JULIANO MARÇAL LOPES

Stochastic optimization and machine learning applied in the demand forecast, allocation and distribution of vaccines between Brazilian states

São Paulo
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Professor Dr. Eduardo Mario Dias

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It's temporary
Goes fast
Avoid the minimum

- Unnamed Mantra -
Doctoral Student

RESUMO

LOPES, Juliano Marçal. **Stochastic optimization and machine learning applied in the demand forecast, allocation and distribution of vaccines between Brazilian states**. 2022. 146 f. Tese (Doutorado) - Departamento de Engenharia Elétrica, Escola Politécnica, Universidade de São Paulo, São Paulo, 2021.

Os avanços em pesquisa e desenvolvimento resultaram no surgimento de muitas novas vacinas nas últimas décadas. No entanto, a distribuição de vacinas e o combate de doenças imunopreveníveis ainda é um desafio para os gestores da cadeia. A cadeia de suprimentos de vacinas normalmente possui orçamentos limitados, dificuldade em controlar a temperatura dos produtos, gerenciamento deficiente de inventário e falta de protocolo para alta demanda e situações incertas. O mau gerenciamento da cadeia de suprimentos da vacina pode levar a um surto de doença ou, na pior das hipóteses, a uma pandemia. Felizmente, um grande número de desafios da cadeia de suprimentos de vacinas, como alocação ideal de doses, melhoria da estratégia de vacinação e gerenciamento de inventário, entre outros, pode ser aprimorado por meio de abordagens de otimização. Diante desse cenário, o objetivo desse trabalho é o de propor métodos de redução de custos da cadeia. Isso se deu por meio da criação de um modelo de *machine learning* para previsão de demandas e um modelo de otimização estocástica para melhoria da distribuição de imunobiológicos entre estados brasileiros. Os modelos aqui apresentados, apesar de considerarem o cenário brasileiro, possuem o potencial de terem suas aplicações estendidas para a cadeia de suprimentos de vacinas de outros países. Para realização desse trabalho, primeiramente foram realizadas visitas em cinco estados brasileiros para entendimento e mapeamento dos processos da cadeia de distribuição de vacinas do Ministério da Saúde. Este mapeamento permitiu que as soluções aqui propostas fossem elaboradas levando em consideração o cenário atual da cadeia. O modelo de *machine learning* desenvolvido engloba o uso das técnicas de *Gradient Boosting* e *Random Forest Regressor*, e seus resultados são utilizados como dados de entrada do modelo de otimização proposto. O modelo de otimização estocástica considera a demanda incerta de três cenários. Os resultados do estudo mostram que o modelo de *machine learning* apresenta uma previsão da demanda com erros relevantemente mais baixos do que os que cadeia atualmente apresenta. E ainda, os resultados do modelo de otimização auxiliam os tomadores de decisão com uma sugestão do número de doses que devem sem enviados para cada estado em cada um dos meses do período considerado, reduzindo assim, a chance de falta de vacinas.

Palavras-Chave – Previsão de demanda, Demanda de Imunobiológicos, Vacinas, Otimização estocástica.

ABSTRACT

LOPES, Juliano Marçal. **Stochastic optimization and machine learning applied in the demand forecast, allocation and distribution of vaccines between Brazilian states**. 2022. 146 f. Tese (Doutorado) - Departamento de Engenharia Elétrica, Escola Politécnica, Universidade de São Paulo, São Paulo, 2021.

Advances in research and development have resulted in the emergence of many new vaccines in recent decades. However, the distribution of vaccines and the fight against vaccine-preventable diseases is still a challenge for chain managers. The vaccine supply chain typically has limited budgets, difficulty controlling product temperatures, poor inventory management, and lack of protocol for high demand and uncertain situations. Mismanagement of the vaccine supply chain can lead to a disease outbreak or, at worst, a pandemic. Fortunately, a large number of vaccine supply chain challenges such as optimal dose allocation, improving vaccination strategy and inventory management, among others, can be improved through optimization approaches. Given this scenario, the objective of this work is to propose methods to reduce costs in the chain. This was done through the creation of a machine learning model to forecast demand and a stochastic optimization model to improve the distribution of immunobiologicals among Brazilian states. The models presented here, despite considering the Brazilian scenario, have the potential to have their applications extended to the vaccine supply chain in other countries. To carry out this work, first visits were carried out in five Brazilian states to understand and map the processes of the vaccine distribution chain of the Ministry of Health. This mapping allowed the solutions proposed here to be elaborated taking into account the current scenario of the chain. The developed machine learning model encompasses the use of Gradient Boosting and Random Forest Regressor techniques, and its results are used as input data for the proposed optimization model. The stochastic optimization model considers the uncertain demand of three scenarios. The results of the study show that the machine learning model presents a demand forecast with errors significantly lower than those that the chain currently presents. Furthermore, the results of the optimization model help decision makers with a suggestion of the number of doses that should be sent to each state in each of the months of the considered period, thus reducing the chance of vaccine shortages.

Keywords – Demand forecast, Immunobiological demand, Vaccines, Stochastic Optimization.

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LIST OF NOMENCLATURE

AM	Amazonas (Brazilian state)
BPMN	Sistema Único de Saúde
CAPES	Coordination for the Improvement of Higher Education Personnel (from Portuguese: *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior*)
CENADI	National Center for Immunobiological Storage and Distribution (from Portuguese: *Central Nacional de Armazenamento e Distribuição de Imunobiológicos*)
CGPNI	General Coordination of the National Immunization Program (from Portuguese: *Coordenação Geral do Programa Nacional de Imunizações*)
CONAHP	National Congress of Private Hospitals (from Portuguese: *Congresso Nacional de Hospitais Privados*)
CRIE	Reference Centers for Special Immunobiologicals (from Portuguese: *Centros de Referência para Imunobiológicos Especiais*)
DATASUS	Department of Informatics of the Unified Health System (from Portuguese: *Departamento de Informática do Sistema Único de Saúde*)
IBGE	Brazilian Institute of Geography and Statistics (from Portuguese: *Instituto Brasileiro de Geografia e Estatística*)
IEEE	Institute of Electrical and Electronics Engineers
INESC	Institute of Socioeconomic Studies (from Portuguese: *Instituto de Estudos Socioeconômicos*)
IT	Information Technology
MA	Maranhão (Brazilian state)
MS	Brazilian Ministry of Health (from Portuguese: *Ministério da Saúde*)

PDSE	Sandwich Doctorate Program Abroad (from Portuguese: *Programa de Doutorado-sanduíche no Exterior*)
PNI	National Imunizations Program (from Portuguese: *Programa Nacional de Imunizações*)
RJ	Rio de Janeiro (Brazilian state)
RMSE	Root Mean Square Error
SIES	Health Strategic Inputs System (from Portuguese: *Sistema de Insumos Estratégicos em Sáude*)
SIPNI	National Immunization Program Information System (from Portuguese: *Sistema de Informações do Programa Nacional de Imunizações*)
SP	São Paulo (Brazilian state)
SUS	Brazil's Unified Health System (from Portuguese: *Sistema Único de Saúde*)
SSA	Sample Average Approximation
UF	University of Florida
UNDP	United Nations Development Programme (in Portuguese: *Programa das Nações Unidas para o Desenvolvimento*, PNUD)
UNICEF	United Nations International Children's Emergency Fund
USP	University of São Paulo

CONTENTS

1 INTRODUCTION

"I believe there are phases, cycles, beginnings, new beginnings. And I think I'm right in the middle of one of them."

-- Clarissa Corrêa

In the 1960s, vaccination campaigns were carried out worldwide with the aim of eradicating smallpox. In Brazil the campaign was successful, and the disease was considered eradicated in the 1970s, with the last case reported in 1971. In order to keep the campaigns coordinated and to increase the coverage of the campaigns, the Brazilian Ministry of Health (MS) formulated in 1973 the National Immunization Program (PNI) (Ministério da Saúde, 2017). Only later the Unified Health System (SUS) was created through the 1988 Brazilian New Constitution. SUS is a complex public health system, with free and full access to the entire population of the country.Thus, the PNI became part of the SUS. PNI is currently part of the World Health Organization Program, with support from UNICEF, Rotary International and the United Nations Development Program (UNDP).

The PNI currently aims to eradicate measles, neonatal tetanus, and control immunopreventable diseases such as diphtheria, pertussis, accidental tetanus, hepatitis B, meningitis, yellow fever, severe forms of tuberculosis, rubella, and mumps, as well as the maintenance of polio eradication. The PNI is also responsible for the acquisition, distribution, and standardization of the use of special immunobiologicals, which are indicated for specific situations and population groups. These are attended at the Reference Centers for Special Immunobiologicals (CRIE) (Ministério da Saúde, n.d.).

PNI's infrastructure now has a total of over 38,000 vaccination rooms. In its traditional operation, 49 products are distributed throughout Brazil, including vaccines, heterologous sera (animal immunoglobulins) and homologous sera (human immunoglobulins). In addition to these, other case-specific vaccines are distributed in CRIEs (Universidade Aberta do SUS, 2021b).

Immunobiologicals are perishable products with a short expiration date that require tight temperature control. Many of them should not be exposed to temperatures outside the range of 2°C to 8°C. Others should be kept frozen. Temperature control during

storage and transportation must be performed carefully to ensure product quality and effectiveness (Universidade Aberta do SUS, 2021a).

Another challenge for PNI is the planning of demand and setting the vaccination schedule for the whole country in advance. As there are not many producing laboratories and their capacities are limited, vaccines must be ordered six months to one year in advance. Errors in the planning stage, or the emergence of unexpected situations such as an outbreak, require rapid and efficient measures from PNI. An example of this was the decision made during the yellow fever outbreak between 2016 and 2018. If we consider only the period between July 2017 and February 2018, 723 cases of the disease were confirmed, entailing a total of 237 deaths (Ministério da Saúde, 2018b). In that situation, in order to meet the increasing demand, the MS decided to proceed with the administration of fractional doses in the states with the highest demand and population concentration (Ministério da Saúde, 2018a). Thus, immunization of the vaccinated population would be guaranteed, but with the need for a new administration of doses after 10 years (previously, with the standard dose, only one dose was sufficient for life-long immunization).

PNI's supply chain is quite complex and Brazil's continental characteristics further increase the challenge of managing the chain. The subject of this doctoral thesis arose from an approximation of the Gaesi Group, from the Polytechnic School of the University of São Paulo and the Brazilian Ministry of Health. This partnership was made with the objective of bringing improvements to the processes of the MS. The first activity to initiate the collaborations was a mapping of the processes of the PNI's vaccine logistics chain. For a year, technical visits were made in four Brazilian states, ranging from federal, state, regional, municipal distribution centers, vaccination rooms and CRIEs. The visits included close monitoring of the distribution of immunobiologicals by boat in the Amazon rainforest region, in the Amazonas state.

After mapping the processes and identifying the weaknesses of the chain, the next steps of the project were defined. In addition to the previously known challenge of immunobiological demand prediction, failures in vaccine allocation among Brazilian states were identified. One of the problems pointed out by the technicians working in the chain is that in the same period, there are states with a high stock of a given product and others with a lack of the same vaccine. Still related to this problem, Brazilian states do not have the habit of exchanging vaccines among themselves.

The objective of this work is therefore to propose models that can be used by managers (both from the Brazilian Ministry of Health, as well as from other countries with similar

management characteristics) to forecast immunobiological demand within a year and also to better allocate vaccines between states.

The proposed demand forecasting model is a machine learning model composed of two forecasting techniques: Gradient Boosting and Random Forest Regression.

To improve vaccine allocation, a two-step stochastic optimization model was proposed. The model created aims to define the optimal number of vaccines that should be distributed to each Brazilian state and also whether the states should exchange vaccines with each other. The stochastic optimization model takes into account the uncertainty of demand. Thus, three demand scenarios were considered for each of the twelve months, for the 27 Brazilian states: low, medium and high demand. The low and high demands were defined through an analysis of the PNI historical data. For average demand, the output data from the previously mentioned machine learning demand forecasting model were used. The development of the optimization model is presented in Chapter 5.

1.1 Motivation

For many years Brazil has stood out for its public health policies, providing basic and advanced care to all citizens. However, managing existing programs today with limited resources is quite challenging. In order to improve the use of public resources, avoiding losses and waste, as well as ensuring public health, this work aims to create solutions that can bring improvements to the vaccine supply chain.

The initiative of this work came from the partnership between the Gaesi group of the Polytechnic School of the University of São Paulo (USP) and the Brazilian Ministry of Health. The main objective of the partnership was to bring improvements to the MS's logistics chain.

This partnership has resulted in several research projects that address the challenges of MS management in various directions. The motivation for this specific work came from the observation that the planning of the MS vaccination schedule is carried out at least one year in advance. Because it is a long term, the demand for forecasting activity is even more challenging. Another challenge that motivated this work is that the decision on the number of vaccines sent to the states is almost unilateral, and the responsibility of the federal government. In addition, as the MS sets the vaccination schedule well in advance, they have little freedom to change vaccine allocation plans during the operation.

1.2 Objectives

The aim of this work is to propose improvements in public resource management to improve the availability and distribution of vaccines among Brazilian states.

1.3 Research tasks

The activities of this work can be divided into three main steps. The first is the business modeling of the Ministry of Health vaccine supply chain. This first step (which is best presented in Chapter 3) involves visiting various PNI sites in five Brazilian states. This step provided data for defining the next two steps of the work. The second step is the application of machine learning techniques to forecast vaccine demand for the 12-month period (see Chapter 4). And the third and final step is to develop a stochastic optimization model to improve vaccine allocation among Brazilian states (see Chapter 5).

Both the machine learning model and the stochastic optimization model were developed in partnership with professors Dr. Michelle Alvarado and Dr. Panos M. Pardalos, both professors of the Department of Industrial and Systems Engineering at the University of Florida (UF), Gainesville, FL, USA. The activities at UF were carried out by the author during his sandwich doctorate period, between April 2018 and December 2019. The activities in the USA were funded by Coordination for the Improvement of Higher Education Personnel (CAPES) through the Sandwich Doctorate Program Abroad (PDSE) grant, process: 88881.187765/2018-01.

1.4 Research contributions

Both the Brazilian public health system and the PNI have very particular characteristics when compared to other countries. This work was done with the care that the solutions proposed here meet the needs of the PNI chain. Even the scope design of the work was finalized only after visits to states with different realities was done (such as São Paulo, Amazonas, Rio de Janeiro, and Maranhão). Still, even if directed to the Brazilian scenario, this work can be easily adapted to the reality of other countries.

1.5 Publications during the doctorate

During the period of the doctorate, the author published three papers and two were submitted in indexed journals (one of them is under minor reviews). Also, one work was presented in an international conference and two in national conference. Details are presented below.

