handle new requests through postponement and greedy policies. Zahiri et al. (2018:4) allow transshipments "in order to meet the fluctuating and dynamic demands through required redistribution of inventories in the whole system." Papers that do not label themselves as dynamic or explicitly thematize data that becomes available during the planning horizon are classified as static.

De Magalhães and De Sousa (2006:181) point out one important limitation which is that "a problem is not dynamic if changes in data along the planning horizon, could be predicted by the decision maker. This means that if data are not deterministic but the problem can be solved based on some probabilistic assumptions, the problem should not be considered as dynamic." Wang et al. (2015:28) elaborate on typical solution techniques for both the static stochastic VRP (SSVRP) and the dynamic stochastic VRP (DSVRP). As classic solution methods for the SSVRP, they name the "re-optimization" approach and the "two-stage method". In the first of the two stages, an a-priori sequence is proposed, and in the second, after the uncertainty is revealed, recourse actions are taken. An example for such recourse actions can be seen in Hemmelmayr et al. (2010) or in Wang et al. (2015). Consequently, by these standards, their own problem should be considered a SSVRP. In contrast, they point out that in the DSVRP no a-priori solutions are used.

Unscheduled requests for the collection and delivery of medical products arrive frequently, not just in emergency cases, but also in day-to-day pharmaceutical delivery where just-in-time policy is common practice (Bouziyane 2020:300, De Magalhães and De Sousa 2006:178). Considering the abundance of unplanned requests in real life, I was rather surprised to find how few publications featured dynamism. De Magalhães and De Sousa (2006:178) confirm this impression: “An important part of the research in this domain has been done assuming static conditions.” By this they mean that, even though not all relevant information is available at the beginning of the planning horizon and a dynamic approach is needed, many cases are formulated as static problems and solved a-priori, with stochastic data. The obvious drawback is that solutions collapse if the assumed conditions do not come to pass. Reading these elaborations from 2006, I theorized that dynamic approaches may be impossible to implement in reality for lack of technological advances, and in fact, Bouziyane et al. (2020:300) confirm the need for “the support of technology to detect the position of the vehicle and inform drivers of the revised plan.” However, such technological solutions are widely available nowadays, and can no longer help explain why solution approaches still resort to assuming static conditions when reality calls for dynamism.

Dynamic approaches saw a short spike of interest in the mid-2000s. After that, they did not receive much attention until 2018. As such, 8 out of 10 papers featuring dynamic approaches were published in the past five years.

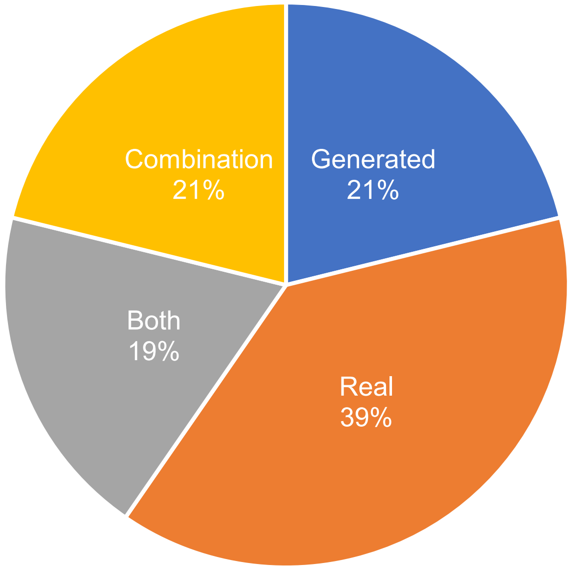
Proportionally, both stochastic and dynamic methods are applied most frequently for drug delivery problems. The significance is even higher when looking at just vaccine delivery: 3 out of 4 papers[32] apply dynamic approaches, while the 4^{th} uses a fuzzy approach to tackle uncertainty (see chapter 5.5). Meanwhile, only 1 paper from the blood cluster features a dynamism, but 5 out of the 16 papers include uncertainty. Publications from the specimen cluster, on the other hand, included uncertainty in 4 out of 22 contributions, but dynamic approaches in 3 papers. That all papers on cancer drugs assume a deterministic environment and only 1 addresses the possibility of dynamic orders through quick recalculation might be due to the characteristics: Since this product is only produced on demand and the production and delivery are planned on short notice, there might be less need to accommodate additional uncertainty than for other products.

[32] The papers by Petronaiu et al. (2021) and Zabinsky et al. (2021) are listed separately in this evaluation, but could be counted as one (see chapter 5.3). The ration would then be 2/3 instead of 3/4, which is still higher than for all other products.

5.7 Test Instances

I distinguish between four categories based on the data provenance: Randomly generated, real case studies, both (usually two data sets, of which one is based on real and one on generated information), or a combination of generated and real data (the data is largely or partly real, but generated or estimated data was used to fill in the gaps in available data). The "combination" option is also selected if the data is "generated based on real data", when it is no longer transparent which aspects are real and which are adapted or estimated. Only one study does not provide any information on where the data is from.[33] From the remaining 52 papers, about 21% use purely generated data (11 publications). All other papers feature real data in some form: 10 papers use both generated and real data sets, 11 publications feature a combination of real and generated data, and the remaining 20 papers (or 39%) use only or almost exclusively real case studies. Altogether, 79% percent of reference papers proclaim to include real-life data.

Figure 3: Data provenance



Di Mascolo et al. (2021) highlight papers that use benchmarks that already exist in the literature. I tried to do the same, but quickly discovered how few authors use benchmarks. Only three benchmark sets are ever mentioned: That of Solomon (1987),[34] used by Malladi et al. (2022) and adapted to the problems of Shahnejat-Bushehri et al. (2021) and Lee et al. (2014); that of Fischetti et al. (1998), used by Tlili et al. 2022, and a combination of those by Taillard (1999) and Golden et al. (1984) applied by Wu et al. (2022). Wen et al. (2016) use a "public dataset" which they also provide access to in their appendix. Since the dataset could not be identified, it is not counted towards benchmarks. All academic benchmarks are counted towards generated data unless the authors contrast and complement it with a second, real case study. Meanwhile, some authors lament the lack of adequate benchmark problems: "Since there are usually no accepted benchmark sets in the literature or the respective data sets are not fully available, this study cannot provide a comparison with real or benchmark examples" (Entezari and Mahootchi 2021:3709). Similar to what Di Mascolo et al. (2021:15) observe, almost all authors use their own instances. While in their survey, 20% of the literature use benchmark sets, in mine, this was only true for 9,4% (5 out of 53 papers).

Since more than half of the papers were published from 2020 onwards (27 out of 52), it is difficult to make on observation on a possible historical development regarding the data used. Looking for a pattern, a slight move away from randomly generated, but also largely real data towards hybrid forms can be observed. 6 out of 10 papers that used both generated and real data were published from 2020 onwards, as well as 8 out of 11 papers using a combination of data. Especially the move away from purely real to combinatorial data ought to be viewed critically, however: in this case, it is hard to say whether the shift towards combined data is a trend or whether authors are simply more transparent when it comes to filling gaps in available

[33]The paper is question is Yücel et al. (2013B). In all likelihood, the data in question is identical with that in their other publication (Yücel et al. 2013A), and the analysis is therefore not distorted.
[34]For full references to this and the following benchmarks, please consult the reference papers that cite them.

real-life data with estimations and generated information. What can be said with more certainty is that 4 out of 5 papers that use benchmark problems were published after the year 2020.

Trying to compare the instance sizes is even more difficult. Authors provide different measures of problem sizes: some give very detailed information on the number of customers, vehicles, depots, etc. while others provide only partial information; some simply name the number of instances without specifying how these instances differ or how they are composed, and still others simply say they use “small, medium and large”-sized problems (or any other combination of these). Depending on the authors’ definitions, a “large”-sized instance may contain over 1000 potential infections to be tested each day (e.g., Benini et al. 2022, Wolfinger et al. 2023) or “just” 50 transportation requests (Anaya-Arenas et al. 2016, 2021).[35] The conclusion at which Di Mascolo et al. (2021:15) arrive also applies to the reference papers in this thesis: “The considered size varies a lot from one paper to another.”

In their analysis, Pirabán et al. (2019:19f) identify “countries with more than two data contributions”: for their survey of the blood SC, the United States and Iran count the largest number of research projects. For this thesis, only publications that use real-life data and make it unmistakably clear where their data is from are assessed.[36] Overall, most studies use data from the USA (5), followed by Austria (4). Breaking down these results by medical product to identify possible research clusters, I observed the following: Most papers on blood have been published in Austria (3), followed by Iran and the USA (2 respectively). For cancer medication, only half of the publications work with real-life data, all of which comes from France (2).[37] As for biological specimens, 3 papers are published in the USA and Canada respectively, while 2 use data from Israel. Finally, drugs and vaccines are mostly researched in China (2) and Mozambique (2), although both case studies from Mozambique are published by the same research team (Zabinsky et al. 2021 and Petronaiu et al. 2021). Another observation is that 3 studies use data from Morocco, but for 3 different medical products (blood, specimens and drugs). 2 of them cite El Midaoui as the first author (blood and drugs).

These observations need to be treated with caution, however: First, due to how much of my literature search is based on snowballing, there might be a strong bias in favour of some research traditions. For example, the entire cluster around Anaya-Arenas et al. (2016, 2021) and Naji-Azimi et al. (2016) use data provided by the same laboratory in Quebec, Canada. Second, considering how little literature I found on some topics, it is difficult to make any statistically relevant claims. For example, 100% of the real case studies on cancer research came from France. What might sound impressive at first look, reduces to only 2 publications upon closer examination. Finally, in a globalized world, research transcends national borders. An example that comes to mind is the research by Zabinsky et al. (2021) and Petronaiu et al. (2021), where an international team tries to improve the vaccine supply in Mozambique using a tool that had been developed in papers using a case study from the USA (Zabinsky et al. 2020) and randomly generated data (Ren et al. 2010).

5.8 Perishability

Perishability can be included in a variety of ways. In this chapter, I show whether perishability is addressed directly or indirectly; through an objective function, constraint, both, or

[35]All four examples concern the same medical product: biological samples.

[36]This means that all generated data is excluded, but also the paper by Yücel et al. (2013A) because the authors do not state whether the clinical testing laboratory that they collaborated with is located in the US, in Turkey, or somewhere else entirely.

[37]A third paper, that of Chahed et al. (2009), is excluded for using an artificial case, but also references the French healthcare context. The fourth and final paper in the cluster (Lee et al. 2014) is published by an international team, but the leading author as well as the research grant are from the Republic of Korea.

neither/different means; how perishability is addressed in these models, what time limits are commonly used, and when the countdown begins.

By addressing perishability directly, I mean that the presence of perishability in the optimization approach is clearly visible and identifiable without further interpretation or explanation, for example through a lifetime constraint (e.g., Kergosien et al. 2017). In contrast, only choosing the shortest travel route in order to quickly deliver a product is considered indirect (e.g., El Midaoui et al. 2020 / 2021). Direct time limits may refer either to a process (transportation or processing), or to the medical products themselves (lifetime). The boundaries between these categories are sometimes blurred. Delivery due dates may be implicitly restricted by the products' stability time, while other authors make it very clear that they choose a transportation time limit below the products' lifetime to ensure that the products arrive on time: Malladi et al. (2022), for example, assume that specimens degrade within 3 hours after extraction, so their shifts (routes) are limited to 150 minutes (2 ½ hours). Yi and Scheller-Wolf (2003) argue that, according to regulations, fresh blood has a shelf life of 8 hours, so they reserve 2 hours for processing and allow the blood to stay in the vehicle for a maximum of 6 hours.

From the 52 papers analysed,[38] 6 papers address perishability only through their objective function, 27 papers have elements in their objectives and constraints relating to perishability, 11 only use constraints to limit product lifetime, and 8 are classified as "other"[39]. An "x" means that perishability is addressed outside of the mathematical model (e.g., Lee et al. 2014 or Wen et al. 2016, see below).

Looking back at chapter 5.3 on the objective functions, the following objectives are most often connected to perishability: travel distance (8), travel time (5), cycle/completion time (here: processing time; 6), tardiness (7), objectives relating to the output of medical products (3), and "other"[40] (2). Costs may reflect perishability in terms of a penalty cost for late delivery (Elalouf et al. 2018).

[38]Like in chapter 5.3, Zabinsky et al. (2021) and Petronaiu et al. (2021) are counted as one.

[39]"Other" at this point means that the papers lacked MIPs, used simulation only, or addressed perishability mathematically but not through just objectives or constraints (e.g., Yi and Scheller-Wolf 2003 who presented Properties 1 and 2).

[40]"Other" encompasses the papers by Tlili et al. (2022), who maximize their patients' priority scores, and Zahiri et al. (2018), who maximize the freshness of the blood products transported to the hospitals.

Table 9: Perishability

Authors	Year	Product	(In-)Direct	Objective or Constraint?	Max. Lifetime	Max. Transportation time	Processing Time Limit	Tardiness	Amount	Route Length	Other
Anaya-Arenas et al.	2016	Specimen	direct	Both	x	C				OF	
Anaya-Arenas et al.	2021	Specimen	direct	Both		OF; C					
Andoh and Yu	2022	Vaccines	direct	Simulation and Constraint		x				C	x
Aydınalp and Özgen	2022	Drugs	indirect	Constraint						C	C
Benini et al.	2022	Specimen	direct	Both	C					OF	
Borumand and Beheshtinia	2018	Drugs	indirect	Both		C	C	OF			
Bouziyane et al.	2020	Drugs	indirect	Both		OF; C		OF			
Chahed et al.	2009	Cancer	direct	Both	C	OF					
Chen et al.	2021	Drugs	direct	Constraint [partial MIP]		C	C				
De Magalhães and De Sousa	2006	Drugs	indirect	[no MIP]		x	x			x	
Dörner et al.	2008	Blood	direct	Both	C					OF	
Eisenhandler and Tzur	2022	Blood	direct	Constraint	C						
El Midaoui et al.	2020	Drugs	indirect	Objective						OF	
El Midaoui et al.	2022	Blood	indirect	Objective						OF	
Elalouf et al.	2018	Specimen	direct	Both		C		OF (cost penalty)			
Elalouf et al.	2021	Specimen	direct	[no MIP]	x				x		

Entezari and Mahootchi	2021	Specimen	direct	Both		OF		OF			C
Ghandforoush and Sen	2010	Blood	direct	Constraint			C				
Grasas et al.	2014	Specimen	direct	Constraint		C					
Haitam et al.	2021	Specimen	direct	Both			C	OF		OF	
Hamdan and Diabat	2020	Blood	direct	Both		OF			C		
Hemmelmayr et al.	2009	Blood	direct	Both	C	OF; C					
Hemmelmayr et al.	2010	Blood	direct	Both	C	OF; C					
Kergosien et al.	2017	Cancer	direct	Both	C	C		OF			
Lee et al.	2014	Cancer	direct	Calculated separately	x				x		
Liu et al.	2020	Blood	direct	Constraint	C				C		
Malladi et al.	2022	Specimen	direct	Constraint	C	x					
McDonald	1972	Specimen	direct	Both	C		OF				
Mobasher et al.	2015	Blood	direct	Both			C		OF		
Naji-Azimi et al.	2016	Specimen	direct	Both		C	OF				
Özener and Ekici	2018	Blood	direct	Both			C		OF		
Petroianu et al.	2021	Drugs / Vaccines	indirect	Both		OF; C					
Pirabán-Ramírez et al.	2022	Blood	direct	Both		C	C	OF (cost penalty)			
Ren et al.	2010	Specimen	indirect	Both				OF (cost penalty)			C

Revere and Roberts	2004A	Specimen	direct	[no MIP] (probably both)	x	OF					
Rezaei Kallaj et al.	2022	Blood	indirect	Objective		OF					
Robbes et al.	2022	Cancer	direct	Both	x	C		OF			
Şahinyazan et al.	2015	Blood	indirect	Constraint							C
Secundo et al.	2022	Drugs / Vaccines	direct	Both	C		OF				C
Shahnejat-Bushehri et al.	2021	Specimen	direct	Constraint		C					
Tlili et al.	2022	Specimen	indirect	Both		C					OF
Wang et al.	2015	Specimen	direct	Constraint		C					
Wen et al.	2016	Blood	direct	Objective + calculated separately						OF	x
Wolfinger et al.	2023	Specimen	direct	Constraint			C				
Wu et al.	2022	Drugs	indirect	Constraint		C					
Yi and Scheller-Wolf	2003	Blood	indirect	Objective + Properties 1 and 2		x				OF	
Yücel et al.	2013A	Specimen	indirect	Objective					OF		
Yücel et al.	2013B	Specimen	direct	Objective			OF				
Zabinsky et al.	2020	Specimen	direct	Both			OF				C
Zahiri et al.	2018	Blood	direct	Both	C						OF
Zangeneh-Khamooshi et al.	2013	Specimen	direct	Both			OF				C
Ziya-Gorabi et al.	2022	Specimen / Drugs	indirect	Objective				OF		C	

Travel time is the only category wherein some problems have both an objective (minimize travel time) and a constraint (maximum route duration), for example Petronaiu et al. (2021). Meanwhile, lifetime perishability is the only aspect that is exclusively addressed through constraints, but never the objective function. “Other” constraints refer mostly to time windows if the authors put particular emphasis on them (e.g., Aydınalp and Özgen 2022, Entezari and Mahootchi 2021, Ren et al. 2010), maximum shift durations (e.g., Secundo et al. 2022, Zabinsky et al. 2020, Zangeneh-Khamooshi et al. 2013) or other delivery time constraints (e.g., Şahinyazan et al. 2015, Zangeneh-Khamooshi et al. 2013).

Despite stressing the perishable nature of these medical products in their publications, some authors only incorporate it very loosely or indirectly into their actual optimization. One such example is the paper by El Midaoui et al. (2022), where deterioration of blood products is tackled indirectly at best. The authors aim at “find[ing] the shortest routing and shortest time” (El Midaoui et al. 2022:1060), but their two variants of mathematical models feature no time-related aspects at all. Moreover, (variable) routing cost and distance seem to be used interchangeably, so even considering distance minimization as a way to address the bloods’ perishability feels like a far stretch. Finally, the authors mention “consumption time” (2022:1065) or “time-consuming in minutes” (2022:1067) in their chapter *Results and Discussion*, where the best time is 70 minutes; nevertheless, the text does not make it perfectly clear whether this refers to the time needed to solve to problem or the time for the vehicles to perform the tour. In another example, the paper by Aydınalp and Özgen (2022) features time windows and road length limitations, but only in their introduction do they allude to the shelf-life and product perishability associated with the medication. Publications featuring objectives and constraints that limit the maximum duration of transportation without clearly linking them to product perishability are also classified as indirect.

There are some unique approaches that are still directly related to the problems perishability. Before tackling their routing-scheduling problem, Lee et al. (2014) adjust production quantity and timing based on drug's half-life. Similarly, Wen et al. (2016) consider the transportation time to calculate the needed amount of appendage (cooling or warming agent) to keep the blood at a stable temperature during transportation.

Anaya-Arenas et al. (2021) do not set a fixed maximum transportation time but make it dependent on the most urgent specimen. Wang et al. (2015) follow a similar approach: In their model, drop-off times are linked to each individual samples rather than a tour or pre-fixed time limit. Regular requests need to be dropped of 2 hours after their earliest pickup time, while for urgent requests, the latest drop-off time for is 1 hour after its earliest pickup time.

In this, Wang et al. (2015) also have the shortest pre-specified time limit. The only suggested time limit that would be even shorter is mentioned by Shahnejat-Bushehri et al. (2021:2): “there is perishability for biological samples from some patients whose care procedure needs to be tracked. For example, for glucose measurements, the allowable time for centrifuging the drawn blood samples is 20–35 min.” This seems to be only an example, however, that does not limit their actual routing decisions. The longest time limit, meanwhile, can be found in the papers by Hemmelmayr et al. (2009, 2010), whose multi-period model sets the maximum shelf life of regular blood products to 41 days. Additionally, Hemmelmayr et al. (2009) set a second limit of 11 days for special blood products, which is the second longest spoilage period. In general, inventory-related problem scenarios such as those by Hemmelmayr et al. (2009, 2010), Liu et al. (2020, who assume a shelf life of 7 days) and Eisenhandler and Tzur (2022; several days), allow for the longest deterioration times. All time limits that extend over a day relate to the resource blood and use multi-period planning (see chapter 5.2).

Average time limits extend from a few hours to a day. A day is a common upper limit used for the transportation of every resource (blood, specimens, drugs/vaccines) except for cancer medication. For reasons explained in chapter 4.4, timely delivery is of particular importance in the case of cancer medication, so in addition to having a stability / shelf life / half-life associated with the product itself, these types of problems usually minimize travel time (Chahed et al. 2009, 2011) or the delivery tardiness (Robbes et al. 2022, Kergosien et al. 2017) in their main function. Lee et al. (2014), as mentioned previously, take a separate approach. Theirs is the only publication on cancer medication that attaches a precise numerical value to their time limitation: 110 minutes is the half-life of radioisotope F-18, in other words, the timeframe within which number of atoms in their nuclear medication reduces to the half of its initial state.

A day can stretch over a full 24 hours or refer to a workday (typically 8 hours) and indeed, not one paper sets a time limit between 8 and 24 hours. All papers with a limit between 8 and 5 hours relate to the resources blood and drugs/vaccines.[41] Meanwhile, every time restriction below this 5-hour-threshold regards the transportation of biological specimens.[42]

It can be observed that the timespans within which one and the same resource is thought to spoil vary. Take the processing time limits for blood as an example: Dörner et al. (2008) state that all blood must be processed within five hours of being collected whereas Mobasher et al. (2015) set a more generous time limit of eight hours for the production of platelets alone. After this time, they consider the blood still useful to produce red blood cells or plasma. It appears that such differences are mostly due to country legislation:

> *"In the U.S., FDA and the American Association of Blood Banks (AABB) regulate collection, processing and storage of blood and its components. According to these regulations, whole blood must be processed within 8 h of donation to extract platelets (Yi & Scheller-Wolf, 2003). Similar regulations are imposed in other countries such as Austria and Turkey as well[.]" (Mobasher et al. 2015:260)*

There are differences as to when the spoilage process sets in. Some authors remain rather vague in their wording or do not name a beginning at all while others state very specifically when the deterioration starts:

> *"Unlike other related contexts, such as blood collecting (Doerner et al. 2008; Doerner and Hartl 2008) which considers that the product starts deteriorating right after the donation, we assume that as long as samples are kept at SCCs [sample collection centre], their deterioration is slowed down due to the controlled temperature and optimal storage conditions. However, as soon as samples are out of the SCC facilities, the samples integrity cannot be guaranteed, even if they are transported in cooler boxes." Anaya-Arenas et al. (2016:603)*

In line with what Anaya-Arenas et al. (2016) explain, I, too, have found that the two most frequent scenarios are these: Medical products may begin deterioration either right after production (e.g. Chahed 2009, Dörner et al. 2008, etc., Benini et a. 2022, Elalouf et al. 2021) or as soon as they are picked up by the vehicle (e.g. Anaya-Arenas et al. 2016, Revere and Roberts 2004A). I take the expression "the time the sample is available" (e.g., Zangeneh-Khamooshi et al. 2013, Zabinsky et al. 2020) to mean "right after production", that is, when a product has been successfully extracted or produced and would theoretically be ready for transport if the vehicle were already waiting. Rarely, other possible starting points are selected. Wen et al. (2016) begin counting down the maximum shelf life as soon as the appendage (cooling or

[41]This is true in my reference papers but might not apply to all vaccines. As Secundo et al. (2022:3) point out, different types of vaccines have different shelf lives.
[42]The only exception to the observations in this paragraph is the paper by Elalouf et al. (2018), who experiment with a time span of 4, 6 and 10 hours and whose resource is blood samples (classified, within this thesis, as a biological sample, although these times suggest that it might be closer to the resource blood).

warming agent) for transporting the blood is added. Rather than waiting until production is finished, in one example, the delivery countdown starts with the beginning of production: "the duration between the production starting time and the time of delivery for injection cannot exceed the stability time" (Kergosien et al. 2017:288). Earlier still, the throughput time in the model by Chen et al. (2021) starts as soon as the drug order arrives at the pharmacy. Wolfinger et al. (2023) differentiate between the time-to-test limit (that is, the time between when a potential case becomes known and the taking of the test swab from this potentially infected person) and the time-to-result limit (that is, the time between taking the test and attaining its result). In this context, the term "collection" may be misleading especially in combination with blood and/or specimens since it could refer both to the donation/extraction of the resource and to the moment when a vehicle comes to pick it up (e.g., Elalouf et al. 2018, Ghandforoush and Sen 2010, Haitam et al 2021, McDonald 1972).

Contrary to what Anaya-Arenas et al. (2016) in the above-cited extract imply, however, I find that when deterioration starts is generally not dependent on the type of medical product. The assumption that it can be properly stored until the start of transportation is found in papers relating to different products. Especially for vaccines, the countdown often starts when efficient cold-chain storage ends, that is, when they are extracted from a refrigerator and placed in (less efficient) cooling boxes for transportation (Petronaiu et al. 2021, Secundo et al. 2022). While postponing the products' deterioration until pickup or delivery is fairly common, Benini et al. (2022) are the only ones to allow actively extending the products' shelf life after the beginning of transportation. However, they are careful to specify that there are limits to prolonging the samples' lifetime: the specimens may undergo the stabilization process only once, and the shelf life cannot be preserved indefinitely.

5.9 Production Scheduling

The final aspects to highlight are production and appointment scheduling. In this chapter, I take a closer look at production scheduling, while appointment scheduling will play the prominent role in the next chapter. At the end of this and the next chapter, I will also comment on whether the hypotheses I put forth in section 2.2 proved to be correct.

As it turns out, production scheduling, in this type of problem, is not always straight-forward and can mean a variety of things. Classic examples include the production of medication or blood products from fresh blood. Meanwhile, some authors refer to the drawing and collecting of blood or the taking of medical samples as "production" (e.g., Dörner et al. 2008, Benini et al. 2022). Other authors call the testing of specimens "processing" and model this stage as a production scheduling problem (e.g., Yücel et al. 2013A / B), since the samples undergo a production-like evaluation process that yields test results. In both cases, output products are being generated. The prerequisite to be counted towards production scheduling in this thesis is that in the problem, decisions related to production need to be optimized (e.g., the amount of donated blood is not considered deterministic but has to be maximized). In other words, production aspects are only recognized as production-subproblems if they form part of the optimization.

I found that when the production step occurs depends strongly on the type of medical product. Typical problem configurations are to either integrate collection and production/processing, which is common for biological specimens, or production and subsequent distribution, which is typically the case for drugs including cancer medication. Blood can fall into either category, or even include all three stages (collection – production – distribution). Few papers acknowledge and elaborate on the theory of the subsequent production and delivery stages, but practically only focus on the collection (e.g., Grasas et al. 2014).

The ways how to include production scheduling in the problem differ as well. One approach is to optimize the **output and/or the initial production quantity with regards to the product lifetime**, so that enough products are available when they are needed.[43] Due to the short half-life of their nuclear medicine, Lee et al. (2014) plan the production amount with the transportation duration in mind. With the same aim of optimizing output, Yücel et al. (2013 A/B) plan the transportation and then the processing of their medical samples, so that the amount of specimens processed by the next morning is maximized. Zahiri et al. (2018) optimize both the collected amount and the production of blood components in a way that maximizes the freshness of the delivered blood products. In the papers by Yi and Scheller-Wolf (2003) and Hamdan and Diabat (2020), the collection (quantity) of fresh blood is optimized together with the transportation of blood products. In the case of blood, the amount of donated and collected blood is frequently maximized in blood mobile (location) routing and scheduling problems like in Şahinyazan et al. (2015) and Ghandforoush and Sen (2010). They chose their blood mobiles' location, duration of stay and travel route in a way that maximizes the amount of collected blood.

Alternatively (or sometimes additionally), the production problem can consist in processing donated blood to produce blood products such as platelets. In such cases, the papers usually work with **processing time limits**. Ghandforoush and Sen (2010) and Özener and Ekici (2018) gear their collection amount and transportation scheduling to maximize platelet production. With the same goal of optimizing platelet production, Mobasher et al. (2015) even synchronize the donation appointment and collection times with the processing time limit. Yi and Scheller-Wolf (2003) plan the routes in a way that 2 hours remain to process the blood and produce platelets. Similarly, Pirabán-Ramirez et al. (2022) and Haitam et al. (2021) plan the collection and transportation of blood to leave enough time for processing. Wolfinger et al. (2023) coordinate the collection of the samples with the subsequent assignment to evaluation runs, so that the time-to-test and time-to-result are respected.

Processing time limits and due dates are also common in medication production, particularly cancer medication. In their chemotherapy SRPs, Kergosien et al. (2017) and Robbes et al. (2022) integrate the production problem (composed of several production stages) and the subsequent delivery to reduce the overall tardiness of delivery. Minimizing delivery tardiness is also one of the objectives by Borumand and Beheshtinia (2018), who integrate a transportation and a production scheduling problem in a two-stage pharmaceutical supply chain. Chen et al. (2021), in their problem that so resembles cancer medication production, minimize the maximum throughput time of medication.

In some works, like that of Elalouf et al. (2021) and Benini et al. (2022), samples undergo a processing stage as part of their journey to the testing laboratory. In Elalouf et al. (2021), this is a centrifugation step, and in Benini et al. (2022), specimens can be brought to stabilization hubs. Both processes serve the use of prolonging the samples' shelf lives, and they are associated with a certain duration, but other than that, treated as yet another node to visit before bringing them to the testing lab.

Some authors speak of linkage or coupling constraints that connect their subproblems. In Eisenhandler and Tzur (2022), the processing stage functions as a linkage constraint that connects the collection to the distribution subproblem. Chahed et al. (2009:186) mention coupling constraints when referring to the interdependencies in their problem: "The production and

[43]Some papers do not optimize the production quantity itself, but comment on its immediate effects. Dörner et al. (2008) consider the drawing of fresh blood their production problem. They specify a production time window which, in combination with the deterioration time, allows to calculate the minimum amount of customer visits, but is not itself subject to optimization. Liu et al. (2020) do not optimize a production problem, but in their sensitivity analysis comment on the effects that the production capacity, and consequently the quantity of available blood platelets, has on their VMIRP.

delivery dates are interdependent. The delivery and the administration of the drug have to be carried out within the drug shelf life time period (i.e. coupling constraint)."