1.5.1 Manuscript published in journal I

The manuscript entitled "Smart Cities through Smart Regulation: The Case of São Paulo" was published in March, 2019, by the journal IEEE Technology and Society Magazine (ISSN 0278-0097; Impact Factor JCR=1.022; Qualis B1 in Engineering IV). This work was carried out in partnership with the professors Eduardo Mario Dias and Augusto Ferreira Brandão Junior, and the master degree candidate Gustavo Gil Gasiola, all from the Department of Electrical Engineering at the University of São Paulo.

1.5.2 Manuscript published in journal II

The manuscript entitled "Health 4.0: Challenges for and orderly and inclusive innovation" was published in September, 2019, by the journal IEEE Technology and Society Magazine (ISSN 0278-0097; Impact Factor JCR=1.022; Qualis B1 in Engineering IV). This work was carried out in partnership with the professors Eduardo Mario Dias and Sergio Pereira, and the doctoral candidate Patrícia Veras Marrone, all from the Department of Electrical Engineering at the University of São Paulo.

1.5.3 Manuscript submitted in journal III

The manuscript entitled "Improved predictive models for acute kidney injury with IDEA: Intraoperative Data Embedded Analytics" was published in April, 2019, by the journal PLOS One (ISSN 1932-6203; Impact Factor JCR=3.040; Qualis B1 in Engineering IV). This work was carried out in partnership with the professors Dr. Azra Bihorac, from the department of Medicine, College of Medicine, University of Florida. This publication was the result of a period in which the author spent studying data analysis in the PrismaP laboratory so that it could be possible to gather knowledge to carry out this study.

1.5.4 Book chapter published

The book chapter entitled "Proposal for sustaining innovation by strengthening the field of science, technology, engineering and mathematics" (from Portuguese: *Proposta de sustentação da inovação por meio do fortalecimento do campo da ciência, tecnologia, engenharia e matemática*) was included in the book entitled "Automation & Society: Fourth Industrial Revolution, a look at Brazil" (from Portuguese: *Automação & Sociedade: Quarta Revolução Industrial, um olhar para o Brasil*), ISBN 9788574528762. The book was published in February, 2018. This book was organized by Dr. Elcio Brito da Silva and Dr. Maria Lídia Rebello Pinho Dias Scoton, and the professors Dr. Eduardo Mario Dias and Dr. Sergio Luiz Pereira, all from the Department of Electrical Engineering at the University of São Paulo.

1.5.5 Manuscript submitted in journal I

The manuscript entitled "Optimization methods for large-scale vaccine supply chains: a rapid review" was submitted to the journal Annals of Operations Research (ISSN 1932-6203; Impact Factor JCR=4.854). This work was carried out in partnership with the professors Dr. Panos Pardalos and Dr. Michelle Alvarado, from the department of Industrial and Systems Engineering, University of Florida. Additionally, professor Dr. Eduardo Mario Dias, Dr. Vidal Augusto Z. C. Melo and the doctorate candidate Leonardo Batista Paiva, all from the Department of Electrical Engineering at the University of São Paulo.

1.5.6 Manuscript submitted in journal II

The manuscript entitled "Paradigms and new perspectives on the debate about the increase in health costs related to the incorporation of new technologies" was submitted to the journal IEEE Technology and Society Magazine (ISSN 0278-0097; Impact Factor JCR=1.022; Qualis B1 in Engineering IV). This work was carried out in partnership with professor Dr. Panos Pardalos and Dr. Mahdi Fathi, from the department of Industrial and Systems Engineering, University of Florida. Additionally, professor Dr. Eduardo Mario Dias, Dr. Vidal Augusto Z. C. Melo, Dr. Maria Lídia R. P. D. Scoton, and the doctorate candidates Leonardo Batista Paiva and Patricia Véras Marrone, all from the Department of Electrical Engineering at the University of São Paulo.

1.5.7 Work presented in International Conference

The study entitled "Rapid Review: Application of Optimization in the Supply Chain of Vaccines" was orally presented in the Technical Sections of the Conference INFORMS Healthcare 2019, in Cambridge, MA, USA. This work was carried out in partnership with professors Dr. Michelle Alvarado and Dr. Panos Pardalos, from the department of Industrial and Systems Engineering, University of Florida. Additionally, professor Dr. Eduardo Mario Dias and Dr. Vidal Augusto Z. C. Melo, from the Department of Electrical Engineering at the University of São Paulo.

1.5.8 Work presented in National Conference I

The study entitled "Electronic Prescription (RM-e): Automation for Health Safety" (from Portuguese: *Receita médica eletrônica (RM-e): automação à serviço da segurança na saúde*) was presented in the Technical Sections of the Conference 5º CONAHP - National Congress of Private Hospitals (from Portuguese: *Congresso Nacional de Hospitais Privados*), in São Paulo, SP, Brazil. This work was carried out with the professors Dr. Eduardo Mario Dias and Dr. Augusto Ferreira Brandão Junior, with the Master Degree student Melissa Pokorny, all from the Department of Electrical Engineering at the University of São Paulo.

1.5.9 Work presented in National Conference II

The study entitled "Data Governance of Unique Medical Device Identifiers in Brazil" (from Portuguese: *Governança de dados de Identificadores Únicos de Dispositivos médicos no Brasil*) was presented in the Technical Sections of the Conference 5º CONAHP - National Congress of Private Hospitals (from Portuguese: *Congresso Nacional de Hospitais Privados*), in São Paulo, SP, Brazil. This work was carried out with the professors Dr. Eduardo Mario Dias and Dr. Sérgio Pereira, with the doctorate candidate Patricia Véras Marrone, all from the Department of Electrical Engineering at the University of São Paulo.

1.6 Dissertation structure

This dissertation is divided into six chapters. The first one is an introduction to the subject, and where we present the objectives of the study, the publications related to the dissertation, and the dissertation structure. The second one presents a theoretical

foundation, where the current work is related to the state of art of the field.

As this study was derived from a robust and more general study of the vaccine supply chain of the Brazilian Ministry of Health, the third chapter presents the business modeling process and design of the study.

The fourth chapter presents the development and results of the machine learning model for vaccine demand forecast. In the fifth chapter, it is presented the development and results of the stochastic optimization model for vaccine allocation between states in Brazil.

Conclusions are presented in the sixth chapter.

2 THEORETICAL FOUNDATION

"If root's strong, tree survive."

-- Mr. Kesuke Miyagi

Advances in research have resulted in the emergence of many new vaccines in the last decade. However, vaccine distribution is still challenging for many immuno-preventable diseases. The vaccine supply chain typically has insufficient budgets, difficulty in controlling temperature of items, poor inventory management and lack of protocol for high demand and uncertain situations. Poor management of the vaccine supply chain can lead to a disease outbreak, or at worst, a pandemic. Fortunately, a large number of vaccine supply chain challenges such as optimal allocation of resources, improving vaccination strategy, and inventory management, among others, can be improved through optimization approaches.

The purpose of this chapter is to investigate and understand how optimization has been applied to vaccine supply chain and logistics. Hence, here a rapid review methodology is used, and a search for peer-reviewed journal articles, published between 2009 and 2019, in four scientific databases was made. The search for the terms vaccine, optimization, distribution, logistics, and supply chain resulted in 388 articles, of which 19 unique studies met the inclusion criteria. This analysis focused on the identification of each article's main goal, the component of the vaccine supply chain that was studied, the type of optimization method used, and whether outbreak scenarios were considered.

Approximately 58% of the studies included in the study dealt with vaccination strategy, and the remainder dealt with logistics and inventory management. Only a small part addressed finances (5%). There were 14 different types of optimization methods used, but linear programming and optimal controlling were the most common (16% each). Approximately 42% of the manuscripts considered uncertainties in their models. One resulting observation was the lack of studies using optimization for vaccine inventory management and logistics.

This chapter is composed of the following structure: in Section 2.1 an introduction on the subject is brought. Section 2.2 brings an introduction to the vaccine supply chain.

In Section 2.3, the rapid review methods used to identify relevant papers is presented. In Section 2.4, it is presented the results and a discussion of the content of the selected papers. Concluding remarks are given in Section 2.5. Appendices A1 and A2 brings more information related to the manuscripts included in this Rapid Review.

2.1 Introduction

Efficiently operating large-scale vaccine supply chains is a global challenge. Optimization is one decision tool that can help mitigate challenges in this $59.2 billion industry (GUZMAN, 2018) of large-scale vaccine supply chains. Those challenges include budget limitations, transportation, temperature control, inventory management, and high and uncertain demand. Poor management of the vaccine supply chain can lead to a disease outbreak (SHAROMI; MALIK, 2017), or at worst, a pandemic. The purpose of this work is to understand how optimization has been applied to large-scale vaccine supply chain and logistics in the past. This paper utilizes a rapid review method to systematically analyze optimization models in four areas of the vaccine supply chain. The rapid review methodology was selected because it provides a structured search, organization, and analysis technique for investigating a topic of interest (GANANN; CILISKA; THOMAS, 2010; KHANGURA et al., 2012; TRICCO et al., 2015). Specifically, this rapid review investigates vaccine inventory management, vaccination strategies, vaccine logistics, and vaccine market competition.

2.2 Vaccine Supply Chain

Vaccine supply chain management is the general set of processes and activities involved in the planning of a vaccination campaign, including production and procurement of vaccines, vaccine inventory management, vaccine distribution, vaccine logistics, vaccine administration, vaccination strategies, among other activities. The main difference when comparing a normal supply chain with that of vaccines is that it has great uncertainty of demand and supply. When it comes to the prevention of vaccine-preventable diseases, it is crucial that combat actions are taken quickly, otherwise, the demand for immunobiological can increase exponentially. Another important point considering the vaccine supply chain is that the vaccine allocation decisions are taken by the government, often politically influenced.

It was identified unique characteristics of the vaccine supply chain: high uncertainty

in both supply and demand; misalignment of objectives and decentralized decision making between supplier, public health organization and end customer; complex political decisions concerning allocation and the crucial importance of deciding and acting in time.

Vaccine supply chain management exists in every country where it adapts to local characteristics and obstacles regarding prevalent diseases, population, geographic distribution, infrastructure, and economic power. Even though the fight against immuno-preventable diseases and vaccine development is not new, management of the vaccine supply chain still faces a number of obstacles; this paper will investigate how operations research has been used to overcome these obstacles (LEMMENS et al., 2016a; ASHOK; BRISON; LETALLEC, 2017; KASONDE; STEELE, 2017; LEE; HAIDARI, 2017).

Four sub-components were investigated at a deeper level: inventory management, strategies, logistics, and market competition.

- **Vaccine inventory management** involves the stock management, storage, rationing, and demand-side management of the vaccine supply chain (LIM; NORMAN; RAJGOPAL, 2017; GAGNON; LAMPRON; BUYL, 2016). Due to the manufacturing lead time of the producers, vaccine production and planning is carried out over a long period (e.g., sometimes over a year). Thus, population growth, vaccination schedules, regional characteristics, etc., can drastically change inventory levels. Misaligned planning with the current scenario can reflect negatively on the vaccination campaign, especially when demand is underestimated and left unmet. In contrast, overestimating demand can also have negative impacts on the vaccine supply chain since the vaccines are perishable and incur large refrigeration holding costs. As could be observed during the COVID-19 pandemic health crisis, vaccine manufacturing is an extremely important issue and one that directly affects the vaccine supply chain (DUIJZER; JAARSVELD; DEKKER, 2018; LEMMENS et al., 2016b). However, this issue requires that the approach consider the availability of raw material, government purchase planning, as well as demand estimation itself. Thus, this Rapid Review does not address manufacturing problems, focusing on managing these products as soon as they are available on the market.

- **Vaccination strategies** refer to the decision-making behind who should be given vaccines, when they should be given, and how often they should be given (KRESS, 2006). Some vaccines are a very limited and costly resource, so some research has focused on the optimization of the distribution among the population (considering, for example, age, gender, location, etc.) (HARVEY et al., 2016; SHOUKAT et

al., 2016; GIERSING et al., 2017; KUROSKY; DAVIS; KRISHNARAJAH, 2016; HARDT et al., 2016).

- **Vaccine logistics** refers to the manufacturing and distribution of vaccines to the population. This stage of the vaccine supply chain management can be disrupted when it is difficult to access a region (mainly in developing countries (ANPARASAN; LEJEUNE, 2018)), or due to unexpected vaccines loss when the physical integrity of the vaccines is compromised due to breakage, improper handling, or temperature deviation (LEE et al., 2017; MVUNDURA et al., 2017; LLOYD et al., 2015; UDDIN et al., 2016). This type of uncertainty in the vaccine supply chain causes challenges with the optimal allocation of vaccines across a region. It is common that in the same country two regions face completely different scenarios such as lack of vaccines and loss due to expiration (HUANG et al., 2017; MOORE; LESSLER, 2015; YUAN et al., 2015).

- **Market competition** refers to the laboratory competition on the price of vaccines. This stage refers to the use of pricing models with respect to supply, demand, peer competition, contracts, and insurance (LAUTON; ROTHKOPF; PIBERNIK, 2019).

In addition to those challenges just described, another critical challenge in large-scale vaccine supply chains is that most operate at a budget limit which is often far from ideal (LOZE et al., 2017; ONISHCHENKO et al., 2019), making financial decisions a challenge. Likewise, supply chain management operations are also complex and challenging due to the batch sizes, expiration date, temperature control, vaccination strategies, disease outbreaks, among others (RAEVEN et al., 2019; CHEN et al., 2018).

These problems have a common feature: solutions can be developed through optimization methods. In view of this, a rapid review was conducted to investigate how optimization has been used to improve the supply chain of vaccines worldwide. To the best of the knowledge, there exists three literature reviews related to the topic of this paper. First, Lemmens et al. (LEMMENS et al., 2016b) reviewed models on general supply chain network design (SCND) and discussed whether these models could be applied to the key issues of the vaccine supply chain, specifically the case of the rotavirus vaccine. They focused on the distribution and production phases of the supply chain and concluded that existing general SCND models cannot address the complexities of the vaccine supply chain.

Meanwhile, Duijzer, van Jaarsveld and Dekker (DUIJZER; JAARSVELD; DEKKER, 2018) reviewed operations research and operations management (OR/OM) literature

already applied to vaccine supply chains and categorized it into four supply chain components: product, production, allocation, and distribution. They identified the main challenges of vaccine logistics and shed light on ways that the OR/OM community can contribute to improving the vaccine supply chain components and integrations among them. In contrast, the search method for this rapid review only overlaps that of Duijzer, van Jaarsveld and Dekker in four articles, meaning that 21 new manuscripts were reviewed.

Lastly, Boeck, Decouttere and Vandaele (BOECK; DECOUTTERE; VANDAELE, 2020) dove into the specifics of vaccine distribution chains (VDC) within low- and middle-income countries and included both quantitative and qualitative studies (i.e., case studies, interviews, etc.) in their analysis. They classified studies into four VDC parts (sourcing, storage, transportation, and administration of vaccines) and discussed the gaps between the qualitative and quantitative works within these countries to make results relevant to both practitioners and the OR/OM community.