Without explicitly calling their problem production scheduling, some authors highlight the parallels between this problem type and their approach. They do not include an actual production step but mirror the structure of production/machine scheduling. Ren et al. (2010) use overtime as a performance measure and state: "It is common in the production planning and scheduling literature to use overtime as an option for shift scheduling" (Ren et al. 2010:1988). Zangeneh-Khamooshi et al. (2013:1220) describe how they incorporate elements that are traditional for scheduling problems, most prominently the objective of minimizing cycle time, into their routing problem. Zabinsky et al. (2020:539f) compare their problem to a machine scheduling problem with the objective of minimizing the completion time, which they explain is analogous to the make span, before presenting their Vehicle Routing and Scheduling Algorithm (VeRSA).[44] Secundo et al. (2022) use PS terminology in their vaccine delivery and administration problem and present it as a job-shop type of problem.

In summary, the main elements to link production and transportation in combined SRPs are (1) optimizing the production amount in a way that the right amount of product can be delivered at the right time,[45] and (2) collecting and delivering products while reserving enough time for the following production stage (processing time limit instead of just transportation time). These are not mutually exclusive. Moreover, some papers explicitly point to how their subproblems are linked.

In line with my hypothesis, production scheduling proved most relevant for particularly time-sensitive medical products: cancer medication and blood platelets. It can be noted that most authors who concentrate on producing a specific blood product choose blood platelets as their focus. This seems reasonable since they are the blood component with the shortest lifespan. Mobasher et al. (2015:261) even point out that if blood is not returned to the depot in time for platelet production, it is not fully wasted and can still be used to harvest other components, such as plasma or red blood cells. Ghandforoush and Sen (2010:33) give insight into the challenges and cost factors associated with the production planning of platelets. The remaining hypotheses will be evaluated at the end of the next chapter.

5.10 Appointment Scheduling

As for production scheduling, I figured that appointment scheduling would be most prominent in disciplines where the medical products' lifespan is very short, like in the cancer treatments, and this turned out to be true. As drug medication is made-to-order, the treatment appointment (or time of administration, which is either identical or closely related to the delivery due date) must be known to determine the starting time of production, or it must be scheduled together with production and delivery. Thus, cancer treatment requires the coordination of drug production, medication delivery and patient treatment. Since all these steps follow in quick succession, this is the product cluster where production and appointment scheduling are most relevant and yield the biggest potential for efficiency. Especially the chemotherapy supply chain was identified in the literature as one of opportunity, for example by Garaix et al. (2020:131): "Appointment scheduling in highly constrained health care services has been identified as research challenges in 2008 (Gupta and Denton 2008). Chemotherapy appointments make one of these challenges, as a multistep scheduling in a dynamic and uncertain context." Another source states:

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[44]Ren et al. (2010), Zangeneh-Khamooshi et al. (2013) and Zabinsky et al. (2020) form part of the same research strand and build on each other's work.

[45]Warranting, of course, that the products are still sufficiently fresh at the time of delivery.

"After choosing the treatment days using the planning scope, the exact appointment, drug preparation, and drug delivery times are defined in the scheduling scope. We observed that, in the scheduling scope, significantly more attention is focused on patient scheduling than the scheduling of nurses, drug preparation, and drug delivery." (Hadid et al. 2022:6)

Apart from cancer medication, appointment scheduling is featured most prominently in the work of Mobasher et al. (2015). In their *Integrated Collection and Appointment Scheduling Problem (ICASP)*, they synchronize the appointment and collection schedules in the blood supply chain to improve the availability of platelets, which are the most time-sensitive component of fresh blood. Mobasher et al. (2015:261) claim that this combination of coordinating the pickup of donated blood and appointment schedules in order to maximize platelet production "has not been studied in the literature before", and indeed I could not find any evidence that proved them wrong. They explain that their study is different from others in the way the appointment scheduling is handled: "instead of assuming that the appointments at a donation site are uniformly distributed throughout the day (or scheduled a priori), we determine appointment and collection schedules in an integrated manner in order to improve platelet supply" (Mobasher et al. 2015:262). For example, they cite the papers by Ghandforoush and Sen (2010), Dörner et al. (2008), and Yi and Scheller-Wolf (2003) as the most related studies in the literature and add: "Although the processing time limit is considered in all these studies and multiple visits to donation sites are allowed in Doerner et al. (2008) and Ghandforoush and Sen (2010), they all ignore the appointment scheduling aspect and assume that the donation times are predetermined" (Mobasher et al. 2015:261). Such an approach is neither uncommon, nor unreasonable. Özener and Ekici (2018:114) confirm that assuming fixed donation times is common practice, and that it by no means devalues the importance of appointment scheduling:

"In the current practice, most of the donation sites are working on an appointment schedule […] in order to plan and utilize their personnel effectively, reduce waste due to the outdated products and increase the donor satisfaction by reducing the waiting times. Hence, most blood donation organizations encourage scheduling appointments in advance and keep only limited (if any) slots for the walk-in donors […]. Following this practice, in this study we assume that the donation times are known ahead."

Donation appointment scheduling is the most relevant form of AS at the operational level of the blood SC (Baş Güre et al. 2018:87, Pirabán et al. 2019:8, Williams et al. 2020:203). The relevant decisions consist of the appointment duration and the time slot during the planning horizon (Pirabán et al. 2019:8). Moreover, Baş Güre et al. (2018:87) point out that few publications on this topic exist and that "their scope generally considers only the service provider viewpoint (collection clinic). An approach that integrates clinic planning with production requirements has not been explored so far." Williams et al. (2020:203) also observe a lack of research with regards to appointment scheduling in the blood supply chain, especially in combination with other goals. Indeed, the paper by Mobasher et al. (2015) is the only one from the blood cluster that features AS.

Another area where appointment scheduling might prove useful but is currently not prominent is vaccinations. As mentioned in chapter 4.3.1, Andoh and Yu (2022:2; 8) explain that the high uncertainty associated with the supply of COVID-19 vaccines exacerbates the planning situation in the vaccination centres: "Based on the vaccines received from the NIPH at the beginning of each week, the vaccination centers at the municipal level can only plan the administration in a responsive way. However, the number of vaccine doses received is uncertain, which leads to a complex planning problem" (Andoh and Yu 2022:8). This results in many cancellations and rescheduling, which of course slows down the vaccination coverage rate, decreases patient satisfaction and might, in the worst case, even lower their likelihood to get the vaccination at all. Despite the difficult planning situation, there would definitely be a need for appointment scheduling. In their own problem, Andoh and Yu (2022) do not optimise the administration appointments together with the delivery schedule. Zabinsky et al. (2021) and Petronaiu et al. (2021) concentrated uniquely on the distribution. In the paper by Secundo et al. (2022), who consider home-visits for vaccination, the patient visiting times coincide with the vaccination appointments.

Still with the recent pandemic in mind, another promising area of application for AS would be to schedule patients' (PCR) test appointments. Scheduling the test appointments together with the subsequent transportation of the samples to the laboratories might prove useful. In the case of sizable test centres, like in a pandemic situation, where patients only travel to give samples, scheduling their appointments might reduce their waiting times but also play an important role with regards to their samples' lifetime, which is considerably short as we have seen in chapter 4.2. Wolfinger et al. (2023), who consider both patient visits at their homes and at such test centres, specifically assume that their test centres "do not accept bookings or drop-in patients, but only service cases that have been assigned by a public health institution." Potential cases get assigned to timeslots and depending on how large or small these timeslots would be in real life, patients might know the timing of their tests fairly accurately. Apart from that, in the literature on specimens, (patient) appointment scheduling is almost completely neglected. The one paper that mentions appointments is that of Anaya-Arenas et al. (2016:603), who use the term only in connection with the pickup times of the samples in the collection centres.

In chapter 2.2, I put forth the following conjectures: My first hypothesis was that PS and AS would be of particular importance in my type of problem largely because of the patient focus, as service levels would increase, and real and perceived waiting times would be reduced. This could not be confirmed. Although patient satisfaction, service levels and waiting times were given as reasons or goals of efficient planning (e.g., Chen et al. 2021), they played much less of a role than expected, especially in direct relation to PS and AS. Second, I predicted that PS would prove more relevant than AS. This was true in all product clusters. Finally, I expressed the belief that integrating processes would be particularly beneficial in this type of problem. I still believe this to be true, and although integrated problems have not received all that much attention in the research up to this point, all authors seem to agree that they should. (Part of) the reason for this may be that there exist clear precedence relations between the optimization stages and tasks in all these problems. Process Y (e.g., delivery) cannot start before process X (e.g., production) is finished. If processes or subproblems are optimized individually, waiting times are more likely to occur, which proves particularly problematic for easily perishable resources.

After this deep dive into the literature, I would say that I overestimated the importance of appointment scheduling. In this, I see great potential for future research since I still believe that integrating these processes with other stages of the health product collection and distribution can be very beneficial.

6. Discussion

6.1 Literature Search: Learnings and Suggestions for a more Refined Search

I feel it is necessary to review my approach to finding and selecting literature critically. This way, mistakes I made can be avoided and my learnings may be put to use during future research.

First off, I want to point out one major shortcoming in my search process. Similar to local optima during an optimization process, through snowballing alone, one might easily get stuck in certain research traditions or clusters. Within these clusters, authors know about each other's contributions and keep citing one another. This is clearly visible from Figure 5 and from the fact that I found many papers by the same authors. It is interesting, on the one hand, to see how a problem evolved over time, as did the solution techniques. Certain papers that were written by (largely) the same team or funded by the same institution build directly on each other. Examples for this are: Anaya-Arenas et al. (2016), Naji-Azimi et al. (2016) and Anaya-Arenas et al. (2021) or Ren et al. (2010), Zangeneh-Khamooshi et al. (2013), Zabinsky et al. (2020), Petronaiu et al. (2021) and Zabinsky et al. (2021).

On the other hand, one remains blind to what else is out there. Suppose there was a similar but different cluster, cluster B, with different authors focusing on the same topic. Since these two clusters A and B are unaware of each other, through snowballing alone, one could never get from cluster A to cluster B.

One possible strategy to escape this is through another keyword search. Selecting new and different core papers from which to start the snowballing process might reveal an entirely new cluster of research. In order for this to succeed, the keywords would have to be different from the ones in cluster A. This was not the case in this thesis since the keywords for the optimized search were largely derived from or inspired by the keywords in the publications I had already found. They led to some previously unknown texts, but also to many publications that were on the list already (see chapter 3.2).

As for the keywords themselves, after experimenting with various combinations, I decided to start with a very generic initial search in order not to miss any relevant contributions. This decision was mainly due to the initial difficulty of including the perishability-dimension of the medical products into the keywords. Table 3: Literature search 1.1 (chapter 3.2) includes an example of how frustrating this early search was, and how few results my searches yielded. Thus, I let the relevant keywords reveal themselves to me over time. As the list of relevant publications grew, I became aware of more and more synonyms and alternative designations for the perishability-characteristic of the products, including *perishability, deterioration, spoilage, life-span, shelf-life, half-life*, and many twists on the keyword *time*, such as *life-time, turnaround-time, processing time, transit time, delivery time* and by extension even *travel time, overtime, completion time and cycle time*. Related, but not synonymous was wording like *make span and tardiness*. The most relevant of these keywords were then incorporated into a more targeted search string. The goal was not to find every relevant article, but to attain the best possible percentage of relevant contributions among the search results without setting the focus too narrow.[46] To this end, keywords were swapped out one by one, the changes in search results were be compared to the previous search, and then the swap would either be accepted or discarded. For example, summarizing *("cycle time" OR time* OR "processing time" OR*

[46]A search that is too narrow would be oriented so close towards articles that were already on the list that no new contributions could be found.

"transit time" OR lifetime") under just **time* was accepted, whereas the change from *("half-life" OR "shelf life")* to simply **life* was rejected (worse result), as was the inclusion of *deteriorat** or *spoil** (no change). A learning curve can be seen between the first generic and the second optimized literature search (from 3,76% to 39,47% relevance). Still, I feel there is still room for improvement.

The optimized search string looked like this. I split it into the 4 major semantic segments to explain my reasoning for choosing these keywords, but also reflect on what could have been improved:

Table 10 : Analysis of the optimized keyword search string

1	2	3	4
((routing OR routeing) AND scheduling)	AND (production OR appointment OR transportation OR collection OR delivery)	AND (perishab* OR *time OR "cold chain" OR "half-life" OR "shelf life")	AND (drugs OR pharmac* OR blood OR platelet OR cancer OR chemo* OR "nuclear medicine" OR specimen OR "bio* sample" OR vacci*)

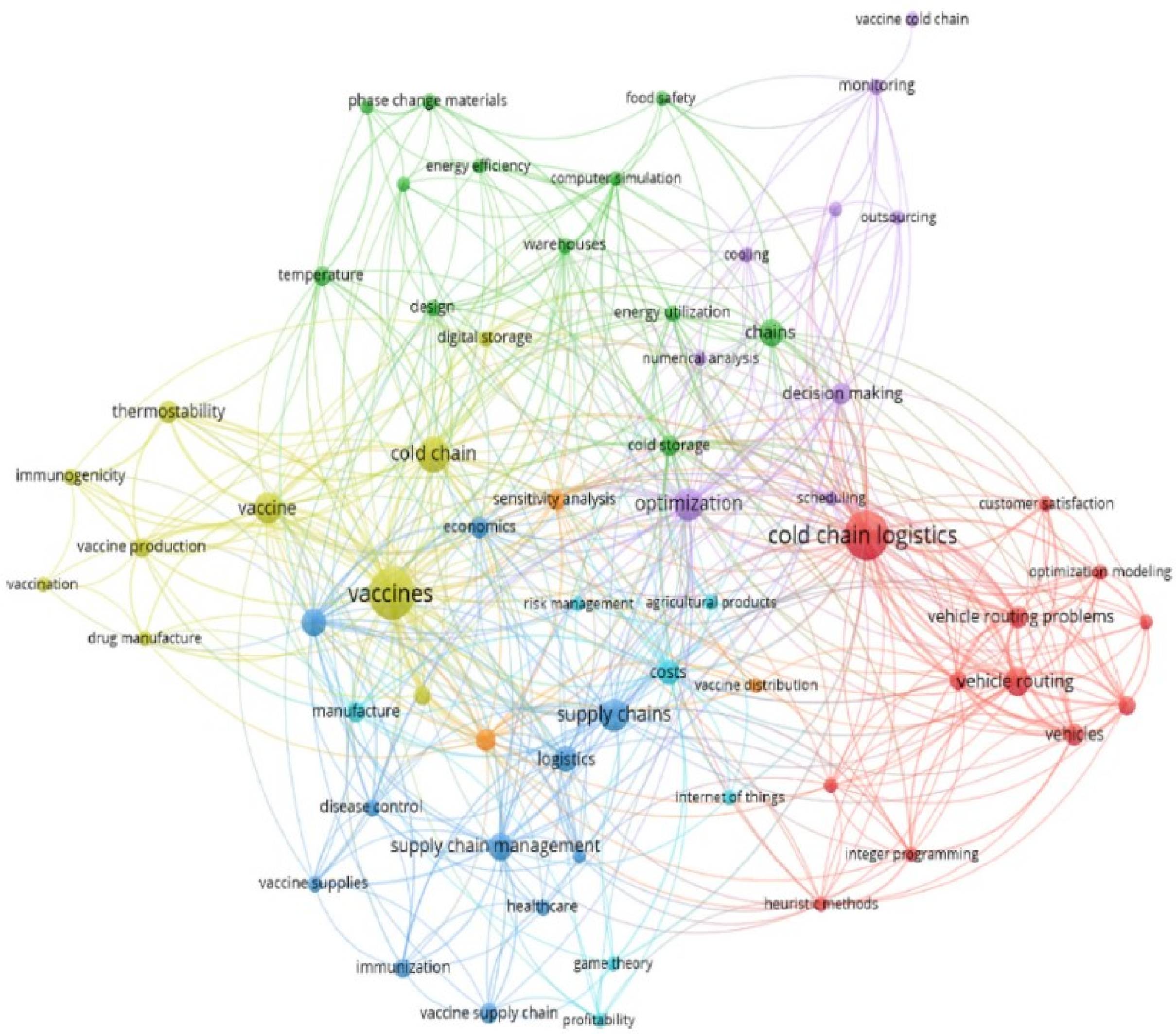
Segment 1 is supposed to limit the results to routing-scheduling problems only. Segment 2 was included after some experimentation to restrict the results to and strengthen the relation with the OR-discipline. On Web of Science, the addition of segment 2 reduced the search hits from 349 to 80 results, which seemed like a reasonable limitation.[47] Segment 3 addresses the perishability-dimension as explained above. All combinations with time are subsumed under **time*, both to shorten the search string in a sensible way, but also to include keywords relating to time that had not shown up during the keyword collection and analysis. Segment 4 replaces the "healthcare"-section of the original search. During the keyword analysis, I found that most authors mention their respective medical product directly rather than looking for broader synonyms like medical product. On the one hand, this increases the chances of finding papers related to one of the abovementioned products; on the other hand, it drastically reduces the chance of finding literature on different products not considered so far. One strategy to discover new products was to include the keyword COVID-19 in the last segment, hoping that more diverse texts might have been published during the recent pandemic. This attempt was not successful. Removing this extra keyword from the search string reduced the hits from 80 to 68 on WoS and from 26 to 20 on Scopus and increased their relevance.

Despite being at the heart of this thesis, the combination of *(routing OR routeing) AND (scheduling)* in segment 1 is not without drawbacks. These I want to illustrate by the example of vaccine distribution. Andoh and Yu (2022:5) created a keyword co-occurrence map (Figure 4)[48] which may help identify why literature on the topic of vaccines in particular was hard to find. As the red nodes on the righthand side prove, *scheduling* is a very rare keyword to be used in this context. Rather than keyword-searching for routing and scheduling, for the purpose of finding literature on vaccines, it might be a good idea to look for *((supply OR cold) chain)* in the first round and then filter out literature that lacks either routing or scheduling or both. The fact that "healthcare" is also represented by a rather small node explains why my initial search yielded only one result relating to vaccines (Zabinsky et al. 2021). Moreover, *perishability* or similar phrases derived from my keyword analysis were hardly featured. In fact, from the entire

[47] This was during the final search on 05.11.2022, 12:25, with all other setting (Topic; Languages: English; Document Type: Articles) in place.
[48] Figure 4 specifically focusses on the vaccine SC. For a similar co-word cluster diagram on the blood supply chain, please consult Eghtesadifard and Jozan (2022:1195).

section referring to deterioration of healthcare products (segment 3), only *cold chain* is featured in the keyword co-occurrence map. Still, considering how relevant this particular phrase is (represented here in red, yellow, green and purple), it feels like more relevant literature should have been featured in the optimized keyword search. Then again, this lack can probably be attributed, at least in part, to my insistence on the *routing AND scheduling* combination.

Figure 4: Keyword co-occurrence map of the vaccine supply chain and cold chain logistics (Andoh and Yu 2022:5)



Another interesting keyword combination to consider instead of R+S might be *last-mile logistics*, as Lin et al. (2022:9) demonstrate:

> *"The term "last-mile logistics" refers to the movement of goods from the last transportation center to their final destination. This theme has received significant attention (33 out of 46 articles), and seven sub-themes were identified. Our analysis revealed that the major focus in this theme is the distribution of the vaccine, drug, testing specimen, and medical supplier (18 papers). This finding makes sense, given the importance of using pharmaceutical interventions to control the pandemic."*

Some keywords led to unrelated results due to their double meaning. *rout** as an abbreviation for *route* or *routing* had to be omitted since it allowed results for *routine*, which were particularly frequent in medical texts (*routine examination*, for example). The problem of *route* also referring to administration methods of medication (oral route, subcutaneous route, etc.) remained, however. With *(routing OR routeing),* I tried to incorporate two spellings I had found while simultaneously minimizing the risk of false positives caused by different meanings of *route*.

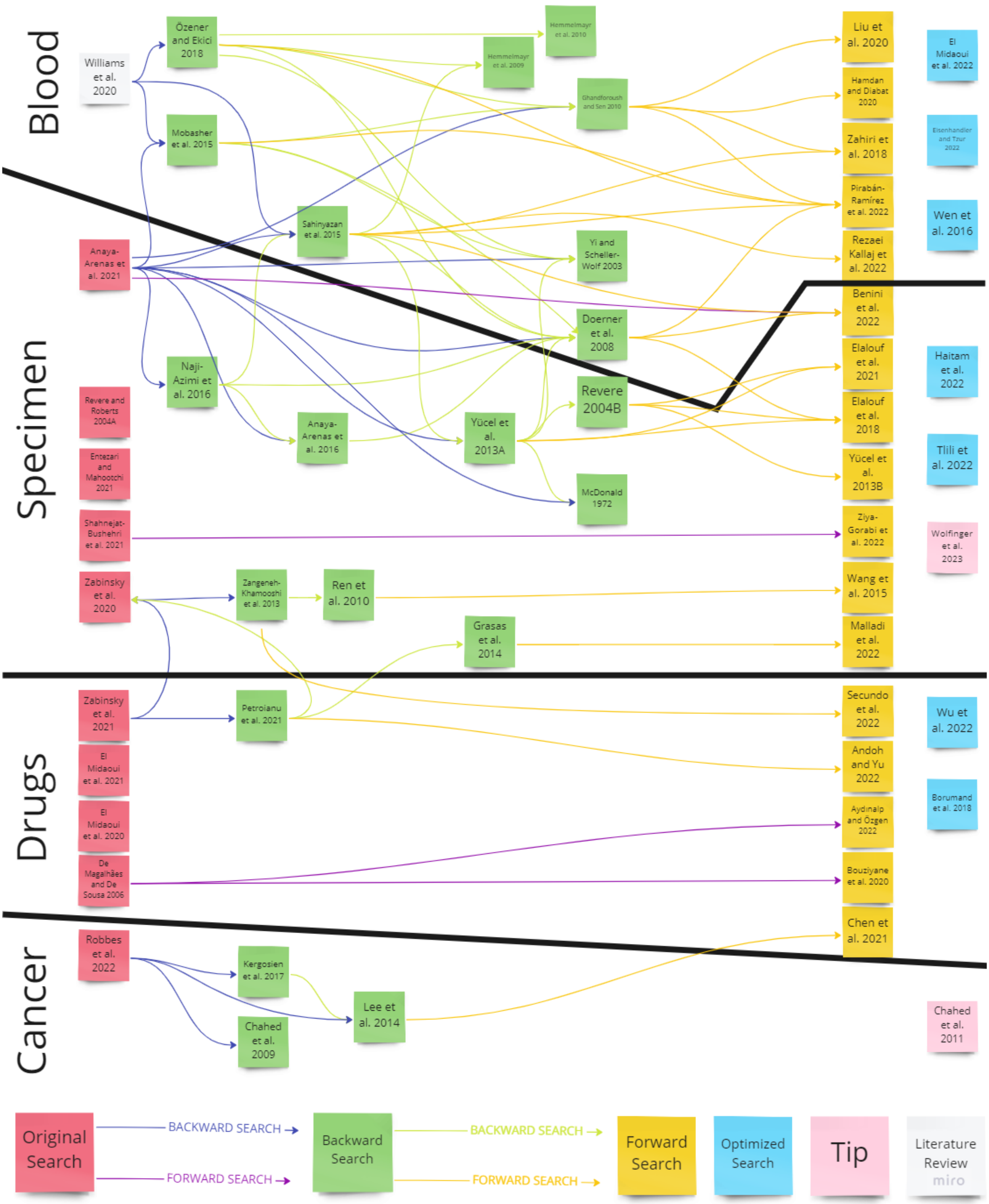
Similarly, in segment 4, *sampl** (as in biological or medical sample(s), sampling) proved to be a very tricky keyword. Due to many false hits related to testing and sample sizes, it was finally excluded from the list of keywords. Instead, the keywords *specimen* and *bio* sample* (*bio** replacing biological and biomedical) were used to refer to this type of medical product during the last, refined keyword search.

If I were to do the literature search again, knowing what I know now, I would do things differently. Even though I still believe starting out with very broad, generic keywords is a valid strategy, especially when one is not yet familiar with the terminology of a certain field, I would skip this step the second time around. Scanning 266 texts and only including 10 is by no means efficient. Instead, I would start out with three or four targeted, but more diverse search strings. I would experiment with leaving out the *routing AND scheduling*-combination entirely and replacing it with something like *(cold chain) AND (distribution OR logistics)* or maybe *last-mile AND (delivery OR logistics)* and then filter out the contributions that do not involve RSPs. Excluding segment 1 altogether and refining segment 2 instead might be worth looking into. I found that snowballing was a useful strategy, but I would start out from a stronger core set of texts found through a more varied keyword search.

Since snowballing was such an essential search technique, I created Figure 5 to visualize how the papers are connected. The papers are colour-coded: Red means that the texts were found during the initial search. Green means they were found through backward snowballing. Yellow texts were discovered through the forward search and blue papers were obtained through the optimized literature search. The colours of the connecting arrows also bear meaning: If a text was found through backward snowballing from one of the core texts, it is dark blue, while purple means that it was found through forward searching these core articles. Light green arrows mean that a text was discovered through backward searching a paper that had itself been found through backward search, and orange arrows connect texts found through backward search to the results from forward searching them. The fat, black lines separate the papers thematically by medical product (blood, specimens, pharmaceuticals, and cancer medication).

In the following two subchapters, I will take a closer look at how these topics turned out to be connected during the search. Moreover, I want to reflect on why it might have been more difficult to find publications on certain topics and put forth some hypotheses.

Figure 5: Cross-citation across all reference papers



6.1.1 Blood and Specimens

Interestingly, the original keyword search with the generic search string did not yield a single article on the resource blood, with the exception of a literature review by Williams et al. (2020).[49] All other publications were found through snowballing and after fine-tuning the keywords, and they would not have found their way into this thesis at all if it were not for Williams et al. (2020) and cross-references from other medical products. Especially the paper by Anaya-Arenas et al. (2021) which focuses on specimen collection led to many RSPs transporting blood. The paper by Dörner et al. (2008), which was not even featured in literature reviews on the blood SCM before the forward search,[50] was instead referenced by many other authors, both from the blood and the specimen cluster. This may also be one of the reasons why the (blood) collection echelon was on my radar much earlier than the delivery echelon: The paper by Williams et al. (2020) focuses explicitly on the collection stage. The paper by Anaya-Arenas et al. (2021), like other papers in its cluster, concentrates on specimen collection, which is thematically closer to blood collection than delivery.

How little blood was featured among the original search results was particularly surprising as it turned out to be one of the most well-researched perishable medical products. Already during the backward search, but especially during the forward search, it became even more apparent how much research has been done on the resource blood. If the focus is broadened from just RSPs to the entire supply chain, including inventory, donor scheduling, blood bank management, etc., blood may easily be more popular than specimen transportation. Especially during the last few years, focus shifted from a single echelon (collection or delivery) to a wholistic approach optimizing the entire blood supply chain, from the donors to the recipients in hospitals or clinics (e.g., Samani et al. 2020, Khalilpourazari and Arshadi Khamseh 2019, Fazli-Khalaf et al. 2019, Haeri et al. 2020). Some of these studies feature transportation issues, some even consider scheduling, but as a rule, routing and scheduling are hardly ever combined in these problems. Instead, several of these approaches feature disaster scenarios such as earthquakes and aim at making the blood supply network more disaster resistant. For more information on the emergency setting, refer to chapter 6.2.2 of this thesis. Inventory and ordering policies in blood banks and hospitals have also been studied extensively and were featured mostly in the forward search from Ghandforoush and Sen (2010). Theirs was also the most highly cited paper, with a total yield of 90 mentions.[51]

Among the papers optimizing the entire blood supply network, some were excluded due to their assumption that the delivery time of blood products is negligible and has no effect on the age of the products (e.g. Ensafian et al. 2017, Kaya and Ozkok 2020). “Perishability effects are not considered in our model. We assume that the delivered products can all be consumed before their expiration dates and the effects of perishability are negligible,” Kaya and Ozkok (2020:763) clearly state. This may be true especially for products with longer shelf lives (see chapters 4.1, 5.8), but does not meet the inclusion criteria of this thesis.

In contrast to blood, the cluster on specimens was placed at the centre of Figure 5 since it touches on almost all other topics (except for cancer medication, which had almost no overlap with any of the other clusters). It also ended up being the biggest cluster with a total of 23 contributions. Given all of this, I found it all the more surprising that this was the only topic I could not find a literature survey on.

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[49] Please note that Williams et al. (2020) is the only literature review included in Figure 5. Only literature reviews found among the initial search results were used as a basis for snowballing.

[50] The paper is cited neither in Williams et al. (2020; original keyword search), nor in Beliën and Forcé (2012), Osorio et al. (2015) or Baş Güre et al. (2018; all three found through backward snowballing); it is, however, included in the reviews by Pirabán (2019) and Torrado and Barbosa-Póvoa (2022).

[51] On Scopus and WoS (after the removal of duplicates) during the last forward search on the 30th of September 2022.

6.1.2 The Pharmaceutical Supply Chain: Drugs, Vaccines, Cancer Medication

Against my initial hypothesis that the literature on the delivery of drugs would be the most vast and diverse of all topics, I did not find an abundance of publications. The most obvious explanation might be that I overestimated the amount or relevance of fresh drugs like cancer medication. It also stands to reason that the lack of literature on the PSC might be caused, at least partly, by my search process. Still, this experience was mirrored by other authors. According to Wu et al. (2022:657), even in the year 2022, literature on drug distribution is scarce:

> *"There are few literatures based on drug delivery characteristics and study VRP with the constraints of load capacity and maximum distribution time simultaneously. […] Although the research on the vehicles routing problem of heterogeneous fleet is rich, there are relatively few studies on its application to pharmaceutical logistics."*

Petronaiu et al. (2021) and Zabinsky et al. (2021) made a similar discovery when looking for easy-to-use software tools they could adapt to their problem. Through analysing 33 possible tools, Petronaiu et al. (2021:2338f) realized that "[m]ost of the software that provide decision support systems for humanitarian logistics focus on inventory control and are primarily used for disaster preparedness and response but do not incorporate routing. These systems also primarily address management but not operational issues." Besides IRPs, drug delivery is sometimes featured in HHC problems before 2020 (e.g., Liu et al. 2013, several publications by Fathollahi-Fard et al. 2018 / 2019) but usually only in terms of vehicle capacity, with neither timing constraints, nor in any other product-specific role. Wu et al. (2022:680) confirm: "Prior research has predominantly focused on the load weight in vehicle capacity […] and rarely considered the volume and time requirement of pharmaceutical." In literature surveys evaluating OR-methods to optimize the pharmaceutical supply chain (e.g., Narayana et al. 2014, Settanni et al. 2017), RSPs are not even mentioned, and even for vehicle routing alone, few studies are cited. Part of the reason may be that, apart from De Magalhães and De Sousa (2006) and Borumand and Beheshtinia (2018), all relevant publications in the drug/vaccine cluster were published from 2020 onwards, which amounts to 83% of all reference papers on this topic. This field of research has grown explosively in the last few years (chapter 5.1), especially regarding the vaccine supply chain. The recent COVID-19 pandemic can definitely be seen as a driver in this boom (Andoh and Yu 2022:6, Lin et al. 2022:9).