Our work contributes a different perspective on the OR/OM literature on vaccine supply chains. First, this rapid review process is more systematic and reproducible than the literature reviews in those papers. Second, an analysis of the type of optimization methodology used in each study was performed. Finally, vaccine supply chain was characterized into four stages: vaccination strategy, inventory management, logistics, and market competition. Therefore, the results show how different studies applied different optimization methods to the identified stages and what their objectives were. In addition, the rapid review notes what optimization methods have been used and whether the manuscripts addressed data uncertainties and outbreak scenarios. Thus, additional interesting optimization research opportunities within the vaccine supply chain were identified.

2.3 Method

In this section, it is defined the method used to conduct the review. In general, a review can be defined as the analysis of evidence that seeks to answer a clear question. It consists of selecting, evaluating and criticizing relevant primary research. The basic premise of a review is that your methods are clearly presented and reproducible (GANANN; CILISKA; THOMAS, 2010; HARKER; KLEIJNEN, 2012).

There exists several types of reviews like Systematic Review, Rapid Review, Mapping Review, Meta-Syntheses, Mixed Methods Review, Overview of Reviews, Accuracy Review, Network Meta-Analysis and Living Systematic Review, to mention a few. Each type of

review has a characteristic regarding their final objective, scope definition, time availability, available resources, etc. (GANANN; CILISKA; THOMAS, 2010; KHANGURA et al., 2012; TRICCO et al., 2015; SHAROMI; MALIK, 2017).

The type of review adopted in this work was that of Rapid Systematic Review, also known as a Rapid Review. This method follows similar procedures of a full-systematic review; however, it aims to answer a more restricted question and has its execution in less time (from 4 to 8 weeks, depending on the scope of the research, whereas other methods can take many months). The databases searched are also limited due to the execution time. However, the studies included in the review are selected in a careful, transparent, and replicable manner. And yet, the evaluation of the studies is critical and rigorous, and findings can be both qualitative and quantitative. Rapid reviews can be opportune to bring synthesis of evidence to decision-makers. They are designed to address new or emerging issues, to update previous analysis, or to assess what is already known (KHANGURA et al., 2012; TRICCO et al., 2015; KRESS, 2006).

Each step of this Rapid Review is described below and is organized as follows. Subsection 2.3.1 presents the question aimed to be answered with this review, subsection 2.3.2 presents the search strategy used to find the manuscripts, subsection 2.3.3 presents the eligibility criteria, and subsection 2.3.4 presents how data were organized and analyzed.

2.3.1 Focused question

Faced with the challenge of managing the supply chain of vaccines, this review intends to shed light on how optimization has been used to aid decision-making in these problems. Given that, the question to be answered was the following:

How has optimization been applied to the fields of vaccine strategy, logistics, inventory and market competition?

2.3.2 Search strategy

This rapid review of scientific studies followed the guidelines of the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) (MOHER et al., 2009). Four databases were systematically searched for applications of optimization in the vaccine supply chain as presented in Table 1.

Table 1: Search strategy and bibliographic databases used to retrieve the articles falling into the scope of this rapid review

Bibliographic Databases (Primary Sources)	**Search Strategy (Descriptors and Boolean Operators)**
SciVerse Scopus - Elsevier	(optimization OR optimisation) AND (distribution OR logistics) AND vaccine
Compendex – Engineering Village	
Web of Science	
Google Scholar	Manual searches according to the reference lists of the articles

2.3.3 Eligibility criteria

Papers written in English, Spanish, and Portuguese, and published between 2009 and March 2020 were accepted (considering that in innovation a lot can change in a short period of time, 10 years is a lot). Only original studies presenting new OR models (that excludes reviews) were included in this rapid review. Although the search already contemplated the language, dates and peer-reviewed journal papers criteria, that information was verified again during a full-text screening. The inclusion criteria for the supply chain aspect of papers was that studies should apply optimization in one of the following activities of vaccine supply chain: (1) Vaccination strategy; (2) Logistics; (3) Inventory management; or (4) Supply Chain Management (Competition). The definition of each of these four areas is presented in Table 2.

2.3.4 Data pooling and analysis

The search for manuscripts was performed by one reviewer in the four databases following the definition of descriptors presented in Section 2.3.2. The search process resulted in 345 articles. Of this total, 172 were from Scopus, 90 from the Web of Science, 79 from Compendex, and 4 were included after manual search in Google Scholar. Figure 1 presents the screening and selection processes. The records retrieved from the search were analyzed by one examiner in RefWorks (ProQuest), a web-based bibliography and database manager, and 193 duplicate manuscripts were removed. The remaining 152 articles were initially screened by title and abstract, at which point 110 were excluded. The remaining 42 papers then went through a full-text screening, resulting in 26 included manuscripts. In questionable cases during screening, the final verdict was reached by having two reviewers

Table 2: Division of the manuscripts into four vaccine supply chain components and their corresponding descriptions

Vaccine supply chain components	**Description**
Vaccination strategy	Decision-making to reduce the proliferation of vaccine-preventable diseases by determining which populations (e.g., identified by age, location, gender, risk of disease contagion, etc.) should receive vaccines
Logistics	Transportation and distribution of vaccines to the population in order to meet the pre-defined vaccination schedules and demand
Inventory management	Stock management, storage, rationing, and demand-side planning of vaccines
Market competition	Impact of laboratory competition on the price of vaccines

discuss the classifications and reach a common agreement. The reasons for exclusion of articles in both screenings (that is, manuscripts excluded during the title and abstract screening and the full-text screening) were: *1.* out of the original scope of the research, *2.* focused on health care instead of vaccines, *3.* optimization approaches were not used, and *4.* optimization was not applied to the supply chain aspect of vaccines (i.e., optimization of vaccine efficacy in the human body).

Two publications were related to the same project, so their information was combined. After all the steps, a total of 25 unique studies met the search criteria (Appendix A). The manuscripts that met the inclusion criteria were extracted from the RefWorks platform and their information was organized into an Excel table. With the information compiled and organized, it was possible to proceed with the exploratory analysis according to the study design explained below.

For each of the manuscripts included, it was identified the main objective, type of vaccine, the supply chain stage being studied, country of study, and the optimization method used. The main objectives were identified with free text. The types of vaccines under consideration in the studies are classified by the name of the specific vaccines or the disease being studied (in cases of studies of developing vaccines). The supply chain stage is classified within four key areas of the chain as defined in Section 2.3.3. Under this characteristic, it was also analyze whether or not the study considers outbreak (or

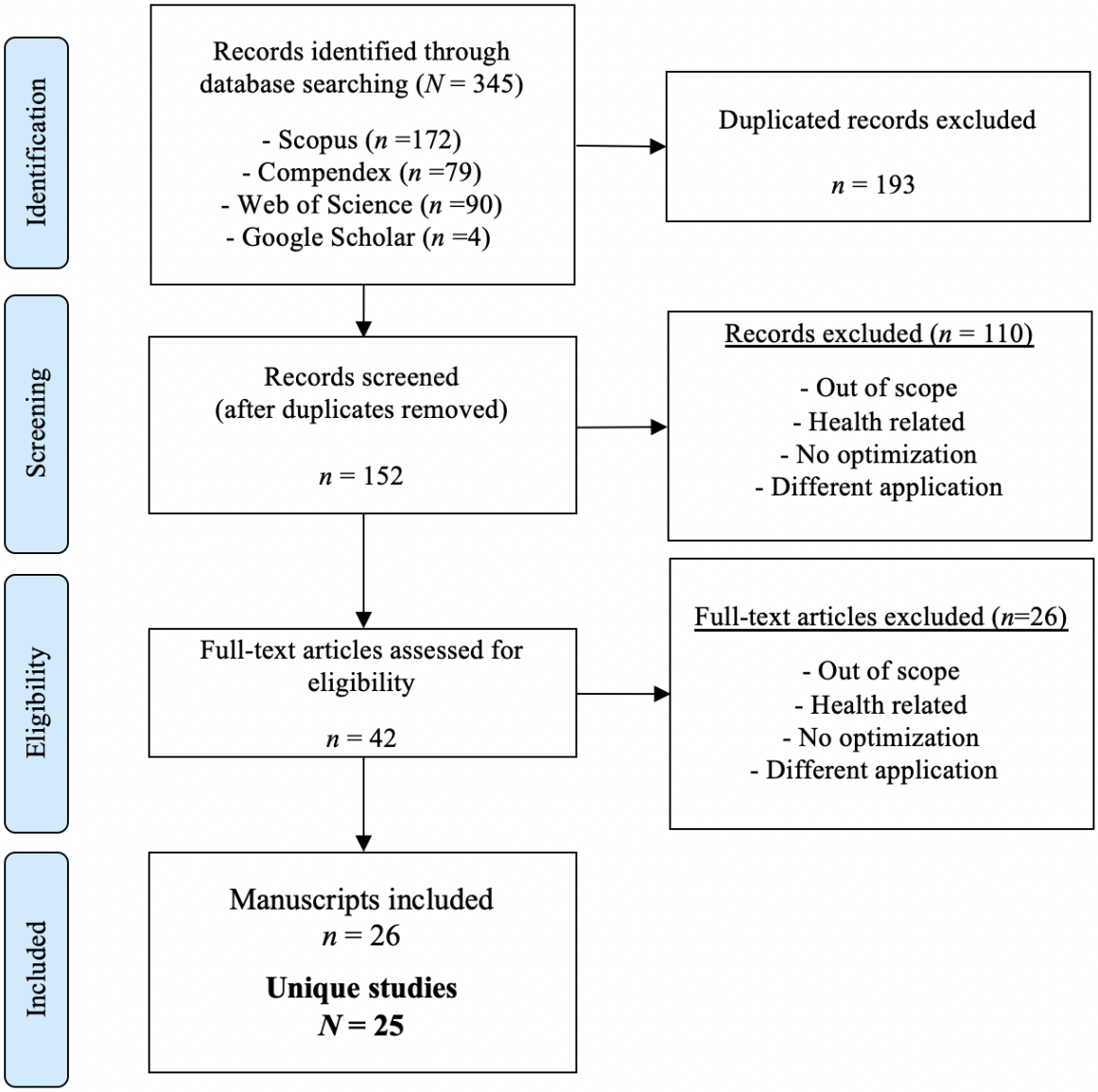


Figure 1: PRISMA flow diagram of the search strategy comprising the identification of potentially relevant material, preliminary screening, and final selection of the studies included in this review (based on PRISMA guidelines) (MOHER et al., 2009).

pandemic) scenarios. The country of study refers to where the application of the solution occurred or where the data was retrieved from, not the country of affiliation of the authors. The optimization method characteristic is also binary. Information on whether the studies considered uncertainty and whether they dealt with the problem as a network problem were also collected under the optimization method characteristic.

2.4 Results and Discussion

In this section, it is presented and discuss the characteristics of the papers that met all of the eligibility criteria of this rapid review. The characteristics discussed below are: country of study, type of vaccine, study objectives, supply chain stage, and optimization method. The following subsections address each one individually.

2.4.1 Country

It was identified the countries of origin of the data used by the studies. Data from the United States was used in 28% of the studies, data from Pakistan was used in 8% of the studies (AGUSTO; KHAN, 2018; THAKKAR et al., 2019), and data from Brazil (FERREIRA; ARRUDA; MARUJO, 2018) and Israel (HOVAV; TSADIKOVICH, 2015) were used in 4% each. Data from more than one country was used in 20% of the studies—these included the UK, Wales, France, USA, Niger, Thailand, Vietnam, Brazil, and the Netherlands. The other 36% of the studied were general applications, not directed to a specific country.

2.4.2 Type of vaccine

The manuscripts included in this review dealt with different types of vaccines as shown in Figure 2. The vaccine with the highest number of studies was Influenza/H1N1 with 32%, followed by Dengue with 8% (AGUSTO; KHAN, 2018; RODRIGUES; MONTEIRO; TORRES, 2014), and HPV (DEMARTEAU; BREUER; STANDAERT, 2012), Measles (THAKKAR et al., 2019), Pertussis (GIRARD, 2010), and Polio (TEBBENS et al., 2010) were each considered in 4% of studies. Addressing vaccines and other products (including antidotes, vital vaccines, medicines to treat HIV/AIDS, malaria, tuberculosis, among others) occurred in 12% of papers, and 4% of studies addressed multiple vaccines (ENGINEER; KESKINOCAK; PICKERING, 2009). A total of 20% of the studies were included in the general category (which includes articles that exclusively deal with vaccines but do not specify which).

2.4.3 Study objectives

The studies were divided into six categories according to their objectives. Many of the studies, 40%, aimed at reducing impacts of an outbreak or pandemic by helping in

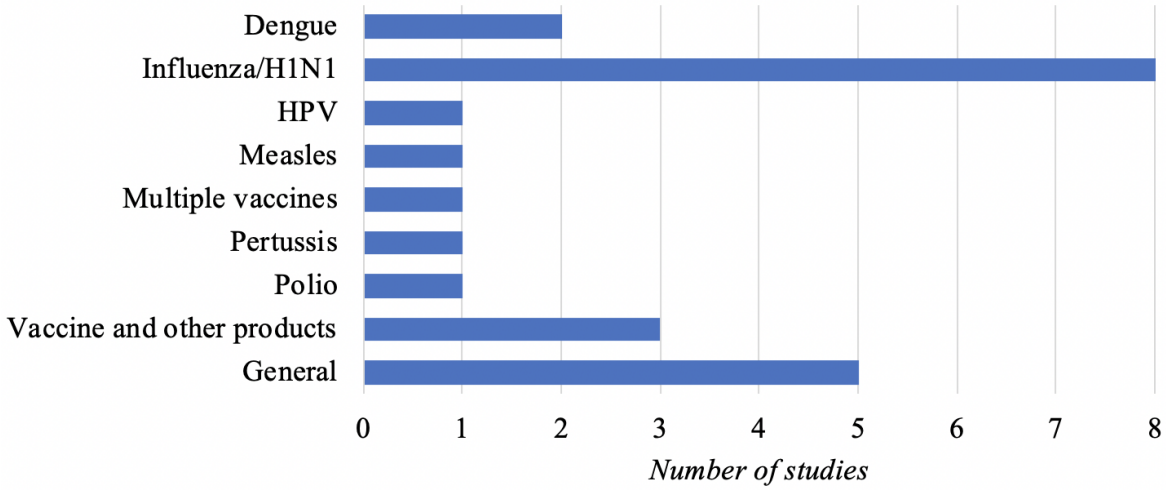


Figure 2: List of vaccines addressed by the studies included in the rapid review.

the decision-making process under such situations. The cost reduction with vaccination or vaccine allocation limited by budget was the goal of 20% of the studies. Meanwhile, allocation or availability of vaccines was sought to be optimized in 20% of the studies (CHEN et al., 2014; PRECIADO et al., 2014; SAMII et al., 2012), and another 20% of studies dealt with the general reduction of disease impacts (ENGINEER; KESKINOCAK; PICKERING, 2009; FERREIRA; ARRUDA; MARUJO, 2018; MEDLOCK; GALVANI, 2009; MEYERS; GALVANI; MEDLOCK, 2009). Two other objectives that were identified, each of them addressed in 4% of the studies, were: to understand the impacts of new manufacturers on vaccine prices (LAUTON; ROTHKOPF; PIBERNIK, 2019) and to improve stockpile management of vaccines for eradicated diseases (TEBBENS et al., 2010), which are common operations research applications.