Still, it seems strange that the topic apparently had not received more attention before 2020. Pharmaceutical transportation is not a new problem that emerged during the pandemic. Since the outsourcing of drug production to increasingly large pharmaceutical companies, medication needs to be transported to small pharmacies, hospitals and healthcare centres. Why, then, have Supply Chain Management and Operations Research discovered this field only recently? I want to put forth four hypotheses:

1. The problem is too generic. Dry-storage pills with long shelf lives require no special transportation. They are small in size, lightweight, and no different from any other product that needs to be delivered. Even the need for a dynamic ordering policy (e.g., De Magalhães and De Sousa 2006), is not confined to the pharmaceutical supply chain and might have been easily adapted from any other, non-healthcare-related scenario, thus reducing the interest in drug transportation as a stand-alone problem.
2. The problem is too hard. Particular problem characteristics like the need for temperature control, risk management by factoring in road conditions, or the various interdependencies and very tight TWs (cancer medication) might have been too difficult to model, program or test a few years ago. For example, the ground-breaking paper on HHC and cancer treatments by Chahed et al. (2009) presented many reflections and theories that went far beyond the stripped-down version of the problem they actually

modelled. As the available technology improves, new research directions open up, and that is why the research interest is expanding just now.

3. The knowhow was there, but the academic interest was not. Research was conducted, but by private companies who hoped to gain competitive advantages and, thus, did not make their findings publicly available. This might be more relevant in this cluster than others if, as Wu et al. (2022:654) write, competition is fierce and investing in faster, more cost-efficient supply chains might give enterprises an edge over their competitors. Profitability and competitiveness might be less of an issue for other products, e.g., for the collection of blood which is often organized by a public aid organization like the Red Cross / Red Crescent. Meanwhile, for non-commercial research, the specific problem extensions might not have received as much attention before the outbreak of the COVID-19 pandemic, when aspects like cold chain transportation did not seem as critically relevant.
4. Research was conducted and is publicly available. The reason why I did not find more literature is the search methodology (the databases I used, the keywords I settled on, etc.). That other authors made a similar experience might not mean that there is insufficient literature, but that it is scattered and difficult to identify. Conducting a thorough review on the topic of RSPs for perishable pharmaceutical products alone and using all available capacities on finding and reviewing each and every possible publication in this field might be an interesting project for future research.

As for cancer medication, this strand of research looked more promising at first than it ended up being. The literature search initially yielded only one article, that of Robbes et al. (2022), that fit all the inclusion criteria. The remaining articles in this chapter were found through snowballing. At the time they were writing their article, Robbes et al. (2022:786) only knew of two other publications addressing the combined production and delivery of cancer-drugs within operations research: Chahed et al. (2009) and Lee et al. (2014). They further claimed that the delivery-dimension of the problem was not taken into account until the writings of Kergosien et al. (2017). The authors then went on to review similar and related problems in operations research, which, however, did not specifically address the combination of characteristics arising from the healthcare context that is essential to my work. The forward search from Robbes et al. (2022) yielded a review published very recently by Hadid et al. (2022) who confirm that research on this type of problem is scarce: “[D]rug delivery from the pharmacy to the infusion bed or chair, drug expiration periods […] have attracted minimal attention from scholars.” (Hadid et al. 2022:17) In fact, out of the 45 studies they included in their review, only 7 were of initial interest for this thesis:

> *“After choosing the treatment days using the planning scope, the exact appointment, drug preparation, and drug delivery times are defined in the scheduling scope. We observed that, in the scheduling scope, significantly more attention is focused on patient scheduling than the scheduling of nurses, drug preparation, and drug delivery. Sadki et al. [23][52] presented one of the first attempts to combine patient planning and scheduling scopes. There is a chain of publications that focus on the scheduling of drug preparation and delivery. Drug preparation scheduling was addressed by Mazier et al. [24] and Billaut [25], while Ta et al. [26], Kergosien et al. [27], Robbes et al. [28], and Robbes et al. [29][53] studied the scheduling of drug*

[52]This work by Sadki et al. (1) does not include drug preparation and (2) is a conference paper, which excludes it for this analysis. For the full reference, please resort to Hadid et al. (2022).

[53]The paper by Mazier et al. (2010) is mentioned in the review part of this study but was ultimately excluded for lack of a routing aspect. The papers by Billaut et al. (2011), Ta et al. (2015) and Robbes et al. (2019) are conference papers and therefore not considered within the scope of this thesis. For the full references, please resort to Hadid et al. (2022).

preparation and delivery as a flow shop production and outbound distribution scheduling problem." (Hadid et al. 2022:6).

Out of these seven, only two could finally be included: Kergosien et al. (2017) and Robbes et al. (2022). Similarly, in their study on OR techniques in cancer care, Saville et al. (2019) mention only two papers that combine production routing and scheduling: the one by Chahed et al. (2009) and the one by Lee et al. (2014). Sahin and Matta (2015) cite both contributions by Chahed et a. (2009, 2011) and a couple of conference papers. All three surveys were found through forward search / snowballing from the very papers they cited, which stands to show how difficult it was to find literature on this particular combination of problem characteristics. In summary, I found all four papers relevant for this cluster from the one core text and its reference list, but beyond that was unsuccessful in recovering more texts through the successive searches.

Another observation I want to discuss is how isolated the cluster on cancer medication is from the rest of pharmaceutical problems. Against my initial belief that there would be many similarities between these two product types, Figure 5 shows that the cancer medication cluster is almost completely detached from the other topics. This surprised me with regards to the drugs / pharmaceuticals cluster in particular since one might think there should be cross-references or at least mutual acknowledgement of such seemingly similar research directions. In fact, the paper by Chen et al. (2021) is the only one from the drug cluster citing references from the cancer medication cluster. Their medicine production and delivery process strongly resemble that of cancer medication, so much so that I shortly considered moving the paper to cluster 4 despite the authors not explicitly mentioning drugs for cancer treatment except in their literature review. Moreover, Figure 5 reveals that the paper by Chen et al. (2021) had only been found through the cancer-cluster. Consequently, this paper as well as the entire cluster on cancer medication would not have been found if it were not for the one paper by Robbes et al. (2022), which was the only one featured among my initial search results. This implies that there might be entire perishable medical products missing from this paper, simply because the initial search did not yield a relevant paper in that field. One idea I could think of was organ transplantation. Searching for this type of medical "product" and analysing how it related to the other papers might be an interesting future research direction.

6.2 Related Topics

In this next section, I want to present related clusters that formed during the literature search: Home Health Care, Emergency Setting, Drone Usage and Medical Waste Management. They may either be popular research topics (HHC) or promising future research directions (ES, DU and MWM). The bibliometric analysis of the BSC by Eghtesadifard and Jozan (2022:1196) confirms this initial impression by identifying disasters as well as medical waste management as hot topics in the BSC literature. Meanwhile, the high amount and frequency at which LRs on HHC are published speaks for itself (chapter 6.2.1.1). Some of these topics provide the background (HHC, ES) or an interesting extension (DU, MWM) to RSPs with perishable products. Of course, there are overlaps at times. Moreover, these specific topics are highlighted since the literature search yielded a conspicuous number of texts that fall into one or several of these categories, and the aim of this thesis is to uncover research potential as well as the current problem environment. Other popular topics of research are intra-hospital routing and/or surgery room scheduling, pickup and delivery of non-time-sensitive medication and biological samples and non-emergency ambulance transfers.

6.2.1 Home Health Care

In contrast to blood, whose importance was not immediately visible from the first search results, it quickly became apparent that Home Health Care (HHC) is an immensely popular branch of research. Despite a possible distortion through my first search string that might have inflated its perceived significance (see chapter 3), it remains relevant upon closer examination. Especially over the last ten years, this field of research has been hugely expanded. Due to its popularity and the number of detailed surveys on HHC that resulted from it, this chapter makes no pretence of coming close to the other reviews' level of completeness and shall only give the reader a short introduction to the topic.

Home Health Care, also called the nurse routing problem, is one of the most well-researched problems in healthcare RSPs. Home Health Care means that patients stay in their familiar home environments where they are serviced by healthcare providers. In its most basic form, this requires routing staff members and scheduling services in a way that meets the requirements of both patients and healthcare providers.

The types of patients this service is most relevant for are the elderly, people with disabilities or patients with chronic conditions. In fact, any patient with an illness or injury who receives treatment outside of a healthcare institution can be considered a case for HHC, as the following definition by Becker et al. (2019:16) shows: "The term home health care refers to 'the provision of healthcare services to people of any age at home or in other noninstitutional settings.'"

The healthcare providers may be nurses, but also therapists, physiotherapists or social workers, and they provide all types of medical, paramedical or care services (including, sometimes, meal delivery, bathing, or related tasks). Based on the type of service provided, Becker et al. (2019:16) differentiate between home care and home *health* care: "To distinguish skilled medical services and non-skilled services, like personal care routines, household maintenance, and social service, the latter is described using the term home care, while home health care includes medical treatments, nursing services, and physical therapies." In practise, authors are not always as rigid with the terminology, and many papers on HHC problems include HC services. Some even consider staff with different skills in their optimization. Liu et al. (2013:475) demonstrate how HHC has evolved into more and more complex and diverse activities over the last years, from basic nursing "to complex and technical cares such as chronic cares, rehabilitation, end-of-life palliative cares, and home chemotherapy." As Grieco et al. (2021:1960) point out, "the face-to-face delivery of care" is crucial, meaning that telediagnosis or -therapy is not an option in this case. The services are hands-on and require the healthcare provider to be in the same location as their patient. Therefore, using cars or some other form of transportation,[54] HHC providers need to be able to arrive at their destination.

Shifting healthcare operations from hospitals to patients' homes has many advantages, not just for patients and caregivers, but for a variety of different stakeholders. The welfare of entire communities may be improved by investing in better HHC practises (Entezari and Mahootchi 2021:3715). Grieco et al. (2021:1960) point out HHC's "potential role in addressing two key policy initiatives within health and social care across many nations", and Cissé et al. (2017:2) give these same main reasons: Firstly, admissions to healthcare facilities and hospitalization durations are reduced. Since HHC covers mostly routine care operations that do not require special infrastructure or equipment, they can easily be moved to the home environment. Meanwhile, beds in healthcare institutions stay available for more urgent or critical patients. This point was also raised by other authors (e.g., Liu et al 2013:475). Secondly, the option to stay in their own home is of particular interest towards the end of a patient's life, be it through old

[54]Some authors, for example Szander et al. (2018), examine the impact of different means of transportation on HHC operations.

age or disease. Prolonging the time people can live in their familiar surroundings is interesting from a humanitarian perspective, of course, but also economically quantifiable: Demand for long-term residential care facilities is reduced. In this regard, HHC might provide some much-needed relief for retirement homes and similar institutions. As life-expectancy goes up, so does the need for nursing homes and specialized personnel – a growing, increasingly concerning trend in many parts of the world:

> *"The World Health Organization has announced that the rate of care-dependent elderly people in Europe will strongly increase in the coming decades […] In recent years, the health care industry has become one of the largest sectors of the economy in developed countries such as France, Germany, Australia, etc. Due to the issue of global aging and the improvement of treatment conditions, there is no doubt this trend will continue." (Shi et al. 2017:160)*

Population aging has been identified as one of the major engines that drive research on OR in Healthcare by many authors (e.g., Sahin and Matta 2015:355, Fikar and Hirsch 2017:86, Di Mascolo et al 2021:1, Abdalkareem et al. 2021:445, Fathollahi-Fard et al. 2022). Particularly in developed and developing countries, these problems are further aggravated through the decline of informal care (Becker et al. 2019:13, Fikar and Hirsch 2017:86), through decreasing birth rates, demographic change and urbanization (Becker et al. 2019:13), and serious nurse and caregiver shortages (Demirbilek et al. 2021). Especially this last point underscores the importance of efficiently planning with whatever resources are available.

The resulting Home Health Care Routing and Scheduling Problem (HHCRSP) combines the routing aspects from planning a tour of numerous, geographical disperse customers with the scheduling problem of developing itineraries that fit both the patients and the healthcare providers. Patients need to be visited during (usually predefined) hard or soft time windows dictated either by medical necessity or by patients' preferences. Services may be associated with synchronization or precedence constraints (e.g., Shahnejat-Bushehri et al. 2021, Nasir and Kuo 2020), which Huvent et al. (2021) describe as follows:

> *"According to the surveys of the HHC companies, each day, an HHC company carries out various logistics activities including the delivery of drugs or medical services from caregivers to patients and medical samples to the laboratory. […] Interdependent services can be defined as having temporal dependencies between two services, or as synchronized services [12] (also called shared services), or as services with priority constraints. Thus, it is possible for a single patient to need a pair of services that must be separated from a given time interval." (Huvent et al. 2021:1f)*

Moreover, constraints linked to continuity of care (e.g., Shahnejat-Bushehri et al. 2021, Entezari and Mahootchi 2021) require that the patient is either visited around the same time every day and/or by the same service provider. Ensuring that patients are treated by the same caregivers has multiple benefits: service quality improves since the caregivers get to know their patients and their particularities, and customer satisfaction goes up since the patients can bond with their caregivers – all at the expense of increased optimization effort. Time windows associated with healthcare suppliers usually have to do with working hours and break regulations. An in-depth description of the HHCRSP, its main characteristics and extensions, is given by Di Mascolo et al. (2021:3-4), Fikar and Hirsch (2017:87), and Cissé et al (2017:3).

In addition to the inherent difficulties posed by the problem characteristics, like its NP-hardness, and operational constraints, regulative limitations need to be taken into account. Cissé et al. (2017:2) point out that the "problems considered often originate from different national and regulatory settings." I have addressed different regulations for blood transportation and cancer treatment, but the same is true for HHC, for example when it comes to staff working hours. These settings make it harder to generalize the problem since provisions in Germany might differ from those in Japan, for example. Matters can be complicated even further if regulations that constraints are based on are not addressed explicitly. Another difficulty arises when not just internal, but "external resources (such as liberal professionals, laboratories, etc.)" (Di Mascolo et al. 2021:1) need to be included in the planning. Despite the problems' complexity, some healthcare institutions still resort to manual planning: Fikar and Hirsch (2016:86-87) point out that "routing and scheduling of HHC services are often done manually […] resulting in high organizational efforts and potentially sub-optimal solutions." This is where optimization techniques can make a significant difference.

6.2.1.1 Literature Reviews of HHC

Interest in solving the HHC problem is growing rapidly (e.g., Di Mascolo et al. 2021:1-2, Fikar and Hirsch 2017:86, Shi et al. 2017:160). In recent years, numerous surveys have appeared. The following list is by no means complete, but it includes some recent and exhaustive reviews and gives the reader an idea of the topic's popularity among researchers, and a starting point for further research:

In mid-2021, Di Mascolo et al. published a systematic review on routing and scheduling in HHC. They found "96 journal papers (J) and 69 conference papers (C) to analyze, i.e. 165 papers, from 1997 to mid-May 2019" (Di Mascolo 2021:6) while testing "the four databases classically used in the area of OR and IE, namely Scopus, Web Of Science (WOS), Google Scholar, and ScienceDirect" (Di Mascolo et al 2021:5) for "generic" (Ibd.) keywords so that they would not overlook papers of importance. They further point out that some of the works that might have been interesting but failed to meet their inclusion criteria had instead been reviewed by Cissé et al. (2017) and Grieco et al. (2021). This is also true for pickup and delivery problems in HC agencies that were specifically excluded by Di Mascolo et al. (2021:6).