2.4.4 Supply chain stage

The studies were separated into four unique categories, as shown in Figure 3, according to the vaccine supply chain stage addressed. More than half, 64%, addressed vaccination strategy. Of these, a portion of the studies focused on the allocation of vaccines in cases of disease outbreak while others focused on the best use of resources in a situation of a limited budget. Studies addressing the inventory management and logistics stages accounted for 12% each, and 8% dealt with both of these stages (shown by the yellow and orange bars in Figure 3) (CHEN et al., 2014; VENKATRAMANAN et al., 2019). Finally, only 4% of studies addressed competition (specifically, the impact of new manufacturers on vaccine prices) (LAUTON; ROTHKOPF; PIBERNIK, 2019).

If it is considered the definition of a vaccination strategy, it could be thought of as

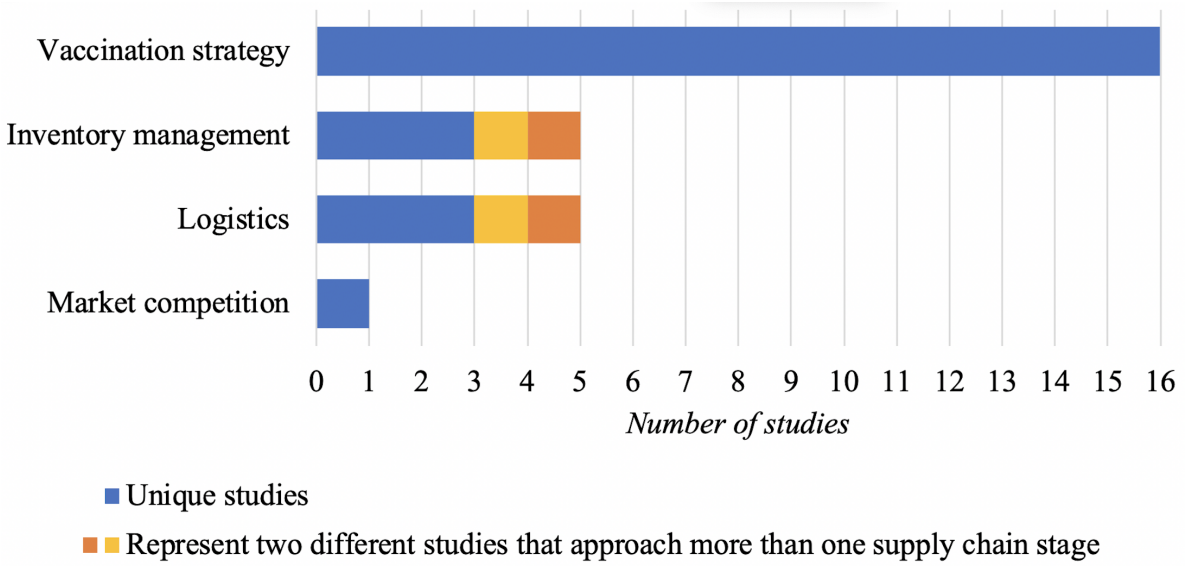


Figure 3: Stage of the supply chain addressed by each study included in the rapid review.

part of strategic planning. However, in this review, it can be observed the difference in studies that focused on general management activities from those that focused specifically on vaccination distribution. This is shown by 64% of the studies which exclusively aimed at improving vaccination strategies. Their strategies were defined in order to meet the momentary needs of a country or region such as increase vaccine coverage of all or a portion of the population, prevent an outbreak, control it or reduce its impact, improve resource allocation, etc.

2.4.5 Optimization

It was identified 14 different types of optimization used in the manuscripts included in the review. Figure 4 presents the identified models. You may notice that there are 29 studies shown in the figure. This is because three studies make use of 2 optimization types and are therefore represented twice in the figure. Many of the studies approached their models from an epidemiological perspective, however, not all specified the optimization type they used. Therefore, the epidemiological model category in Figure 4 is a general category for the studies that do not dive into the specifics of their optimization models. The most common optimization type was Linear Programming (CHEN et al., 2014; DEMARTEAU; BREUER; STANDAERT, 2012; TEBBENS et al., 2010; HOVAV; TSADIKOVICH, 2015), followed by Control Theory (AGUSTO; KHAN, 2018; REN; ORDONEZ; WU, 2013; RODRIGUES; MONTEIRO; TORRES, 2014) and Network Optimization (DIMITROV et al., 2009; HOVAV; TSADIKOVICH, 2015; KIM et al., 2016). It was also looked into the nature of the studies and identified them as theoretical or applied (applied work referring

to articles that applied their model in a real life scenario). Results show that 56% were theoretical papers while 36% had applied content, and 8% conducted simulation using real data (LAUTON; ROTHKOPF; PIBERNIK, 2019; PENG et al., 2019).

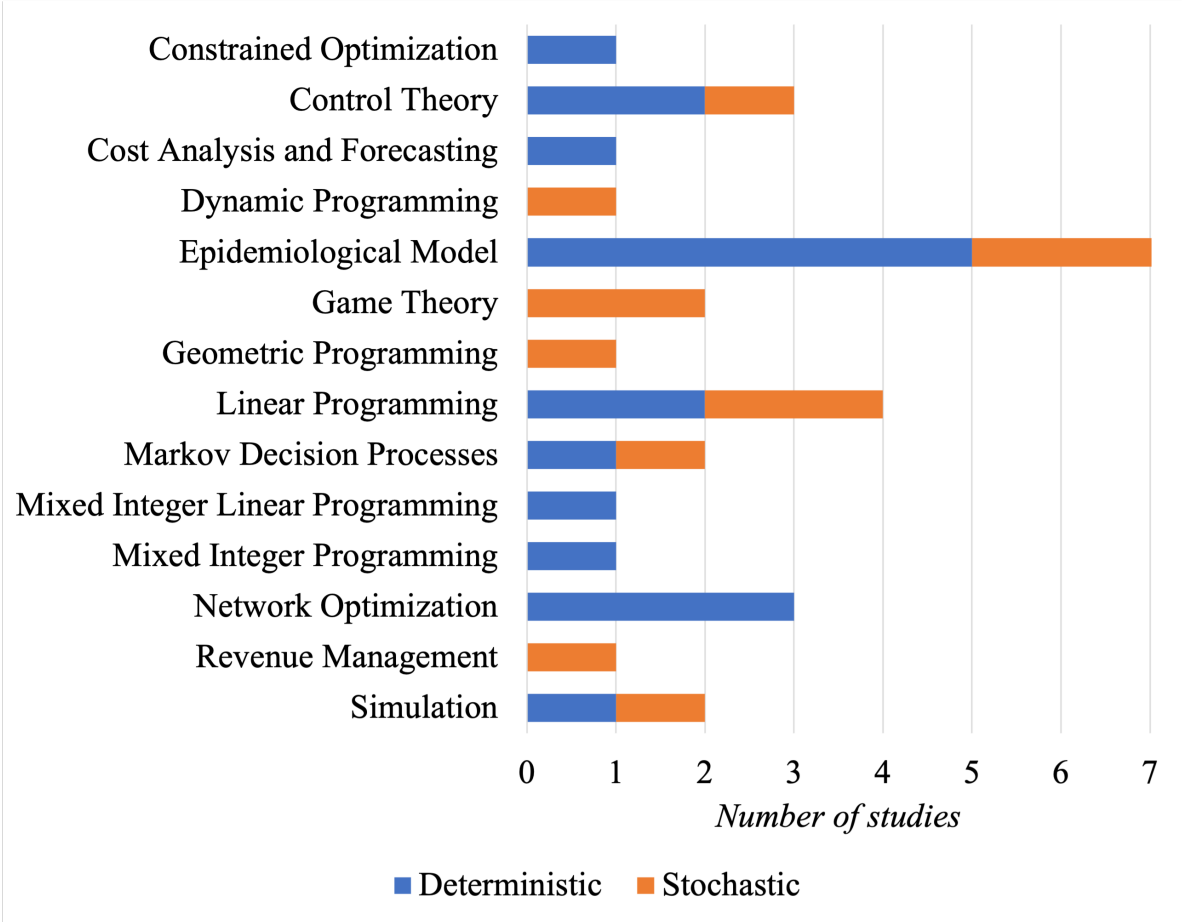


Figure 4: Number of studies included in the rapid review on each optimization approach.

It was also analyzed the studies in order to understand if the authors considered uncertainty in their models . Approximately, 52% of the studies did not consider uncertainties in their models (i.e. models were deterministic, shown by blue bars in Figure 4), while 48% did so, meaning that they included stochastic data in their models. In order to deepen the understanding of how this characteristic was included in the model, it was also identified the variables that were considered to be uncertain. The articles were split into two uncertainty type categories:

1. **Need for vaccines:** Within the vaccine need category, one half considered the demand for vaccines to be uncertain, of which one also considered the uncertainty of the arrival of new donations of supplies (in this case, the work dealt with items that were perishable in humanitarian operations, including other products in addition to vaccines) (FERREIRA; ARRUDA; MARUJO, 2018). The other half of the articles in this

category considered the lead time of the arrival of new vaccines to be uncertain. One of these included warehouse stock uncertainty, vaccine efficacy and disease severity. (LAUTON; ROTHKOPF; PIBERNIK, 2019)

2. **Transmission of disease:** The second category considered disease transmission to be uncertain. One of the papers addressed the probability of a traveler initiating an epidemic at the destination (DIMITROV et al., 2009). And a very specific case considered the rate of mosquito bites as stochastic, as well as the mosquito's lifetime, in the transmission of dengue (AGUSTO; KHAN, 2018). One study dealt with the chances of disease transmission in the face of different perceptions of the transmission scenario and different decision making (HOTA; SUNDARAM, 2019).

2.4.6 Insights

Given the results above, Figure 5 now illustrates how the studies scaled different optimization methods to the different supply chain stages and what their main goals were. All 25 papers are shown by the arrows (dotted arrows of the same color represent the same paper). It it possible to make the following observations and draw some conclusions from this figure. Even though control theory was one of the most common methods, it was only applied within the vaccination strategy stage and addressed decision-making challenges related to budget and outbreaks/pandemics. Similarly, mathematical modeling is also applied to vaccination strategy with the objective of reducing the impact of diseases and managing budget. Linear programming, on the other hand, is seen to be applied to three different stages (vaccination strategy, inventory management and logistics) and with multiple objectives. Likewise, mixed integer programming was applied to vaccination strategy and logistics towards optimal allocation/availability, reducing impact of diseases and outbreaks/pandemics.

In a similar manner, it could continue to trace the arrows and notice that the there's opportunity for future research apply these optimization methods to less common supply chain stages (like supply chain management) and focusing on issues like the impact of new manufacturers or the stockpile for an eradicated disease. There is no doubt that vaccination strategy is one of the most important activities within supply chain management. However, the defined strategies have a direct impact on the other areas of the chain (such as distribution, stocks, etc.). Thus, there is a lack of more comprehensive studies that investigate the effects of such strategies on the rest of the supply chain and a lack of optimization and operations research applications to the integration of multiple stages.

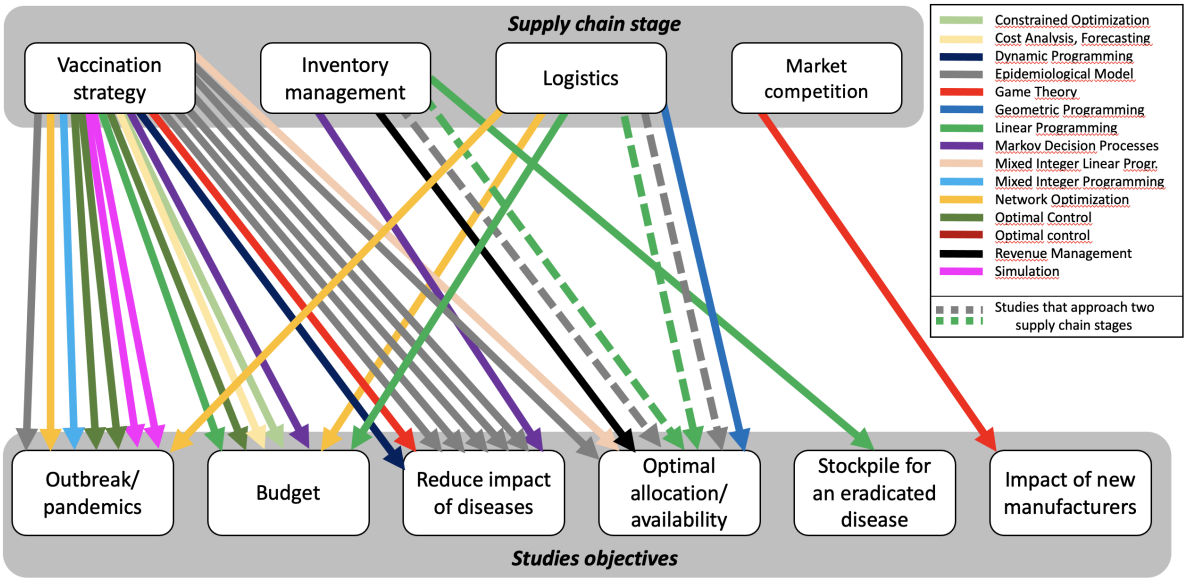


Figure 5: Relation of the supply chain stage, studies objectives and optimization methods addressed by the manuscripts included in the rapid review.

This observation shows how relevant this present doctoral thesis is. It addresses the issue of vaccine distribution precisely where there is a lack of depth. The beginning of this work took place in early 2017, that is, long before the world turned its eyes to the vaccine distribution chain. The existence of a pandemic situation only confirms that the failure in the management of vaccine-preventable diseases deserves attention, and needs to be increasingly optimized. Having its flaws an expensive price to pay: lives.

Finally, this rapid review analyzes 25 articles, of which 21 were not included in the most recent work on this topic (DUIJZER; JAARSVELD; DEKKER, 2018). This study shed light on the applications of optimization methods on the vaccine supply chain and highlight interesting research directions for future works.

2.4.7 Impact of the studies

In 2011, UNICEF, the World Health Organization and various partners and stakeholders from industry and non-governmental organizations released a document entitled "Developing a Vision for Immunization Supply Systems in 2020". The document heralded the vision for the future of the supply chain of immunizations at the end of the decade. The expected scenario for 2020 was that supply systems would adapt to global change to be able to take vaccines to the right place, in the right quantity, in the right conditions, and at a good cost (PATH, 2011; ZAFFRAN et al., 2013). The study also mentioned 5 priority areas for achieving this goal: *1.* Vaccine products and packaging, *2.* Immunization

supply system efficiency, *3.* Environmental impact of immunization supply systems, *4.* Immunization information systems, and *5.* Human resources.

When compared to the priority areas of the 2011 document, it is possible to observe that the studies included in this review are in line with the first four areas. Within the first principle are the studies relating to supply chain management (pricing and funding). Within the second principle are studies that address a better regional distribution of warehouses (optimal design of the supply chain infrastructure), storage management, as well as logistics and transport management. Within the third principle are studies that address route optimization for the delivery of vaccines. The fourth principle, which deals with immunization information systems (planning, immunization records, logistics management, etc.), is contemplated by all the optimization models that have the capacity to be integrated into a supply chain management system.

Additionally, the authors of this review participated in a researched project that aimed to improve the vaccine distribution managed by the Brazilian Ministry of Health. Brazil has a unique public health system (SUS) that includes the National Immunization Program (PNI) which is responsible for combating immuno-preventable diseases in the country. The PNI distributes 45 immunobiological types of vaccine and immunoglobulins to a population of approximately 220 million inhabitants, served by more than 38,000 vaccination rooms. Its size reflects in the complexity of the management of this chain, which is increased by the limitation of resources and by the agency's objective of offering free health services to all citizens at any time. Worldwide, it is estimated that vaccine losses in the chain reach 55% (PARMAR et al., 2010). These losses occur due to a variety of reasons such as poor handling during storage and transportation, expiration, lack of demand for the number of units inside the bottle and poor temperature control. Moreover, it is well known that the latter is responsible for a large share of the losses, and it is one of the great problems still faced by the Brazilian government. However, no study in the review has addressed the issue, which is a lack of optimization application in this subject. Therefore, it represents a new research direction for future work in this field of particular interest to the authors.

2.4.8 Biases

As any scientific study, this Rapid Review can presents biases in its execution and analysis, and it is important to knowledge them. First, the short timeline of the rapid review and the authors' subjective evaluation of inclusions/exclusions criteria undoubtedly introduced bias to the review outcomes. The limitation of years of the study is of 10

years. Considering innovation this is a very much expressive period of time. However, this definition may have left out studies relevant to the discussion. In addition, this Rapid Review considers papers written in three different languages (English, Spanish and Portuguese). In a similar way to what was said about the period of time definition, it could be said that those three languages contemplate the major of the studies available. Even more, because it is very well known that English is the language used by major of the manuscripts of global interest. Even though, it could be said that studies published in languages other than those included in this review may have relevant results that have been disregarded. Reviewers may also have missed some relevant articles during the design of the search process due to double-meanings of certain terms. For example, the term "distribution" has several meanings in the context of vaccines where it sometimes refers specifically to the logistics phase of vaccines and other times to the way in which the vaccines were divided for the population. In these cases, to avoid misinterpretation of the terms, the context of the paper was taken into consideration, and the studies were classified according to the definition of the terms presented in this paper. In some stages, the authors had difficulty classifying the studies. For example, the supply chain stage characteristics were not explicit and their categorization was subjective. In these cases, to reduce bias, more than one reviewer participated in the analysis of the studies, and the categorization was performed by consensus.

2.5 Conclusions

This rapid review summarized how 14 optimization methods are scalable to the challenges of the vaccine supply chain, specifically to the four identified components. The 25 studies that met the inclusion criteria were classified according to their objectives, type of vaccine, supply chain stage and type of optimization used. The manuscripts were also analyzed to see if uncertainties were considered and if the problem was addressed as a network problem.

Results showed that most studies (56%) applied optimization methods to improving vaccination strategies. Under different scenarios, those studies seeked to help decision-makers better distribute vaccines to specifics portion of the population. To a lesser extent, (20%) of studies dealt with inventory management and logistics. Given that these are two areas where optimization is commonly used in general supply chains, it was expected a greater proportion of the studies to address these two stages within large-scale vaccine supply chain. Therefore, future research in these areas are encouraged. There is also

comment on the lack of studies that integrate two or more components of the supply chain. Changes and improvements in one stage will impact other stages, therefore, the OR community should consider this as future research directions.

3 CURRENT SCENARIO OF THE PUBLIC INFRASTRUCTURE OF THE VACCINE LOGISTICS CHAIN

"Sooner or later you're going to realize, just as I did, that there's a difference between knowing the path and walking the path."

-- Morpheus

As is well known in science, research does not follow a linear trajectory, and this work was no different. This work emerged from a partnership between GAESI and the Brazilian Ministry of Health (MS). The MS demand for the University was for improvements to be presented to the ministry as a whole. Based on meetings and discussions, MS managers decided to focus on a large, organized and very important area: the National Immunization Program (PNI). Before any proposal for innovation, technology, or management change, it was important that the researchers first understood the reality of the program's operation. In this way, the author started a process mapping of the entire PNI. For this, it was necessary to visit all kinds of places that were part of the PNI chain, from large centers to the interior of the Amazon rainforest. After a year of study and process mapping, the supply chain qualities and opportunities for improvement were identified and presented to the PNI managers. These, in turn, pointed out the areas that they identified as the most relevant and most likely to have public funding for the implementation of the solutions. One of the areas pointed out was what guided this present study. This chapter aims to present all this work carried out during one year. However, the reader will be able to observe that the research approach was wider than the final objective of this doctoral thesis. After all, the problem that would be addressed, or the solution that would be proposed, was not yet known. Even so, the author believes that this is an important chapter of the doctoral thesis and the trajectory of the research. Where it will be possible to understand the complexity of the chain and the importance that the study has for proposing models that would reduce the waste of public money in the country.

3.1 Introduction

Recent innovations in Information Technology (IT) have led to accelerated changes in supply chain management by redefining organizations and their relationship to management. These changes when related to logistics help control operations and consequently reduce logistics costs.

In this context, technological tools and systems are used as data compilers to provide information to decision makers. Although chain operations are commonly well-divided (eg purchase, storage, and distribution), they are interdependent, and their communication is essential for good planning of the areas. However, in the face of so different activities and needs for information, it is common for each area to have different information systems in use in the operation.

In these cases, the concept of interoperability of these information systems, which consists of the ability of a system (computerized or not) to communicate transparently (or as close as possible) to another system (similar or not) is fundamental.

The impact of disaggregated data on logistics costs can be aggravated when it comes to high value-added or perishable products. Minor errors in the logistics of high-value products can result in significant damage to the operator and, in addition, require safety during handling and distribution. Perishable products have limited shelf life and may require agility between manufacturing and use as well as temperature control during all logistics steps that may pass.

Drug distribution chains have the two characteristics mentioned (high added value and perishable). According to the study "Right to medicines" released by the Institute of Socioeconomic Studies - INESC (DAVID; ANDRELINO; BEGHIN, 2016), the Brazilian Ministry of Health (MS) spending on medicines reached, in 2015, R$ 14.8 billion, which represents a 74% increase compared to 2008. This increase is almost double what was observed in the period for the health area as a whole.

Despite high drug expenditures, MS information systems do not allow robust product traceability. Thus, the MS cannot guarantee the position of the load in the various spheres it passes. This lack of information negatively impacts the distribution of inventories in the country. In some cases, resources are directed to purchase immunobiologicals that are in stock in other states, or there is loss of products due to expiration, while they could have been previously directed to some region that demanded them. In 2014, for example, in Minas Gerais state about R$13 million worth of overdue medicines was discarded. In Rio

de Janeiro state, in 2016, 300 tons of expired medicines were discarded, and it is estimated that another 700 tons were discarded between 2014 and 2015 (SATRIANO, 2016a, 2016b; VEJA, 2016).

Ignorance of the situation of these drugs impacts the programming of their purchase, and also their production. This happens because the raw material of some immunobiologicals is scarce and the production institutions have a maximum limit of production capacity. Thus, it can be said that errors in purchasing planning can lead to risks to the population in case, for example, an increased demand for an outbreak of immunopreventable disease. An example of this is the 2017 scenario where vaccine manufacturers, who due to the outbreak of yellow fever, had to reduce the production of triple viral vaccines (against measles, mumps, and rubella) to meet the new demand (FELIX, 2017).

The MS logistics chain involves several areas, some of which are controlled by spreadsheets and have decentralized planning and execution. These problems increase the inefficiency of the processes, the impairment in the distribution of resources and problems in the care and delivery of health services. MS logistics still faces an interoperability problem between the systems used. The more than 600 information systems available today in MS are fragmented, with non-communicating platforms that make it impossible to integrate the supply chain (demand plan, process manager for procurement, storage, distribution and dispensing).

As the goal of the partnership with MS was to bring improvements to the vaccine supply chain as a whole, it was important that we first knew the current reality of the infrastructure. Given this, the decision was to map out all the processes involved in the distribution of medicines by the MS, so it would be possible to have it clear the operation of its logistics chain, and identify the bottlenecks and opportunities to improve its operation. It would also make it possible to highlight the opportunities for innovation in the MS logistics chain.

Since MS currently has many information systems in operation (it is estimated that over 600), they does not intend to develop new technological systems, but to investigate and map the current situation of their operations, in order to analyze what their real needs are, considering everything they already have.

Thus, this chapter brings the description of the process of mapping the processes of the cold chain of the MS, made by the author during the first year of his doctorate (2017). The mapping was performed in 4 Brazilian states: Amazonas, Maranhão, Rio de Janeiro and São Paulo. In addition, meetings with employees of the General Coordination of

the National Immunization Program (CGPNI) in Brasilia were held to better serve the management of the chain.

3.2 Objective

At this stage, the objective was to understand the environment and the characteristics of the processes and infrastructure of immunobiological distribution in Brazil. The expectation was that after better knowing the operation of the chain, it would be possible to make propositions of ideas and/or projects that would contribute to the improvement of the processes, increasing the control of operations and reducing costs in the logistics of PNI.

3.3 Method

The execution of this phase of the project was carried out through technical visits in four Brazilian states suggested by the team of the CGPNI: Rio de Janeiro, Maranhão, Amazonas, and São Paulo. Two meetings were also held with PNI representatives in Brasília/DF (Figure 6).

The visits were made in the instances illustrated in Figure 7. The division of municipal regional and city regional are not adopted in all states and cities.

3.3.1 Technical visits

The technical visits were carried out as described below:

- Brasilia: The first of the visits. This was a meeting with CGPNI representatives from May 11-12, 2017. Its purpose was to understand the basic structure of the entire Program, from the stages of annual calendar planning, inventory data analysis, vaccine control, adverse events, immunobiological losses, etc., information flow among the various instances of the entire PNI, receiving and releasing requests to states, and other various activities performed by CGPNI; A second visit was made on August 8 and 9 in Brasilia to align the fellowship with the CGPNI team and to present the process maps drawn from the information obtained during the visit to Rio de Janeiro state;

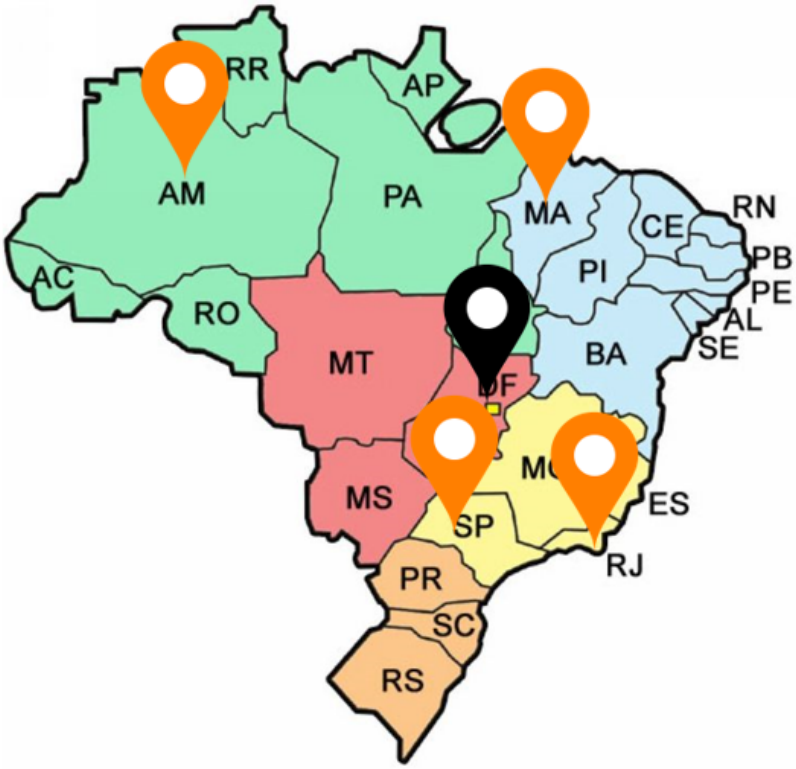


Figure 6: Places of visits.

Source: Author.

- Rio de Janeiro (RJ): From June 19 to 23, 2017. Visits were made to two CENADI warehouses, the state central in Niterói, the São Gonçalo municipal central, the municipal health secretary of Rio de Janeiro, a vaccination room and a CRIE;

- Maranhão (MA): From October 23rd to 27th, 2017. Visits were made to the CRIE and the vaccination rooms in Santa Inês and Santa Inês and Pindaré Mirim, Santa Inês, in the municipality of Pindaré Mirim, in the municipality of São Luís and Santa Inês. São Luís;

- Amazonas (AM): November 20-24, 2017. Visits were made to the state and municipal central in Manaus, central Manacapuru, vaccine room in Iranduba, and vaccine room and CRIE of Manaus;

- São Paulo (SP): From November 27 to December 1, 2017. Visits were made to the Franco da Rocha regional central, São Paulo municipal central, CRIE at the Mario Covas State Hospital in Santo André, São Paulo State Central, and the vaccination room at the UBS of Pinheiros, in São Paulo.

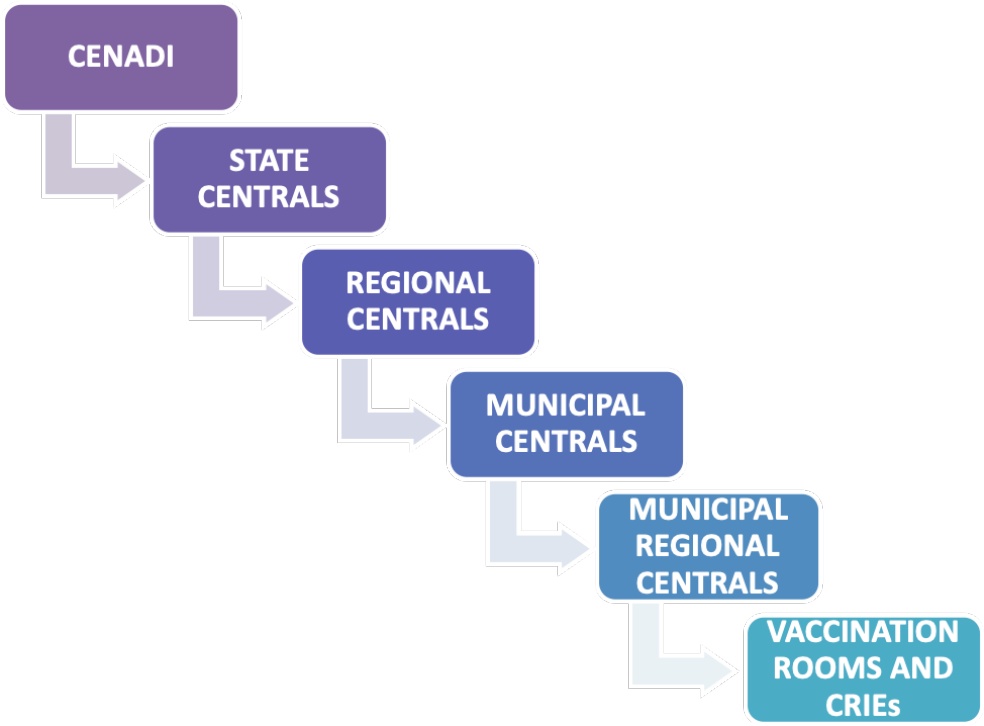


Figure 7: Visited Instances.