Grieco et al. (2021) searched Web of Science on the 28.09.2018, using combinations of keywords specified in their Appendix, and included publications in the English language with no constraints on the publication type or year. They support the claim that HHC problems are among the most-studied logistical challenges in the OR literature (Grieco et al. 2021:1960). The authors built their own review on decision frameworks provided by Gutiérrez et al. (2013) and Sahin and Matta (2015), who conducted systematization of the then-existing literature. Evaluating these earlier texts, Grieco et al. (2021:1960) arrive at the conclusion that there was an abundance of texts on some operational domains, while the strategic and tactical decision levels had not received as much attention.

In 2017, Cissé et al. published a review of OR models developed for the HHCRSP during the last 17 years (presumably 2000-2017). These authors checked 6 digital databases for 5 publication types and 5 keyword combinations, and then screened the publications' lists of references. They identify "features [that] may concern HHC service organization, care workers and patient characteristics" and analyse the papers in terms of constraints (temporal, assignment and geographical), objectives, solution methods and the length of the planning horizon (single or several periods). They address the topic of this thesis, which they consider among the geographical constraints: "The location of the HHC center, medical laboratories, pharmacies and chemotherapy/radiotherapy centers involved in the care provided are among the parameters to be considered in the HHCRSP models" (Cissé et al 2017:8). From the publications cited in this section, two are conference papers, two focus on meal deliveries, two, both by Liu et al., are concerned with medical products delivery and pickup, but without the perishability aspect, and one paper, that by Chahed et al. (2009), is featured in the main analysis of this thesis.

In 2018, Hirsch published a comprehensive overview of the planning and mobility concepts for HHC in Austria, with special attention to disaster management. This review will be referenced again in chapter 6.2.2 on the *Emergency Setting*.

Fikar and Hirsch (2017) reviewed articles on SR-problems in HHC published before October 2015 and compared their objective functions, constraints and solution methods. They set their focus specifically on nurse RSPs, excluding P&D of medical products: "Hereby, in particular HHC papers which deal with the delivery of medicine or equipment were excluded as the focus of this review is set on the routing and scheduling of nurses" (Fikar and Hirsch 2017:87).

Of particular interest to this thesis, albeit a bit older, is the review by Sahin and Matta (2015): not only does it contain a general part on HHC, it also grants special attention to the topic of chemotherapy at home. It helped identify a relevant contribution[55] and contains in-depth information on the chemotherapy at home process, as well as an illustration of the relevant steps and actors. Earlier still, Matta et al. (2014) proposed a framework to better understand the processes and decisions in HC operations.

6.2.1.2 Papers on HHC Problems featuring Perishable Medical Products

Even though the HHC problem has received widespread attention, the extension involving time-sensitive medical products has not been explored in depth. During my search, I could not find many HHC problems that met all the perishability criteria. From all medical products, HHC problems most often feature specimens or medication. As the clustering in chapter 3 shows, transportation of specimens is more often time restricted while drugs, apart from cancer medication, are treated as less time-sensitive and combined with precedence constraints rather than hard time windows. For cancer research, there is Chahed et al. (2009, 2011). For biological specimen, I found the papers by Shahnejat-Bushehri et al. (2021), Haitam et al. (2021), Entezari and Mahootchi (2021), and Wolfinger et al. (2023) also consider home visits. The paper by Ziya-Gorabi et al. (2022) features time-sensitive specimens and less time-critical medication, and the vaccines in Secundo et al. (2022) are also administered in patients' homes. According to Table 1 in Shahnejat-Bushehri et al. (2021:5), the authors were aware of six studies on the HHCP including the collection of biological samples, only two of which take perishability into account. Both these papers were published by the authors themselves. Entezari and Mahootchi (2021: 3696) confirm: "[S]ome real-life constraints (e.g., blood sampling requirements) have received relatively less attention." In fact, other than their own paper, they knew of only one more publication treating this constraint.[56]

This experience was confirmed during my literature search. Since the seminal paper by Liu et al. (2013) it has become somewhat common to consider medical products such as drugs and biological samples in HHCRSPs. However, these are mostly considered in terms of capacity rather than urgency, and in terms of adding additional stops at a pharmacy and/or laboratory before or after visiting the patients. They could not be included in this thesis for lack of perishability: Fathollahi-Fard et al. (2018 to 2022) wrote an extensive amount of work on these types of problems, seven of which featured among my search results. Most of them include laboratories as well as the transportation of medication and biological samples, but only in terms of capacity constraints. Similarly, Shi et al. (2017) only consider drug delivery to patients at their

[55]The work in question is Chahed et al. (2011). This paper should have shown up in the forward search from Chahed et al. (2009) but entering the title on the searched databanks Scopus and WoS yielded no result.

[56]Cited as Elbenani, B., Ferland, J.A., and Gascon, V. "Scatter search approach for solving a home care nurses routing and scheduling problem", In University of Montreal, Canada (2011). Later, the resource Elbenani, B., Ferland, J., & Gascon, V. (2008). Mathematical programming approach for routing home care nurses. In IEEE International Conference on Industrial Engineering and Engineering Management, Singapore (pp. 107–111). was found in Mascolo et al. (2021). Both had to be excluded due to publication type. (The citations were left unchanged from the sources they were found in.)

homes in terms of capacity and demand. Nasir and Kuo (2020) view biological sample collection and drug delivery (as well as meal delivery) as types of services which need to be performed by qualified HHC providers, resulting in a precedence and synchronization problem. Such a problem may be linked to time if, for example, medication must be administered to a patient a certain amount of time before or after a meal. Urgency or timeliness of delivery regarding the product perishability is once again not part of their optimization. The same if true for Chaieb and Ben Sassi (2021), who consider delivery and pickup tasks in their HHC model. Note that these tasks are defined as picking up biological samples and unused drugs only in the abstract. The authors consider these resources in terms of demand and capacity and require the vehicles to visit a laboratory.

One paper that needs to be highlighted is that of Liu et al. (2013). It is among the, if not *the*, first to explicitly include pickup and delivery of medical products in the HHC problem. Although perishability does not feature in this problem, it deserves to be mentioned since it is widely cited across the papers in this thesis and, by consequence, likely raised awareness for this type of problem. Theirs is a daily combined delivery and pickup problem with time windows and the objective of minimizing routing costs. To solve the problem, they propose two mathematical formulations and two heuristic algorithms: genetic algorithm and tabu search. These are then tested on a set of adapted benchmark instances of various sizes, from small to very large. The pharmacy is where all tours begin and end, and one additional stop can be made at a hospital and a laboratory. The authors consider four types of pickup and delivery services: (1) drugs/medical devices to deliver from the pharmacy/depot to the patient, (2) special drugs to deliver from the hospital to the patient, (3) materials to pick up from the patient and bring back to the pharmacy/depot, and (4) biological samples to pick up from the patient and bring to the laboratory. Time windows limit patient visit times as well as the starting and ending time of the tour (which may translate to pharmacy opening times/service hours), but there is no time limit on the transportation of medical products. Liu et al. (2013) only consider the order in which the nodes have to be visited: the vehicle needs to (1) collect special drugs at the hospital before visiting the patients that need said medication and (2) drop off the samples at the laboratory after visiting the patients that require this type of service.

Also worth mentioning is the paper by Huvent et al. (2021), who do not tackle one specific optimization problem, but develop a benchmark generator that considers various constraints encountered in HHC, including biological samples as well as precedence and synchronization of services. They further describe jobs performed by HHC caregivers as having both a priority and an arduousness level relating to the importance of the task. Not the medical product itself, but the related task may thus be associated with a certain timeliness, be it in terms of urgency or precedence. The jobs are linked to time windows for servicing the patient as well as a processing time (Huvent et al. 2021:4). As an example, the authors suggest drug intake that cannot be delayed (Huvent et al. 2021:7), which showcases how the timeliness relates to the task rather than the medication itself.[57] However, in their benchmark generator, collecting biological samples is considered a geographic rather than a temporal challenge: “a caregiver might need to collect a biological sample and bring it to a laboratory for testing. Thus, the location of an HHC center or medical laboratories involved in the care provided are among the parameters to be considered in the HHCRSP models” (Huvent et a. 2021:5).

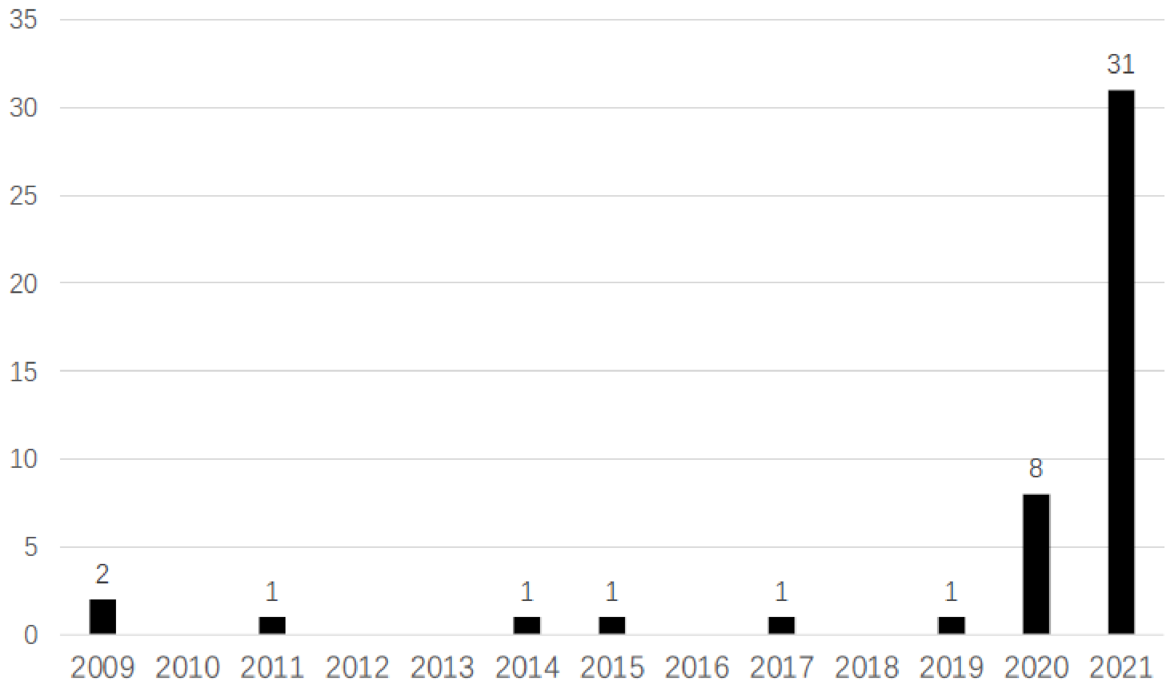
6.2.2 Emergency Setting

Unsurprisingly, the topic of emergency and disaster mitigation has received a boost through the recent COVID-19 pandemic. In 2022 alone, at least two literature surveys on pandemic

[57] With the possible exception of very fragile drugs such as cancer medication, see chapter 4.4. This is my interpretation and not explicitly mentioned by Huvent et al. (2021).

control have been published: Karatas et al. (2022) concentrate on transportation and location planning during epidemics/pandemics while Lin et al. (2022) focus specifically on vehicle routing optimization for pandemic containment. The following graph by Lin et al. (2022:7) shows how the research on infectious disease control has boomed since the outbreak of the COVID-19 pandemic. In addition to the impressive increase in publications (39 of 46 papers, or almost 85% of the literature, has been published from 2020 onwards), they observe that "most of the research efforts before 2020 focused on VRPs in large-scale bioterrorism emergency […], while after 2020 the study of VRPs for use in pandemic control started to attract the attention of researchers and became a hotspot" (Lin et al. 2022:7).

Figure 6: Distribution of articles [on VRPs and infectious disease control] over time (Lin et al. 2022:7)



It does not take much imagination to think of some ideas how OR might help during a crisis like a pandemic: Karatas et al. (2022:7) list a few examples, including "routing of mobile test centers, allocation and distribution of medical supplies from hubs to hospitals, design of cold supply chains for vaccines, determining locations for vaccination centers and test centers, etc." Among the literature I reviewed, there are numerous papers that attribute a prominent role to COVID-19 (Andoh and Yu 2022, Secundo et al. 2022, Tlili et al. 2022, Wolfinger et al. 2023, as well as a fair share of the literature on drones) or at least mention this recent pandemic (e.g., Chen et al. 2021, Shahnejat-Bushehri et al. 2021, Zabinsky et al. 2021). They all focus on the collection and testing of medical samples, often PCR-tests, or the distribution of drugs, mainly the COVID-19 vaccine.

Naturally, the emergency setting is not limited to pandemics. Lin et al. (2022:3) differentiate between slow-onset disasters like pandemics or droughts, which they find have not been adequately investigated, and rapid-onset disasters like tsunamis, earthquakes, and hurricanes. Similarly, Rezaei Kallaj et al. (2022:2) define a disaster "as an event that occurs suddenly or gradually, saddling society with problems[.]" Furthermore, authors distinguish between natural disasters (earthquakes, wild- and bushfires) and disasters that are human made, like war or political crises (Hamdan and Diabat 2020:1, Rezaei Kallaj et al. 2022:2). In addition to all the pain and hardship they cause, both types of disaster can severely impact or damage the infrastructure. Al-rabiaah (2022:1) show that "disasters present obstacles to healthcare workers attempting to provide essential treatments to patients and victims, which may exacerbate the spread of epidemics and increase the number of fatalities." Short response time save lives, but sites of disasters are not easily reachable, which makes disaster relief actions even more difficult.

From an OR-standpoint, emergency situations add to the sense of urgency and put increased pressure on the timely delivery and careful handling of fragile, perishable medical products. In this sense, I want to contrast them mainly with HHC, where consistency is key (continuity of care, routine visits and treatments, etc.). Of course, these categories are not mutually exclusive. HHC companies can be affected by disasters like any other healthcare providers. In fact, Hirsch (2018) even grants special attention to the impact of disasters on HHC planning. I only mean to highlight that an emergency is by definition out of the ordinary, that it requires mitigation measures to deal with unplanned events, and that emergency preparedness and response means dealing with unstable demands and urgent requests. Moreover, it is inherently connected to risk. Damaged infrastructure may be at the risk of collapsing, which means that it may become unusable at any point during the planning horizon, and that using it nonetheless puts healthcare providers in danger. Some papers in the emergency setting feature minimization of risk among their objectives (e.g., Nolz et al. 2011, Petronaiu et al. 2021 and Zabinsky et al. 2021). Petronaiu et al. (2021:2339f) provide insight into common objectives:

> *"In humanitarian logistics, most routing problems focus on disaster preparedness, for example, earthquakes (Mete and Zabinsky, 2010; Ahmadi et al., 2015; Tofighi et al., 2015). These problems are commonly modeled as classical vehicle routing or dynamic network problems, having as objective the minimization of total travel time, unmet demand, or cost (Ozdamar and Ertem, 2015). Hoyos et al. (2015) consider the use of operations research in disaster operations management. In 48 papers using mathematical models, the most common goals were to minimize cost (31%), minimize unmet demand (21%), and maximize regional coverage (19%)."*

Closely intertwined with risk is uncertainty that, in disaster management, is even more prevalent than in everyday SCM. In fact, many of the reference papers that address the COVID-19 pandemic or disaster management also feature uncertainty (e.g., Hamdan and Diabat 2020, Rezaei Kallaj et al. 2022, Secundo et al. 2022). The same is true for the other papers on disaster management that emerged during my literature search. I came across at least[58] 33 papers that addresses the emergency/disaster setting, 11 of which met the inclusion criteria. As mentioned in chapter 6.1, I even contemplated including "COVID-19" in my keyword string, but ultimately decided against it. In hindsight, choosing a less specific but still related keyword, like "emergency" or "disaster" might have been an interesting experiment. Papers in which pandemics play a central role have been listed above. Disasters and emergencies are covered in the following contributions:

Zabinsky et al. (2021) and Petronaiu et al. (2021) describe the aftermath of Cyclone Idai in Mozambique to show how disrupted infrastructure can severely impact the storage and distribution of medical supplies. This is particularly true for fragile products like vaccines when damaged roads and disrupted electricity supply take a heavy toll on cold-storage-requirements. Petronaiu et al. (2021:2337) contrast the stable private sector with the lack of predictability often faced by humanitarian organizations. They consider different goals (profitability vs. rapid disaster relief), additional restrictions caused by limited technology, and the consequences for

[58] I say "at least" because there may well have been more papers featuring disaster/emergency response, but if it quickly became apparent that the inclusion criteria were not met, I discarded the publication right away. Only when it became clear that disaster management was frequently featured in my reference papers did I start actively looking for papers on this topic.

supply-chain tools. Zabinsky et al. (2021:3) also highlight "the need for a quick and easy way for logisticians to distribute health products where they were needed most."