Source: Author.

3.3.2 Business modeling

The processes were mapped and elaborated in a flowchart with the aid of Bizagi software using the Business Process Model and Notation (BPMN) methodology.

3.4 Results

This section presents the results obtained through technical visits. Observations were divided into strengths and weaknesses (opportunity for improvement).

3.4.1 Strengths observed

This section presents the strengths observed in the technical visits.

3.4.1.1 Temperature control culture

One of the initial concerns about the chain was the temperature control of immunobiologicals during all movement stages from CENADI to dispensing. Since the temperature

control process is still all manual, its success depends on the professional responsible for sorting, packaging and receiving understanding the importance of temperature control.

During the visits, it was observed that the state and regional centers are attentive to temperature control, as well as the setting of the thermal boxes before filling with immunobiologicals. The most used thermometer is the digital one, which has the ability to measure the internal and external temperature, as well as keeping the record of the maximum and minimum temperatures reached in the indoor environment. This type of thermometer is widely used for temperature control of thermal boxes and household refrigerators. Many states and regions already have a laser thermometer (Figure 8), which facilitates and speeds up the temperature measurement of both products, refrigerants, and boxes.

In addition to temperature control during transport, the temperature control culture of refrigerators was also observed. All refrigerators observed on visits have a manual document on their door where a professional notes the current, minimum and maximum temperature observed since the last measurement. This control is performed even in scientific refrigerators, which are those that have a more accurate temperature control integrated, capable of measuring the current, minimum and maximum internal temperature.

This shows how widespread the cold network is, the importance of keeping immunobiologicals within the proper temperature range. In some cities in the interior of Maranhão, for example, as recurrent situations of power outages, health professionals are organized in shifts on weekends, so that in case of a power outage, they go to the health site to move immunobiologicals to refrigerated coolers. Thus, they can ensure that the immunobiologicals are healthy for being administered.

3.4.1.2 Infrastructure

Although it is a widespread reality and this work has been elaborated based on what was observed in only four Brazilian states, the state infrastructure seems to be sufficient for temperature control. All states central observed have cold chambers and generators. These, besides having a smaller temperature variation than refrigerators, allow the whole separation process to be carried out in a refrigerated environment. Some states such as Maranhão and São Paulo also have their own refrigerated vehicles for distribution to their regional centers (Figure 9).

Manaus city deserves to be mentioned here for presenting an infrastructure with 100% of its refrigerators being scientific, besides presenting a separation environment with

Figure 8: Laser thermometers on the top, digital thermometer on the bottom-left and scientific cooler on the bottom-right.

Source: Author.

adequate temperature for the activity (Figure 9).

3.4.2 Weaknesses observed

This section presents the weaknesses observed in the technical visits.

3.4.2.1 Infrastructure

Immunobiological storage in domestic refrigerators recurs throughout the cold chain. Although scientific refrigerators are more reliable, domestic refrigerators still have the ability to keep immunobiologicals refrigerated at the proper temperature as long as local health professionals are mindful of their performance.

In São Luís/MA municipal central, for example, a large amount of immunobiological is stored, which should serve a population of almost one million inhabitants. Its infrastructure

Figure 9: Refrigerated chamber of AM state, scientific refrigerators of Manaus/AM and refrigerated vans of MA state.

Source: Author.

is all composed of old domestic refrigerators (Figure 10), the separation room is not properly cooled and has no separation bench.

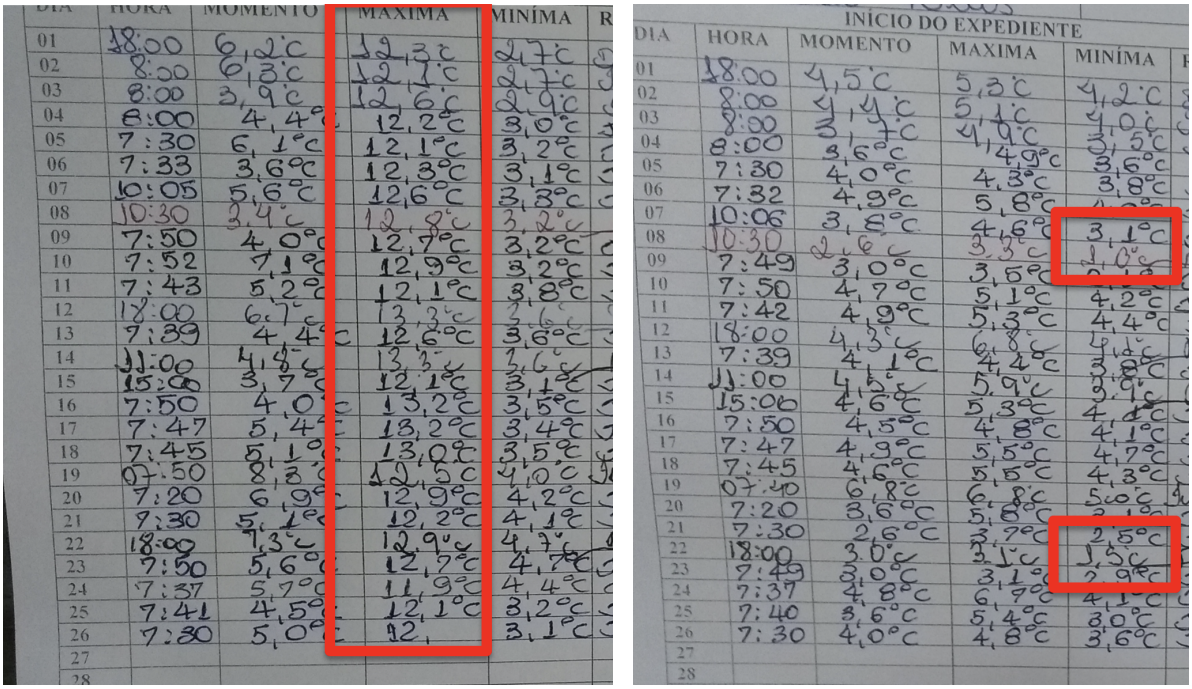
3.4.2.2 Professional training

Associated with the infrastructure problem is the problem of professionals who perform temperature measurements, but do not understand the reason for doing so, or do not know how to proceed in situations where the thermometer points to unexpected temperatures. In some observed cases, the temperature deviation was recurrent, the professional pointed out the refrigerator sheet, but did not take any action regarding this deviation (Figure 11).

Some professionals who are responsible for temperature control of immunobiologicals perform the function without understanding very well the importance of keeping immunobiologicals within the suggested temperature.

Figure 10: Domestic refrigerators of São Luís/MA municipal central.

Source: Author.



(a) Temperature control worksheet highlighting high temperatures (above allowable)

(b) Temperature control worksheet highlighting low temperatures (below allowable)

Figure 11: Refrigerators Temperature Control Sheet.

Source: Author.

3.4.2.3 Syringe model

In addition to the loss of immunobiological due to improper temperature, vial breakage, and technical loss (the loss of dose per vial opening for vaccination of fewer people than

the number of vial doses), there is a very recurrent type of loss in the vaccination rooms. Although immunobiological vials contain 10, 15, 25 or another number of doses, practitioners are often unable to extract the same amount of doses. Some practitioners have argued that it is recurrent that of a 10-dose vial only 6 are actually dispensed.

One of the reasons for this problem is the type of syringe and needle used in vaccination. In some types of syringes, it is common for an amount of liquid in the tip not to be dispensed, such as the syringes in the Figures 12a and 12b. The syringe in Figure 12c has a specific internal part to force the application of fluid that would be lost in previous syringes, however, it is common for health professionals to get confused at the time of fluid collection (for example, In the syringe in Figure 12c some professionals read 1.8ml, which is correct, but others read 0.4ml). The syringe in Figure 12d does not show any loss of liquid because it contains the needle attached directly to the syringe.

(a) Syringe with fluid loss at tip

(b) Syringe with fluid loss at tip

(c) Syringe with no tip loss but may confuse the practitioner at the time of fluid collection

(d) Syringe that does not leak fluid because it contains the attached needle

Figure 12: Syringe Types.

Source: Author.

3.4.2.4 Information systems

The Ministry of Health (MS) has a very large number of information systems in place (see Appendix C for an illustration of all information systems in use) and these have no interoperability. This poses a major challenge for the MS to manage the chain in the face of links that have poor communication. The inconsistency of information from the vaccine rooms, and the difficulty of access by higher levels, leads to imprecise decision making that can hinder chain flow, immunobiological distribution, as well as the entire planning process.

The National Immunization Program Information System (SIPNI) has three modules that seemingly meet the Ministry's data needs. However, in large centers, where demand for vaccines at the stations is very high, SIPNI seems to delay attendance by requiring too much input data. In Rio de Janeiro, for example, where they were experiencing an outbreak of yellow fever, it was observed in a vaccination room that although all of their professionals were committed to entering information on SIPNI vaccines, they were still two months late.

Despite SIPNI failures, non-adherence to SIPNI appears to be even worse as vaccine control data are not captured. Places where they still use the API Web system can only tell how many doses have been applied. However, in metropolitan regions, for example, it is common for citizens to get vaccinated in a different municipality from the one they live in. This may lead to inconsistent data on vaccination coverage, which may generate false information that the entire population of that municipality has been vaccinated.

There are still some cities, such as São Paulo, which have chosen to create their own information systems for vaccination rooms. Although these feed into the Ministry's database, this makes it difficult to standardize data and consolidate databases.

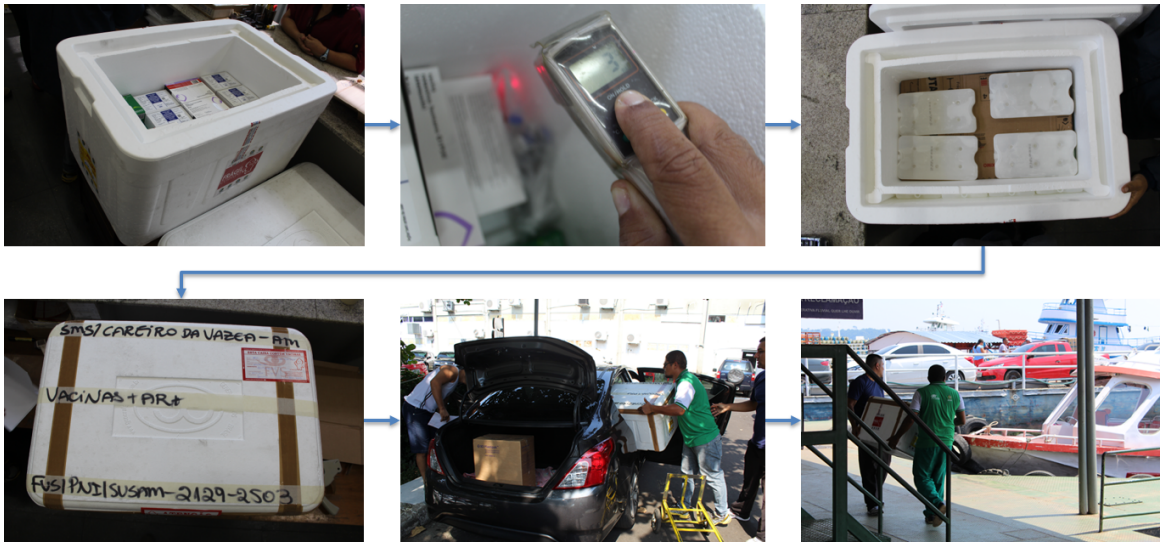
The data and reports generated by the information systems (SIPNI, API Web, etc.) seem to be little used by vaccination room professionals and municipal secretariats to assist in decision making.

3.4.3 Challenges

This section provides information on the challenges of PNI immunobiological supply chain management.

3.4.3.1 Different realities between states

While in some states the distribution is completely managed by road, in Amazonas state, for example, immunobiologicals need to go through the air, road and also river modes to reach several cities. Because it would be too costly for a professional to travel from the country to Manaus to pick up immunobiologicals, they are taken unaccompanied from a health professional from the state central to the city. Figure 13 shows a photographic sequence of the vaccine distribution process between the Amazonas state central to Careiro da Várzea city.



(a) In order: Immunobiologicals in the thermal box; temperature measurement with laser thermometer; preparation for closing the thermal box with cardboard and soda; sealed thermal box; box being placed in the vehicle that will transport it to the port of Manaus; box being taken to the boat that will take it to the city.

(b) Continuation of previous. In order: Thermal box being allocated to the boat for transportation; thermal box in the boat; the gateway to the city of Careiro da Várzea; thermal box seal being removed; thermometer positioned for temperature verification with an analog thermometer; closed box for digital thermometer temperature verification after analog thermometer failure.

Figure 13: Vaccine distribution process between the state central of Amazonas and the city of Careiro da Várzea.

Source: Author.

3.4.3.2 Electricity supply problems

In all states visited there was a complaint of failures in the supply of electricity, which increases the challenge of ensuring the integrity of immunobiologicals at the appropriate temperature. This reality means that the integrity of immunobiologicals in many cities

depends on the dedication of health professionals even outside office hours, by being alert and willing to go to the storage place to move immunobiologicals in the event of a power outage. Especially in places where immunobiologicals are stored in domestic refrigerators and there is no generator.

3.5 Conclusions

The National Immunization Program deal with the challenge of managing a highly complex chain by ensuring that the entire country is immune to preventable diseases. This complexity can be expected due to the extension of the Brazilian territory and the different realities of states and municipalities. One of the major challenges of the project at stake in proposing a chain efficiency improvement solution is that it is currently not possible to generalize the type of infrastructure available throughout the cold chain. There are several types of coolers and thermometers (Figure 14), refrigerators and cold cameras (Figure 15), as well as different realities related to access to computers and the internet.

(a) Digital thermometers (b) Analog thermometer (c) Laser thermometer (d) Datalog

Figure 14: Different types of thermometers and temperature control equipment in use in the chain.

Source: Author.

The turnover of health professionals working with immunobiologicals allows untrained people to handle products without understanding their particularities. This turnover of professionals makes it difficult for the pieces of training that are offered to reach their totality.

(a) Domestic refrigerator

(b) Solar refrigerator

(c) Single door scientific refrigerator

(d) Multiple door scientific refrigerator

(e) Freezer-type refrigerator

Figure 15: Different types of refrigerators in use in the chain.

Source: Author.

The diversity of information systems and their inability to interoperate can be pointed as the main factors that make the chain management difficult for the MS. The non-standardization of the system operating in the vaccine rooms hinders data entry that is paramount to demand forecast analysis, inventory management, vaccine coverage, etc.

Support for information systems does not seem to be very effective either, as many vaccine rooms that have a computer with internet access still make use of SIPNI Desktop instead of SIPNI Web.

The non-standardization of information systems in other instances also makes it impossible to trace immunobiologicals through the chain, which makes it difficult to operate in times of crisis, for example, when some batch needs to be removed from circulation.

4 MACHINE LEARNING ALGORITHM FOR VACCINE DEMAND FORECASTING

"What passed, passed, but what passed glowing, will shine forever."

-- Johann Goethe

4.1 Introduction

One of the problems observed during the Ministry of Health's process mapping was that there are many information systems involved in the management of its immunobiologicals supply chain. This characteristic affects the quality of planning in several ways. With many systems in operation, a lot of important information is lost, or mismatched. Even if good monitoring of the operations is done, it is difficult to compile all this data.

One of the steps of great importance for the fluidity of the chain is the forecast of demand. The forecast data is used for planning an acquisition, storage, distribution, vaccination campaigns, vaccine administration, vaccination coverage, among others. Failure in the demand forecasting process can lead to chain failures, which can have serious public health consequences, such as the lack of a vaccine during an outbreak. Laboratories producing immunobiologicals have limited production, and their operation is planned in advance, which may exceed one year. With this, the purchasing agency must organize itself to carry out the purchase of immunobiologicals with great advance.

Currently, the demand forecasting stage is performed by trained technicians, using various public health indicators, population growth, public data, demographic data, among others. However, it is important to note that all this analysis is manual. This means that in addition to being dependent on an employee, it is subject to parsing errors.

For this stage of the work, a machine learning model was developed, which uses public historical data (applied doses, cases of diseases and population) to forecast the demand for immunobiologicals for a determined period. These selected data are the same that the Ministry of Health technicians use in their analyses. However, biases can be replicated due to the fact that these data are reported manually by employees who work in the vaccination room. This means that in addition to data entry may have errors, it may

happen late, or not at all.

With the advancement of computer technology and capacity, machine learning techniques have been increasingly used to solve classification and regression problems. Thus, the initial hypothesis of this study was that machine learning techniques could bring good results in predicting the demand for immunobiologicals through the use of public data.

4.1.1 Objective

The objective of this stage was to create a tool for forecasting the demand for vaccines for Brazilian states for the period of 12 months, fed with historical data of public access.

4.2 Literature review

Understanding the concepts of inventory management and demand forecasting was of great importance for carrying out this study, as well as the machine learning methods used. This section provides a brief review of these concepts.

4.2.1 Demand forecasting

The demand forecast presents the manager with information that allows for estimating an approximate future demand. This can be qualitative or quantitative. Qualitative forecasting methods make use of information obtained through analysis of scenarios, judgments, research or comparative techniques to produce quantitative forecasting data. These methods are unscientific in nature, and therefore are difficult to standardize (BALLOU, 2006). Quantitative methods make use of historical data, trend and seasonal variations to calculate a forecast through a mathematical approach.

Forecasting methods should be adopted according to the available data and the forecast time horizon (short, medium and long term). The most common short-term demand forecasting methods, as they are simple to apply and commonly present a good approximation of the forecast with the real scenario, are: moving average, weighted moving average and exponential weighting (smoothing) (BALLOU, 2006).

The moving average is a forecasting method applicable when demand is stable, with little variation or seasonality. The weighted moving average gives greater weight to the most recent points. The exponential smoothing is the same as the previous month's forecast plus a part of the error of the same (BALLOU, 2006). However, despite the wide

possibility of application and its ease of understanding, these three methods do not have their use recommended for forecasting products that suffer seasonal or trend effects in their demand. Seasonality can be considered as the disturbance of linearity in the sales data of a product and that occurs with a certain frequency. The trend is the phenomenon close to the linearity of increase or decrease in sales of a product (CHOPRA; MEINDL; GONÇALVES, 2011).

In face of the existence of trend, the Holt model, that is an exponential smoothing method corrected by the trend, is recommended. But only when demand does not present seasonality. Its application consists of performing a linear regression of the demand in the studied period.

For products with more complex demand, that is, those with a trend and seasonality, more complete methods should be applied. Chopra and Meindl (2011) present the application of the Winter method that is appropriate for these cases. Before its application, it is necessary to calculate initial level estimates, trend, and seasonality. The level and trend estimate is initiated by analyzing demand to identify the period in which seasonality occurs. With this, it is possible to perform the calculation of the non-seasonal demand, so that in this way the linear regression can be performed (without this the next analyzes would be incorrect due to the non-linearity of the data) through equations defined by Chopra, Meindl and Gonçalves (2011). With the new demand, linear regression is performed with the pattern, and the non-seasonal demand is then calculated for all periods (CHOPRA; MEINDL; GONÇALVES, 2011).

The seasonal factor for a period is equal to the ratio between real and non-seasonal demand. Considering the period in which the seasonality is repeated, it is possible to identify which periods the seasonal factor should be equal, and this is calculated through the average of data between similar periods. For example, for a 6-month periodicity in 12-month data, the months of January and July are considered to be similar in seasonality behavior, therefore, they will have an equal seasonality factor, which should be calculated using the average between two factors (CHOPRA; MEINDL; GONÇALVES, 2011).

With the values of L_0, T_0 and S for the entire period, the demand forecast is then calculated according to Equations 4.1 and 4.2.

$$F_{(t+1)} = (L_1 + T_1)S_{(t+1)} \tag{4.1}$$

$$F_{(t+1)} = (L_1 + lT_1)S_{(t+1)} \tag{4.2}$$

Therefore, after calculating the demand for period t, the estimates of L, T and S for the

same are revised, respectively according to Equations 4.3, 4.4, and 4.5.

$$L_{(t+1)} = \alpha \frac{D_{(t+1)}}{S_{(t+1)}} + (1-\alpha)(L_t + T_t) \tag{4.3}$$

$$T_{(t+1)} = \beta(L_{(t+1)} - L_t) + (1+\beta)T_t \tag{4.4}$$

$$S_{(t+p+1)} = \gamma \frac{D_{(t+1)}}{L_{(t+1)}} + (1-\gamma)S_{(t+1)} \tag{4.5}$$

Where α, β and γ represent, respectively, the smoothing constants in the level, trend and seasonality (CHOPRA; MEINDL; GONÇALVES, 2011).

An important feature of each of these models presented is that it requires that the person who is forecasting demand, and consequently, applying the models, must identify whether the historical data present a trend or seasonality. Each model has its particularities and requirements regarding its application. Thus, it is possible that the application of a complex and robust model, in historical data that does not present these characteristics, generate results with low confidence. Therefore, it is important that the professional is prepared to execute these predictions. Still, the demand curve can present totally different characteristics when dealing with a specific vaccine or state. Thus, it is important that the prediction activities are carried out in a branched way.

The models presented were considered to be used in this study, but in the face of so many technologies emerging with the fourth industrial revolution, a way to automate and optimize the application of predictive models was sought.

As mentioned earlier, with the advancement of technology computers have become capable of processing more and more data. Artificial intelligence has started to allow us to use algorithms in the analysis, interpretation and decision making in the face of complex problems, which only with the human interpretation would be impossible to obtain insights. In this work, a demand forecasting algorithm using artificial intelligence (machine learning) was developed in order to reduce the need for human interpretation of historical vaccine demand data. And in this way, allow greater automation of demand forecasting activities. Thus, the idea is that with its use human errors can be reduced, and also that it is possible to better adapt to the demand curves of each product and each state.

Machine knowledge (ML) is an example of a technology that is not new, and its application in regression is widespread, even more so in recent decades. The study published by Lopes et al. (2019) shows that from 2000 to 2018 there was a growth of more than 2300% in the number of scientific publications related to ML. In section 4.2.5 a better

description of the ML characteristics is presented.

4.2.2 Inventory management

Stock is defined by Ballou (2006) as the accumulation of products at any stage or point in the production and transportation channels. This accumulation of products may be part of the company's strategy, but when mismanaged it can be considered an activity that, contrary to increasing profits or improving the flow of the operation, can harm the company's results.

The appearance of stocks can have several reasons and/or objectives. The greater the stocks between phases of a process, it is expected that the more independent these become, resulting in fewer chances of interruption due to lack of product (CORRÊA; GIANESI; CAON, 2001). In productive operations environments, inventories can be divided into raw material, semi-finished material, and finished product.

Stocks of raw materials serve to regulate supplier supply rates or demand and may arise due to the forms of delivery by the supplier (batches smaller than the need for the production line, low frequency of delivery, delays or low reliability) or changes in production line demand. Stocks of semi-finished material appear to meet the different demands between two production processes. And inventories of finished products arise so that the company can face variations in the rates of the production process and demand, or unforeseen events and uncertainties, such as machine stops (CORRÊA; GIANESI; CAON, 2001). Table 3 lists the main reasons for having and not having stocks.

In relation to inventories generated with the objective of reducing costs, even though inventories may mean capital in the form of a product, they can indirectly bring benefits in reducing operating costs. Purchases in larger lots allow for better bargaining in negotiation and reduction of transport costs, and when in advance can guarantee security in relation to market and production chain instabilities. In relation to inventories in order to increase the level of service, inventories can allow demand and its variations to be met without interrupting supply, keeping customer service rates high. In this way, it can be said that when mismanaged, inventories can have major negative financial impacts on the company (BALLOU, 2006).

Inventory management is a challenging activity that requires adaptation to the product and market to which it belongs, and its identification is the first step to be taken before choosing an inventory control method. The demand for air conditioning products is

Table 3: Reasons to have stock or not

Reasons to have stock	**Reasons for not having stock**
• Lack of coordination; • Reduction of transport costs; • Speculation; • Response to changes; • Availability in the distribution channel; • Product availability.	• Cost; • Impact on product quality; • Risks of obsolescence and deterioration of products; • Occupation of physical space.

Source: Author.

expected to be different from that of canned soups, for example. Ballou (2004) classifies the types of demand as seasonal (eg swimming pools), terminal (eg aircraft parts), perpetual (eg food) and irregular (eg construction equipment).

It is important to note that although inventory management brings benefits to the supply chain, there are factors that directly influence stocks, but which must be treated separately. For example, if a supplier is unreliable, delays supply, or fails to deliver, the stock action would be to keep it high, however, a possibility to get around these problems could be the approval of new suppliers. Another very recurrent example is a long time to set up machines when exchanging products, which can directly affect the stock (CORRÊA, 2014).

4.2.2.1 Pushed stock

The philosophy of stock pushing is appropriate when production or purchases exceed the need or are the determining areas regarding the quantity of replenishment of stocks. One of the most important decisions when it comes to the push approach is the decision on allocation of stocks (location and quantity), surplus or not, economically (BALLOU, 2006).

4.2.2.2 Pulled stock

The pulled inventory control shows reduced inventory levels in the warehouses due to meeting demand and cost reduction actions (BALLOU, 2006). Table 4 shows the different management methods for established stocks.

Table 4: Pull inventory control methods.

Complexity	*Inventory control methods*	*Characteristics*
Basics	Single order quantity	Used to scale inventory or order for a single demand
	Number of repeated orders	Determines the quantity and frequency of replenishment of stock in the face of constant demand. The replacement can be instantaneous or with delivery time.
Advanced	Order point with uncertain demand	It considers demand perpetually acting to decrease inventories, and calculates a stock replacement point that guarantees the availability of supplies until the next replacement.
	Order point with known out-of-stock costs	Calculates the balance between service and costs. Scales economic lot and resupply point.
	Order point with uncertain demand and delivery time	Increased realism due to the dimension of the uncertainty of product availability during the delivery period.
	Periodic review with uncertain demand	It reviews the inventory levels of various items in order to obtain gains in the acquisition, transportation, and production

Continued on next page

Table 4 – *Continued from previous page*

Complexity	*Inventory control methods*	*Characteristics*
	Joint order	It stops considering items in isolation and proposes a joint order of several items. Creates an inventory review deadline for all items ordered together.
Practical	Min-Max System	Suitable for uncertain demand. Maximum stock is equal to safety stock plus demand during the delivery time and the economical purchased lot.
	Demand stock	A type of periodic review system. It makes use of scaling the demand rate of the item in a specific period during the interval between revisions.
	Control of multiple items and multiple locations	Integrated inventory approach considering economic concerns, applicable when there are several factories, products, and stock points.
	Multi-link control	Applied when stock in the channel is an important factor

Source: (BALLOU, 2004)

4.2.3 Service level

Service level can be considered as the quality in which a service is provided or a product offered to the customer, from the arrival of the order until delivery to the final customer. The control of the service level serves so that companies can measure their performance and quality of operation. In general, small companies adopt the 100% policy as a service level, which considers that every order must be fulfilled on time. However, when it comes to large companies with broader distribution networks, it is practically impossible for this policy to be implemented. Prioritizing delivery times, order fulfillment or keeping costs

down are service-level decisions that impact on-chain and inventory management.

Operating systems that are not prepared to react instantly to customers' requests make use of inventories to provide a level of product availability to satisfy customer requests.

4.2.4 Customer service

Price, quality, and service are items used by customers to assess a supplier's service. In the case of this work, customers are the entire population of a country, and the consequence of bad customer service can be an epidemic. Thus, understanding customer service is indispensable. From this view, it can be considered that determining the level of service that is expected to be delivered to the customer is essential for the elaboration of the Ministry's strategies as a whole, and with stocks, it is no different. According to Ballou (2006), customer service elements can be classified as:

- **Pre-transition elements:** covers the organization's structure, technical services, system flexibility and commitment to the company's procedures and delivery to the customer;
- **Transition elements:** Covers the management of stock levels, elements of the order cycle, system reliability, product replacement, processing time, etc.;
- **Post transition elements:** Covers activities of installation, warranty, repair, packaging, temporary replacement of damaged products, product tracking, etc.

It is common for the logistics professional to consider that monitoring the level of customer satisfaction is the responsibility of the sales or marketing teams. In the case of the Ministry of Health, this means ensuring that the population believes in vaccination strategies, and also monitoring the effects of a vaccination campaign. This said, it is important that the Ministry of Health as a whole is aware of the impact of customer service.

4.2.5 Machine Learning

In 1959, Arthur Samuel defined Machine Learning (ML) as the ability of computers to learn something without being explicitly programmed for it (SAMUEL, 1959). Currently, with the advancement of technology and the capacity of computers, the application of ML has been used to solve increasingly complex problems.