Hamdan and Diabat (2020) and Rezaei Kallaj et al. (2022) show the effect disasters can have on the blood supply chain and highlight the importance of efficient planning to ensure sufficient supply and timely delivery of much-needed blood products. Hemmelmayr et al. (2010) expand their 2009-work by considering blood demands of non-scheduled emergency surgeries, which prompts them to take demand uncertainty into account. Zahiri et al. (2018) assign emergency levels to their patients (low, normal, urgent) and service them according to their priority. This might be a valuable instrument in a disaster situation, where efficient triage might be necessary to save as many lives as possible. Wen et al. (2016) use drones to cope with the restrictions of the emergency setting. Drone usage will be discussed at length in the next chapter.

6.2.3 Drone Usage

Drones or UAVs (unmanned aerial vehicles) are frequently combined with the emergency setting. Their main benefits during and in the aftermath of disasters, both natural and man-made, is that drones are "not affected by damage to transportation infrastructure and […] not significantly more expensive than ground transportation" (Al-rabiaah et al. 2022:2). Medical products can be transported urgently to areas that are difficult to access (Pirabán et al. 2019:20). Al-rabiaah et al. (2022:1) mention damaged roads or bridges and elaborate on the challenges "geographical characteristics such as dispersed islands, poor transportation infrastructure, and limited means of transport" may impose on those who try to reach patients in isolated locations. During rescue-missions in rugged environments, when patients cannot be safely evacuated, medication can be brought directly to them (Wen et al. 2016:1). Combining drones with other means of transport allows for more flexibility, which in turn enables planners to quickly adapt to urgent spikes in demand. Rezaei Kallaj et al. (2022:2) illustrate this by the example of blood shortages in the aftermath of an earthquake:

> *"A fundamental problem in cases of disaster is the shorter blood-collection time because a timely supply of blood can save many peoples' lives. Drones can help transport the blood collected by bloodmobiles to the affected zone. Hence, bloodmobiles can continue their route to gather more blood units. As a result, by the aid of drones, the collected blood units may be transferred to the crisis-stricken city much sooner."*

With or without the emergency context, "[t]hese challenges tend to be particularly severe in both rural and developing countries" (Al-rabiaah et al. 2022:1). Comes et al. (2018) agree that there is considerable potential for UAVs in humanitarian logistics, and Johannessen (2022:2) explains:

> *"[I]n Africa [t]he roads are impassable for much of the year, with no service provided. Even when roads are open, drone delivery may be less time consuming and less expensive than ground transport in many locations. A similar situation may also exist in developed healthcare systems that include geographical areas with long transport distances and scattered populations."*

In summary, drones shine in extreme cases, when the available infrastructure falls short, and the location is either particularly remote or densely populated. This last case is particularly relevant in places with lots of ground traffic congestion (Johannessen 2022:1), which affects traditional vehicles like cars or bikes, but not aerial transportation. Drone usage in urban areas has also received increased attention during the last two years, when the possible contribution of UAVs to slowing down the spread of a pandemic like COVID-19 was studied (Sedov et al.

2020, Park et al. 2022, Karatas et al. 2022). This can be achieved if drones effectively support home quarantine, by eliminating risk factors like personal contact on the way to a public testing station and during testing itself.

Drones can be used to transport all kinds of medical products. Examples mentioned in the literature include blood (Wen et al. 2016, Rezaei Kallaj et al. 2022, Al-rabiaah et al. 2022), test swabs or biological specimens (Sedov et al. 2020, Johannessen 2022), medication and vaccines (Al-rabiaah et al. 2022), organs (Johannessen 2022), and non-perishable medical supplies such as test kits (Park et al. 2022) or defibrillators (Al-rabiaah et al. 2022). Nybo et al. (2019:41) mention that drones are on a par with other transportation methods when it comes to sample delivery, given that "the samples are properly protected from temperature deviation and agitation." Comes et al. (2018) dedicate an entire section to the potential of drone usage in humanitarian vaccine cold chain. Johannessen (2022:2) cites a review paper by Hiebert et al. (2020) wherein the authors identify and study 8 different healthcare applications for drones. Among the 29 articles they include, the most popular topic is the delivery of medical supplies and treatments, both perishable and non-perishable, with 11 contributions. The use of drones for biological sample transportation ranks in 4th place with a total of 6 contributions. Other topics are environmental monitoring (8 texts), the delivery of automated external defibrillators (AEDs; 8 texts), search and rescue operations (4 texts), emergency service delivery and support of first responder safety (3 texts each), and remote medical support (2 texts). For more detail, please refer to Hiebert et al. (2020:5ff).

Johannessen (2022:2) provides some examples of how drone usage in the transportation of biological specimens and blood can lead to significant improvements in service levels and times as well as long-term cost savings. However, he repeatedly stresses the importance of context. Whether or not drones are preferable to traditional transportation methods depends on a variety of factors such as demand amount and type, distances, transportation frequencies, type of drone used etc. I feel this is best explained through an example:

> *"Two minutes saved by a drone carrying a cardiac defibrillator may save a life. However, 60 min saved transporting a routine blood sample may have marginal, if any, clinical significance in certain healthcare systems in which patients may wait for months for their first contact with healthcare provisions." (Johannessen 2022:3)*

Despite (almost) always being faster than ground transportation, drones are subject to restrictions which make them less apt for certain situations. The two most featured shortcomings in the literature are limitations of carrying capacity (Sedov et al. 2020, Wen et al. 2016) and range/distance restrictions due to the limited battery life (Wen et al. 2016, Park et al. 2022). These effects may be mitigated by combining drones with different modes of transportation such as trucks (Park et al. 2022) or blood mobiles (Rezaei Kallaj et al. 2022). After mentioning a variety of new transportation methods, Karatas et al. (2022:10) point out that "robots or drones are generally used for first- and /or last-mile service vehicles." They acknowledge the potential of combining multiple means of transport within the same network.

Especially in recent years, literature on UAVs in healthcare has risen in popularity. Back in 2019, Pirabán et al. (2019:20) found that "drone delivery for healthcare applications is a field with many opportunities for future research because it is rarely tackled." Al-rabiaah et al. (2022:4) still lamented the lack of relevant research in 2022, but they acknowledged that:

> *"The paucity of research in this area has become even more noticeable with the emergence of the recent COVID-19 pandemic, where drone applications have tremendously alleviated the delivery of services to remote areas while being cheaper, safer, and faster than traditional modes of transport."*

Karatas et al. (2022:8f), meanwhile, argue that “AI-driven autonomous transportation technologies such as autonomous logistics vehicles, unmanned aerial vehicles, and drones” have risen in popularity largely due to the recent pandemic. They emphasize that these technologies supported the requirement of social distancing, that their capability of contactless delivery eliminated the need for direct human contact and, thus, reduced infection risks, and argue that these characteristics earned them increased attention from institutions and decision-makers.

With the exception of Wen et al. (2016), all publications that I have found during my literature search were published from 2020 onwards. Sedov et al. (2020), Al-rabiaah et al. (2022), Johannessen (2022), Park et al. (2022), Rezaei Kallaj et al. (2022) were all published very recently, which leads me to believe that this could be a very important future research direction. However, most of these papers had to be excluded from the main part of the analysis for some reason:

In their Maximum Coverage Facility Location Problem with Drones in Healthcare, Al-rabiaah et al. (2022) focus more on the location routing problem and display neither routes, nor schedules in their results despite including the expression “routing and scheduling” among their keywords. Moreover, they mention medical products delivery among the potential application areas but these products’ characteristics, in particular perishability, are not featured in the solution approach.

Johannessen (2022) does not present a new optimization problem. Instead, the author studies the possible time- and cost-saving effects if drones are used in place of traditional ground transportation. He takes the “extended time context [into account] starting from when biologic samples are booked for transport until arrival at their destinations” (Johannessen 2022:19). Transport frequencies, distances, and drone speed are considered the most crucial factors. He arrives at the conclusion that a small improvement can be observed in urban logistics, but significant time savings up to 74% are possible in rural areas.

Park et al. (2022), despite addressing the time-aspect in their main function, focus on a medical product that is not in itself perishable or as easily contaminated as, for example, a specimen. They concentrate on the distribution of testing kits in an attempt to cement at-home-testing as an alternative to public test stations. This way, drones can reduce the mobility of potentially infected persons, and thus help prevent the spread of a virus like COVID-19.

Theirs is very similar to the problem addressed by Sedov et al. (2020), who develop a model of mass-testing during quarantine. They show how drones can be applied to collect and deliver tests and calculate the routes taken by the drones, trying to minimize the total route length because the longest route, “defining the longest time that a person has to wait for the drone” (Sedov et al. 2020:3) is the bottleneck to their problem. Sample perishability is addressed only indirectly in their paper as the authors minimize the longest route length, which is then converted into the “makespan, i.e., the time to fly all routes and thus serve the entire population” (Sedov et al. 2020:3). Another important factor in their work is the capacity of the drones. They quantify the effects of using drones for pandemic control.

The contributions by Wen et al. (2016) and Rezaei Kallaj et al. (2022) meet the inclusion criteria. For a short summary of these works, see chapter 4.1.3. Through the inclusion of drones, Rezaei Kallaj et al. (2022) observe an improvement for both of their objective functions:

> *“Numerical experiments confirm that increasing in the number of drones leads to a rise for blood collected and a reduction in the latest arrival time of vehicles. On the other hand, solving the model without any drones causes a decrease in the amount of collected blood and an increase in the maximum delivery time.“ (Rezaei Kallaj et al. 2022:27)*

This leads them to the conclusion that drone usage is a valuable, potentially life-saving strategy in post-crises scenarios. The integration of new technologies, like drones, is not only promising during emergency situations, but also in Home Health Care (Johannessen 2022, Euchi et al. 2022). Moreover, Johannessen (2022) highlights their usefulness in transporting biological materials while preserving quality and confirms that significant time-savings are possible, always depending on the context of how and when drones are used. He agrees that in healthcare, there is much potential for a considerable market for drone service.

6.2.4 Medical Waste Management

As I was searching literature for this thesis, I noticed that there was a sizeable number of publications on the topic of medical waste management. Indeed, it seems that reverse logistics in health care has received quite a bit of attention over the past years: Sustainable waste transportation strategy has been identified as one of four major pandemic containment measures by Lin et al. (2022), and medical waste management and wastewater-based epidemiology is featured as one of the emerging decision problematics during the COVID-19 pandemic by Karatas et al. (2022). Among the papers I found during my research, some were prompted by the massive increase in medical waste[59] caused by the pandemic (Aydemir-Karadag 2022, Govindan et al. 2021). Andoh and Yu (2022:3) point out that "Yu et al. (2020b) and Tirkolaee et al. (2021) optimized the reverse logistics systems for managing the sharply increased medical waste during the COVID-19 pandemic."

Moreover, the topic kept emerging as I went through the reference papers. Aside from the citation above, some authors like El Midaoui et al. (2022:1067) suggest that reverse logistics may be an interesting extension to this type of RSP, for example to recover the unused or expired blood. Some HHC problems already consider cases wherein medical samples are collected, and unused medication is returned simultaneously (e.g., Ziya-Gorabi et al. 2022). This extra task presents little risk to the caregivers and combining it with the gathering of fresh samples rather than performing a separate tour increases the efficiency of the HHC-companies' operations.

However, integrating reverse logistics into the perishable medical product supply chain may be advantageous or harmful depending on the type of product. Medical waste management is different from classic reverse logistics because it can be considered hazardous: "Medical waste includes sharps (syringes or needles, blades) and materials that have been in contact with infectious patients, and other contaminated materials infected with human pathogens" (Karatas et al. 2022:11). Its storage and transportation are associated with risk and require professional handling. Therefore, some authors argue that they need not consider reverse logistics in connection with their perishable product precisely because "unusable blood products are considered hazardous waste and are therefore collected for disposal separately by other logistic service providers" (Hemmelmayr et al. 2009:709). Lin et al. (2022:9), who review seven papers of infectious waste that were published during the pandemic, highlight that these papers "mainly explored various ways to mitigate the transmission risk." During my literature search I came across at least[60] eight publications on medical waste management, but the abovementioned publications suggest there may be many more to be found. In particular, I wonder whether a survey has been published recently, since the most recent (and only) one I became aware of during my research is a review published in 2007 (cited by Hemmelmayr et al. 2009:709).

[59]For better understanding of the massive increase in medical waste caused by COVID-19, Karatas et al. (2022:11) write: "approximately 30-35 tons of medical waste were collected daily from 252 hospitals in Istanbul in the pre-pandemic period, while this figure has increased to 320 to 620 tons weekly in the first half of 2020."
[60]See: Footnote 58.

I decided against exploring the topic of medical waste management further since by my definition, it goes beyond the scope of this thesis: Reverse logistics come into play *after* the medical products' expiration date has passed. Still, I feel it might be a research direction worth pursuing. Questions to be asked could be for which products, under which circumstances and how it might be advantageous to integrate the disposal of medical products that are past their lifetime into the supply chain.

6.3 Potential for Synergies and Future Research Directions

In this second-to-last chapter, I want to reveal current gaps in the research, propose new directions, and suggest possibilities for cooperation and mutual learning. As the analysis of the reference papers has shown, there are many similarities between the product clusters, yet surprisingly little cross-referencing, mostly between but sometimes also within the clusters (e.g., drugs and pharmaceuticals, see Figure 5, chapter 6.1). Seeing how much alike some of these problems are (e.g., collection of blood and medical specimens, see below), it seems unfortunate that research usually only focusses on one medical product.

Like biological specimen or PCR-tests, blood is a perishable resource that needs to be collected before it can be processed in a laboratory. The way Williams et al. (2020:200;203) describe the collection of blood – either in a facility or through mobile teams – resembles the description of performing and collecting PCR tests given by Wolfinger et al. (2023). This impression is fortified by comparing the process outline by Wolfinger et al. (2023) to the literature on blood collection using bloodmobiles (e.g., Şahinyazan et al. 2015). Bloodmobiles have been in use for several years now, whereas the collection of specimens has traditionally been conducted at fixed healthcare sites such as medical practices or hospitals. In case of a healthcare emergency like the COVID-19-pandemic, mobile testing stations and teams can help identify and trace infected patients much faster and with lower risk to other patients (see chapter 6.2.2). Particularly considering that patients in hospitals and healthcare centres already have compromised immune systems, exposing patients with previous health conditions to potential cases of a new disease should be limited as much as possible. In this regard, the sample testing literature may greatly benefit from the knowledge and progress made in the literature regarding bloodmobile routing and scheduling. As a bonus, the studies conducted on (blood-)mobile location can help identify the best locations to set up mobile testing teams.

While on the topic of bloodmobiles, I found that statements on the relevance of blood mobiles are conflicting: According to Gunpinar and Centeno (2016:97), who cite a statistic from 2005, "[a]pproximately 80% of the blood units donated in the US are collected by bloodmobiles" whereas Şahinyazan et al. (2015:22) state that, despite the mobiles' large potential, "mobile blood collection is not the major part of blood collection in the world (including Turkey). In fact, most donations are taken at fixed locations." Unfortunately, they provide no statistics or reference to support their claim. One possible interpretation might be the authors' location, supposing that there are, in fact, differences between the US' and Turkey's approach to blood collection. In any case, the actual relevance of blood mobiles in global blood collection might be an interesting lead for further studies. Moreover, in light of the recent pandemic, it might be interesting to see whether the rise of mobile PCR testing stations has had an effect on the populations' readiness to take advantage of similar mobile health services, like blood donation.

To give another example of possible synergies, literature on cancer medication seems to be most accustomed to integrating production and route scheduling in order to satisfy short delivery deadlines and minimize product wastage. This kind of knowledge is valuable even under "normal" conditions, but especially in the aftermath of a disaster like an earthquake, the drug and blood product supply chain could immensely benefit from this research to produce and deliver medicines and blood products in the right amounts at the right times and, thus, save lives.

Finally, examples of successful cross-product learnings are given by El Midaoui et al. (2020 / 2021 / 2022) and Zabinsky et al. (2020, 2021). El Midaoui et al. apply their learnings from papers on drug delivery (2020 / 2021) to later tackle the blood delivery problem (2022). Meanwhile, the group around Zabinsky use the program developed for their specimen collection problem (VeRSA) to create a tool for vaccines distribution in LMICs (RoOT).

One possible measure to raise awareness between and for the various strands of literature is to publish review texts that take a cross-product approach and highlight similarities between existing research traditions, which allows researchers to find new sources and approaches that their own problems might benefit from. This even goes beyond the scope of medical products. Other business types that face similar challenges, like the fresh food industry, might also gain insights from more overarching analysis (Wu et al. 2022:681).

Another related approach would be to conduct literature reviews for product types where they appear to be lacking: While the literature on blood and cancer medication has been reviewed repeatedly, I did not find any notable surveys on specimens and drugs, at least not through the search methodology described in chapter 3. Supposing that my approach did not permit me to find all available or relevant texts, focusing on just one of these clusters and conducting a more thorough search might be worthwhile.

A last idea in relation to reviews would be to expand the current work, for example by looking for other medical products that require similar problem-formulations. As suggested in chapter 6.1.2, it might be interesting to see whether donated organs for transplantation might cause similar planning problems. As these are difficult or even impossible to produce artificially and, thus, more valuable than blood or cancer medication, it might be interesting to see whether the transportation and operation processes could be designed more efficiently with the help of RSPs.

To increase comparability between the studies, I believe that research might benefit from benchmark data instances that fit this kind of problems. At this point, hardly anyone uses them, and some authors actively point out the lack of data instances that would fit the problem criteria (see chapter 5.7).

Moreover, many authors believe that the existing literature would profit from newer and better solution methods that minimize the optimality gap for ever-larger instance sizes. For example, Andoh and Yu (2022:6) advocate for the combination of traditional mathematical optimization and simulation techniques. Wu et al. (2022:681) think practical and suggest that such mathematical models may be “integrated into various software and systems” in order to help real-life decision makers in their daily planning tasks. Applying and developing state-of-the-art methods is particularly relevant as new, more easily perishable medical products enter the market and introduce new challenges. The difficulties associated with the development and distribution of the COVID-19 vaccine have been addressed in chapter 4.3 (see also: Andoh and Yu 2022:6).

Thematically, I already discussed at large in chapters 2.2, 5.9 and 5.10 why I believe that the literature on RSPs might benefit from integration more production and appointment decisions. In chapters 5.5 and 5.6, I found that the planning environment calls for stochastic and dynamic approaches, especially since emergency and disaster settings are so frequently featured in optimization for perishable medical products. Incorporating uncertainty into more problems would make them more realistic. Apart from the emergency setting, I presented 3 other related research topics (chapter 6.2) that were addressed by some of the reference papers, and also appeared to be emerging research clusters that have received increasing attention in the last few years and still seem to be growing. Finally, in view of how many papers featured objective function relating to sustainability, this might also be an interesting future research direction. Indeed, sustainability was among the research gaps identified by Andoh and Yu (2022:6).

7. Conclusion

In this thesis, I conducted a literature search and analysis of combined routing-scheduling problems that feature perishable medical products. The main elements of this thesis, including product perishability and production as well as appointment scheduling, were first presented in chapter 2. The reference papers were then analysed with regards to these same elements in section 5. Additional comparisons were drawn regarding planning horizons, objective functions, solution methods and other problem-related characteristics. The research methodology was presented in detail in chapter 3 and later critically reviewed in chapter 6.1, where potential improvements for future literature searches were suggested. In chapter 4, the reference papers were clustered around their primary medical product. Background on the medical products was given and the mathematical problems derived from the scenario- and product-specific characteristics were presented. These clusters were then largely dissolved to allow cross-product analysis in section 5; if, however, characteristics of one specific product group could be observed, they were also highlighted. Finally, in chapter 6, additional insights were discussed, related topics presented, and future research directions proposed.

What struck me the most was how challenging the literature search proved to be. Despite anticipating difficulties due to the combination of characteristics (RSPs + health care + perishability), this step took the most time and the result still leaves room for improvement. Since I decided on conducting a systematic literature review and using PRISMA for orientation (chapter 3.1), I made the utmost effort to adhere to a replicable and transparent search process, even at the cost of missing relevant contributions (e.g., through snowballing from a text that was not designated for snowballing). This is also the reason why I refrained from using technical tools to sort through the potential reference papers, which meant hours and hours of manually screening and filtering the texts. Moreover, finding relevant yet unambiguous keywords, especially for the perishability-aspect, proved surprisingly difficult (chapter 6.1). If anyone were to expand this study or build on this work, I would recommend putting the learnings from chapter 6.1 to use and suggest considering technical tools to sort through the vast amount of literature. These adaptations might permit a more efficient and, hopefully, more effective search.

Without a doubt, the most important finding regarding the texts was that, although routing and scheduling problems have been integrated on several occasions, there is still much to be gained from further exploring RSPs. The benefits of combining these problem types can be applied to numerous other research areas beyond the medical fields, thus increasing the efficiency of operational planning. I found it striking how similar yet isolated these papers are: Despite many strong similarities, not nearly enough papers acknowledged and built on previous work. This is true for the papers in different product-related clusters, but just as much within the clusters. Here I see lost potential for synergies. Moreover, I found it striking how often perishability requirements are acknowledged in theory, like in the introduction or problem description sections of papers, but featured indirectly at best in the actual optimization (e.g., El Midaoui 2020 / 2021 / 2022, Aydınalp and Özgen 2022, Al-rabiaah et al. 2022). Similarly, not all papers that mentioned "routing and scheduling" among their keywords included both routing and scheduling (e.g., Al-rabiaah et al. 2022, see chapter 6.2.3). This stands to show how the emerging concept of combined RSPs lacks recognition and has not yet been coined as a technical term in its own right.

My hypothesis was that this field of research was still very young, with a large percentage of texts published within the last couple of years. As demonstrated in chapter 5.1, this hypothesis proved to be right. I found that interest in this topic has grown massively in the past couple of years. Chapter 5.1 shows that half of these reference papers have been published in the last three years (2020, 2021 and 2022) alone. The impact of the recent COVID-19 pandemic in this and other, related research topics can be seen in chapter 6.2.

Chapter 6.3 presents both current trends as well as concrete ideas for future research. Chapter 6.2.1 shows that Home Health Care is already one of the most well-studied healthcare-related applications for RSPs but the combination with perishable medical products still leaves room for improvement. Similarly promising are the other topics introduced in chapter 6.2 (Emergency Setting, Drone Usage and Medical Waste Management). As for environmental concerns, I had expected to find more papers that bring them into play, but as chapter 5.3 on the objectives suggests, surprisingly few publications chose a sustainability expansion. Still, Andoh and Yu (2022) strongly believe that this topic deserves more widespread recognition, and I also think that there is potential for future research. Further, I found that the approach to uncertainty has become more diversified over the past couple of years, but there remains much potential for further exploring stochastic and dynamic problem setting. Chapters 5.5 and 5.6 have shown, hopefully, how close these aspects are to real-life planning requirements, how natural it therefore seems to choose such extensions for these types of problems, and which papers already laid the groundwork for future research.

As for production and appointment, I initially overestimated their current relevance, especially that of AS. It features as an integral part in RSPs for cancer medication and yet, the appointment forms not in itself part of the optimisation, but rather functions as the prerequisite and initialisation of the planning process. AS played its most prominent role in a single blood collection problem in the form of donation scheduling (Mobasher et al. 2015). Ideas on how AS could be used to further improve HC-RSPs are suggested in chapters 5.10 and 6.3. PS, on the other hand, proved more multifaceted than expected. The applications production scheduling finds in these RSPs go beyond merely planning the production of drugs or blood products and are an excellent example of how concepts from certain academic fields (e.g., machine scheduling problems) can find application in problem settings different from their initial use.

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8.3 Table of Figures and Tables

9. Appendix

Table 11: Literature reviews read during preparation

Authors	Title	Year	Time Frame	Platforms	Publication type	Search Terms	Method
Abdalkareem et al.	Healthcare scheduling in optimization context: a review	2021	2010 -2020	Scopus, Google scholar	articles written in English and published in peer reviewed journals	“nurse scheduling”, “nurse rostering”, “patient admission scheduling”, “patient to bed assignment”, “operating room scheduling”, “operating theater”, “surgery scheduling”, “surgical scheduling”, “physician scheduling”, and healthcare scheduling with “heurstic” or “metaheurstics” “metaheurstics” [sic!].	explained, but not defined
Ahmadi-Javid et al.	Outpatient appointment systems in healthcare: A review of optimization studies	2017	2003 (until probably 2016)	Scopus, Web of Science, and PubMed	papers written in English	(“appointment” OR “outpatient appointment”) AND (“system” OR “scheduling”)	explained, but not defined
Becker et al.	Multiagent Systems to Support Planning and Scheduling in Home Health Care Management: A Literature Review	2019	no constraint, results 2006 - 2017	Google Scholar	scientific papers	Planning and Scheduling (“scheduling” | “roster” | “plan”) HHC (“home-care” | “home care” | “home health-care” | “home healthcare” | “home health care” | “home health nursing” | “caregiver” | “caregiving” | “long-term care” | “long term care”) MAS (“multiagent” | “multi-agent” | “agent-based” | “agent based”)	search key literature via keywords on search engine, then snowballing procedure (forward and backward)

Bvuchete et al.	BEST PRACTICES FOR DEMAND-DRIVEN SUPPLY CHAIN MANAGEMENT IN PUBLIC HEALTHCARE SECTOR: A SYSTEMATIC LITERATURE REVIEW	2020	1998 - 2018	Scopus, Web of Science, Science Direct	scientific journals, conference proceedings, technical reports, and textbooks	((demand driven) AND (supply chain) AND ((visibility) OR (information sharing)))((customer driven) AND (supply chain) AND ((visibility) OR (information sharing)))((pull) AND (supply chain) AND ((visibility) OR (information sharing)))	PRISMA
Cissé et al.	OR problems related to Home Health Care: A review of relevant routing and scheduling problems	2017	17 years of work in this field: presumably 2000-2017	Web of Science, Science Direct, Jstor, semanticscholar, CiteSeerX and using Google Scholar.	journal articles, conference proceedings, book chapters and technical reports, Ph.D. theses	‘‘home health care’’, ‘‘home care’’, ‘‘resource scheduling’’, ‘‘routing’’, and ‘‘vehicle routing problem’’	explained, but not defined
Di Mascolo et al.	Routing and scheduling in Home Health Care: A literature survey and bibliometric analysis	2021	1997 - mid-May 2019 +during peer review process: mid-May 2019 to the beginning of November 2020	Scopus, Web Of Science (WOS), Google Scholar, and ScienceDirect	only journal articles and conference papers	(Home care AND Routing) OR (Home care AND Scheduling) OR (Home health AND Routing) OR (Home health AND Scheduling) OR (Home service AND Routing) OR (Home service AND Scheduling) OR (Hospital at home AND Routing) OR (Hospital at home AND Scheduling).	explained, but not defined; Fig. 3. Bibliography research scheme calls PRISMA to mind

Dobrzykowski et al.	A structured analysis of operations and supply chain management research in health care (1982–2011)	2014	1982–2011	literature search in the scholarly database, EBSCO	Journal articles seven esteemed scholarly journal outlets in the OM and SCM field (see abstract)	hospital, healthcare, health care (two words), medical, outpatient, doctors, appointment scheduling, clinic, pharmacy, and laboratory	4-stages by Mayring (2003)
Fikar and Hirsch	Home health care routing and scheduling: A review	2017	until October 2015	unclear	only published journal articles available online by October 2015	‘home care’ or ‘home healthcare’ as well as ‘routing’ or ‘scheduling’ in the keywords or abstract	explained, but not defined
Grieco et al.	Operational research applied to decisions in home health care: A systematic literature review	2021	no constraint (presumably until 2018)	Web of Science	no constraint (review articles and non-review articles)	extensive list in Appendix 1 of their work	explained, but not defined
Marynissen and Demeulemeester	Literature review on multi-appointment scheduling problems in hospitals	2018	1995 -2017	Scopus, Web of Science	papers in peer-reviewed journal, conference proceedings and book chapters	((multi-appointment OR integrated OR holistic) AND (healthcare OR patient) AND scheduling)	explained, but not defined
Vieira et al.	Operations research for resource planning and -use in radiotherapy: a literature review	2017	2000 (until probably 2017)	EMBASE, PubMed, EBSCO Business Search Elite (BSE), Web of Science, Scopus, ORchestra	Journal paper, conference paper or book chapter in English	extensive list in additional files of their work	explained, but not defined

Wang et al.	Operating room planning and scheduling for outpatients and inpatients: A review and future research	2021	2000 - 2020	Web of Science (WoS)	peer-reviewed articles and conference proceedings	‘(operating room$ OR operating theat* OR operating suite OR surger* OR surgical) AND (scheduling OR planning)’	explained in detail
Williams et al.	Modelling of the Collections Process in the Blood Supply Chain: A Literature Review	2020	1996 - February 2019	Scopus	journal publications from the Clarivate Analytics Journal Citation Report (JCR) in the subject categories of Health Policy and Services (HPS), Medical Informatics (MI), Industrial Engineering (IE), as well as Operations Research and the Management Sciences (OR/MS).	"using a structured search string"; not further defined	explained; initial search, then forwards and backwards search (as suggested by Webster & Watson)
Zhu et al.	Operating room planning and surgical case scheduling: a review of literature	2019	unclear	PubMed, Web of Science, IEEE, Springer and Inspec	unclear	unclear	little information