Simply put, machine learning consists of an algorithm which is fed with a part of the existing data (usually 80% of the data). The algorithm "learns" the characteristics of this data. And then this algorithm is tested with the rest of the data (the remaining 20% of the data). In this way, one can measure how accurate the model was.

Machine learning algorithms can be subdivided into three categories:

- **Supervised learning:** When the computer is powered by a piece of data that serves as a guide. The algorithm then uses this data as a guide for future classifications;
- **Unsupervised learning:** In this case, the computer does not receive a reference, and must learn by itself to differentiate data;
- **Reinforcement learning:** When the computer must learn something in a dynamic environment. Examples of this are models who must learn a game while playing with an opponent. Or even an autonomous car model. In these cases, the models receive feedback (awards and incentives) to improve the model.

Another characteristic by which an ML model can be classified is the task that the model is expected to perform. For example:

- **Classification:** Typically supervised, this model aims to classify data between two or more groups. An example of this could be the classification of an email as spam or safe;
- **Regression:** Also supervised, but has continuous outputs instead of discrete ones;
- **Clustering:** Unlike classification, this model, normally unsupervised, aims to classify data when groups are not known.

In the case of the current study, the problem is classified as a time series regression (demand forecast based on a historical series) of supervised learning. Table 5 provides details of the two optimization techniques used in the study.

Table 5: Gradient Boosting and Random Forest importance and main features

Algorithm	*Main features*	*Importance of predictors*
Gradient Boosting	It aims to combine predictions from a set of classifiers with an error rate only slightly lower than that of a random classification (decision trees with few divisions) to build a committee, responsible for the final prediction.	Tabulation and sum of the relative influence of each predictor in each tree that makes up the final model (empirical improvement resulting from the use of this predictor in making a partition of the tree). Calculation of the average per predictor for all iterations, to get an overview of your contribution to the final model.
Random Forest	It aims to combine predictions from a set of complex classifiers (decision trees with many divisions), applied to bootstrap samples of the training set. Differential: random selection of predictors to be used in order to reduce the correlation between the trees that will be aggregated to produce the final prediction.	In each tree, the precision of the prediction corresponding to the observations that did not compose the bootstrap sample is calculated. This same procedure is performed after exchanging each of the predictors. The difference between these two precision measures is calculated and, subsequently, an average of this difference is computed and normalized, for each predictor.

Source: (SANTOS, 2018).

Both models are widely used for time series regression. And yet, both have numerous programming libraries (in Python) for application. The objective of this work is to offer to technicians responsible for the management of the vaccine chain a robust, intelligent technology, but mainly of easy access and understanding. The intention is that technicians who are not experts in programming or artificial intelligence can apply the model as new data become available. Using complex machine learning models could cause technology adoption to be resisted.

4.3 Method

This section describes the method used to forecast vaccine demand as well as the extraction of public data used in the models.

4.3.1 Data acquisition and cleaning

The Informatics Department of the Unified Health System (DATASUS) was created in 1991 to create information technologies for SUS. Since then, more than 200 SUS support systems have been created (Ministério da Saúde, 2020b). Among them is Tabnet, created to integrate information from several health indicators, such as epidemiological data, morbidity, demographic and socioeconomic data, among others (Ministério da Saúde, 2020a). That means, it is the system that compiles all the data used in this work.

Among the available data in Tabnet, one type were included in this study: the number of doses applied. Its descriptions are presented below. It is important to note that all of these data are publicly accessible.

4.3.2 Doses applied

Within the Health Care section in Tabnet platform there are public access data on Immunizations, fed since 1994. And here the applied dose data were considered. The number of applied doses available covers each city in the country, with numbers compiled monthly, by immunobiological product administered by the National Immunization Program (PNI). The extracted data were compiled by the state, since the objective was to forecast the monthly demand of each Brazilian state. In order to assist in the development of the tool, data were also extracted aggregated for the whole country. Figure 16 presents a photo of the screen of the Tabnet data extraction web page (it was automatically translated from Portuguese to English). The platform offers different forms of data extraction, allowing the selection of data compiled by region, states, health macro-regions, different immunologicals, etc.

The extraction selection used (filters) in this study was as follows:

- **Line:** Month/Year;
- **Column:** Federation unity (state);
- **Measures:** Doses applied;
- **Available periods:** All years available;
- **Available selections:** Each immunobiological at a time.

Figure 16: Screenshot of Tabnet data extraction web page automatically translated from Portuguese.

Source: Author.

The applied dose data were the limit of the study's historical line. As only 162 months of data were available in the public MS database, this was the limiting factor. The data included in the study were from January 2004 to December 2017 (although data from 2018 to 2021 are also available on the platform, until the date of elaboration of this model, they could have been changed due to possible delays in the inclusion of information in the databases).

In order to allow the construction of the models, it was decided to proceed with data from only one vaccine. The model built can be applied to all other vaccines. However, it will be necessary to assess whether the machine learning model provides good results for the demand curves of each of the immunobiologicals. Another point that prevented the application of the model for all vaccines still in this study is that some vaccines have a very recent registration of doses applied. Therefore, as BCG is a vaccine that has the greatest historical data, it was the vaccine of choice.

4.4 Algorithm developed

The developed algorithm was written in Python. The codes are available in Appendix D.

As it is a supervised model, the historical series data was divided between training data and test data. The model adopts a division of 130 months for training and 32 for tests, which is close to an 80/20 ratio.

In order to control the quality of the model's predictions, it also measures the Root Mean Square Error (RMSE) of the predictions. This is a metric widely used to evaluate regression models, and it is also easy to understand. For example, if the order quantity was 100, but the forecast was 99, that -1 is the model error. The RMSE calculation is presented in the Equation 4.6.

$$RMSE = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(x_i)^2} \tag{4.6}$$

To normalize the number of doses applied, the difference between the number of doses applied for the current month and the previous month (p_1-p_0) was calculated. These were the data used by the ML models to predict applied doses.

4.5 Results

This session presents the results generated by developed model. The Appendix E brings graphs that were generated by applying the model to the data compiled from Brazil and also from one state (São Paulo), for comparison purposes. For each model, and each scenario, two graphs were generated, one of the actual and predicted data in the training, and the other of the actual and predicted data in the test.

4.5.1 Scenario: Entire country

This section presents the results of applying the model considering historical data for Brazil as a whole. Table 6 shows the Root Mean Square Error of the model applied In-train, both for the Gradient Boosting and Random Forest Regressor models. The errors for the same models are also shown in the test data. The third data, presented in the last row of the table, is for a model that uses the prediction of both models. The results can be interpreted as follows, for the last model the Root Mean Square Error is 52,991, compared to a number of applied dose units that varied from 670,433 to 1,838,603 units. This error represents a variation of 2.9% to 7.8%.

The data from the third model (which considers the two machine learning methods) is presented non-normalized in Appendix E.3. That is, its scale is a real dose number.

Table 6: Root-mean-square deviation for the model applied to Brazil data

Sample	*Model*	*RMSE*	*Percentage*
In-train	Gradient Boosting	55,927.81	3.0-8.3%
	Random Forest Regressor	67,620.09	3.7-10.1%
In-test	Gradient Boosting	56,324.13	3.1-8.4%
	Random Forest Regressor	60,806.08	3.3-9.1%
	Gradient Boosting and Random Fores Regressor	**52,991.40**	**2.9-7.8%**

Source: Author.

4.5.2 Scenario: São Paulo state

This section presents the application of the machine learning model in the historical data of São Paulo, for comparison purposes

Table 7 shows the Root Mean Square Error of the model applied In-train (that is, in the training data), both for the Gradient Boosting and Random Forest Regressor models. The errors for the same models are also shown in the test data. The third data, presented in the last row of the table, is for a model that uses the prediction of both models. The results can be interpreted as follows, for the last model the Root Mean Square Error is 12,724, compared to a number of applied dose units that varied from 106,807 to 436,477 units.

Table 7: Root-mean-square deviation for the model applied to São Paulo state data

Sample	*Model*	*RMSE*	*Percentage*
In-train	Gradient Boosting	12877.41	3.0-12.1%
	Random Forest Regressor	17202.57	4.0-16.1%
In-test	Gradient Boosting	13604.45	3.1-12.7%
	Random Forest Regressor	13660.23	3.1-12.8%
	Gradient Boosting and Random Forest Regressor	**12724.44**	2.9-11.9%

Source: Author.

4.6 Conclusions

It is possible to observe that the model errs by 2.9-7.8% vaccines for the national model, and 2.9-12.9% in the model for a state. When compared with information that vaccine losses occur in the order of 50%, this result is very much positive.

It is important to note that the model aims to get as close as possible to reality, and despite its error being approximately +50k doses of vaccines per year, in some periods the model presented results below demand. This means that although in the end the model sent more vaccines than necessary, there could be a vaccine shortage at some point. This is because the demand forecast numbers here are not necessarily equal to the number of vaccines shipped to each state. To make these decisions, chain managers must make a decision regarding safety stock. That is, it is necessary to decide, for example, an extra percentage of vaccines to be sent each month. This will decrease the risk of a vaccine shortage, but consequently increase the number of doses sent in excess. However, despite this, this can be a very assertive decision because of the costs that can arise due to lack of doses. This is a strategic decision to make, and it should be based on dose cost, inventory

cost, and vaccine shortage cost.

The model presented here was built based on public data. This data is composed of information that is manually typed in the vaccine rooms. This data is subject to human error. Also, it is very important to emphasize that in this study the demand was considered equal to the number of doses applied, but it is known that this is not true in practice. The demand may be less or greater than the number of doses applied in each state. A number of doses applied considered as demand can ignore the possibility that this state only applied this amount because of available stocks. Even if in fact, the demand could be much higher. Given this, if it were possible to use more reliable data (if they actually exist and are not publicly available), the model's result would be even more reliable.

This work presented here has the potential to have a great impact on Brazilian public health, and also on public spending. However, the ideal would be that the data holders (in this case the Brazilian Ministry of Health) could reassess the study with their internal data. Yet this work has the ability to scale to unimaginable proportions. For example, the machine model could start to consider not only historical data on doses applied, but historical data on disease, vaccination coverage, etc. In view of this, the next section presents the directions that can be taken for the continuity of the study.

4.7 Work to be continued

As previously mentioned, the model presented here has great potential to be optimized and increased.

A first step to improve the model will be a better understanding of the models' quality indicators. The RMSE is a widely used indicator, but others can be tested. And yet, it is known that one of the most recurring problems in Machine Learning is overfitting, that is, when the model adapts so much to a portion of the data that it is difficult to predict new data.

A second step will be the testing of other public data obtained, such as historical population growth and cases of the illness the vaccine is trying to avoid. The objective here is to understand whether the use of this data helps or not in improving the models. The hypothesis here is that knowing how good the vaccine campaign was in the state (vaccination coverage), or how much the population of that state has increased (population growth), it would be possible to better predict the demand for the vaccine will be. That is, a state in which the vaccination campaign was not well conducted, or which grew a lot

in population, may present a more considerable increase in demand than another state that presented less growth and good vaccination coverage. Despite the idea that adding more data can improve the model, it is not necessarily true. The addition of new data can also result in the model overfitting. The overfitting problem happens when a model is so well adapted to the training data that it expects the test data to behave in exactly the same way. So it is to be expected that a machine learning model can make mistakes, but this error must be monitored very well.

Data from the years 2018 to 2021 should be included in the historical data series used feed the model, as soon as they are trustful to be used.

5 OPTIMIZATION MODEL FOR VACCINE ALLOCATION BETWEEN BRAZILIAN STATES

"How wonderful it is that no one has to wait a single moment to improve the world."

-- Anne Frank

A demand forecasting model was presented in Chapter 4. The model aims to help decision-makers in planning the acquisition of immunobiologicals, vaccination calendar, vaccination campaign, distribution to states, among other various activities involved in logistics chain management. Considering that the forecasting activity obtained good results (that is, approximate forecasts of the real operation), good management of the distribution of the products will still be necessary.

In the Brazilian scenario (previously presented in Chapter 3), the Ministry of Health is responsible for the distribution of immunobiologicals to the states. Although the managers of the states send a monthly estimate of the need for the following month (order), it is the managers of the federal agency who decide the quantity sent. The result of this practice is well known in supply chain management, the so-called bullwhip effect. When a state manager notices that the amount of product received was less than what was requested, he tries to adapt the next order. That is, in the next request, the manager will consider a value greater than what he really needs in order to try to force the national manager to meet his demand. The result of the bullwhip effect is that there is a large divergence between the numbers at the ends of the chain (in the case of this work, the national manager and vaccination rooms).

Despite efforts to maintain a good distribution of immunobiologicals, it is common for the country's dynamic characteristics to hamper this activity. It is not so uncommon the scenario in which in some regions of the country there is a lack of an immunobiological product while another region has an surplus (with the possibility of loss due to maturity).

As presented in Chapter 2, several optimization approaches have been applied to improve the vaccine supply chain. However, as the problem here dealt with has many particularities, the systematic review did not bring any model that has been applied to a

problem similar it or with the same objective.

In order to bring improvements to the supply chain management, in this stage of the study it was developed a stochastic optimization model that helps to improve the distribution of immunobiologicals among Brazilian states. One of the important characteristics of the model is that it considers the scenario where states can exchange vaccines with each other. This is a real possibility in the current operation of the chain, but its practice is little used. Although this information was obtained through process mapping carried out in 2017, there are no published data that can confirm the use or not of this practice, or even how little it is used. With this model, it is possible to evaluate whether this practice brings benefits to the chain. The output data of this model should be the information on the number of immunobiologicals that should be sent to each of the 27 Brazilian states, in each month of a period of time, considering 3 possible scenarios of uncertain demand (low, medium and high demand). The model should also decide whether vaccines should be exchanged between states.

5.1 Optimization model for allocation of vaccines between states

In this section, it is first detailed the problem statement. Next, it is introduced the modeling assumptions and provide a mathematical formulation. Due to the probabilistic constraints, it is also present an deterministic equivalent form of the model (this is so that possible changes in the model can be tested in an ideal scenario before a stochastic scenario).

5.1.1 Problem statement

Consider that a federal agency must distribute x immunobiologicals monthly ($k \in K$) to the country. In this way, each of the $i \in I$ states of a country will receive a x_{ik} amount of immunologicals in each k month. If any state $j \in I$ have a need for immunobiologicals and a state i has the capacity to deliver, y_{ijk} immunobiologicals can be exchanged between states. The transport to the states is individual, that is, the products sent to each state go in separate loads (one flight for each state, but the state where the federal warehouse is located). The purpose of this model is:

- To decide the number of immunobiologicals that should be sent to each state;

Figure 17: Illustration of the transport of immunobiologicals between the federal warehouse and the state, and between states.
Source: Author

- To minimize the operating cost of the entire chain.

For this, it is expected:

- To reduce the number of immunobiologicals sent to the states;
- To meet the demand;
- To reduce surplus;
- To avoid lack of product.

The current scenario of the chain's operation has a lot of loss of immunobiologicals due to poor handling during transport, due to failure in the temperature control, and also dismissals with excess or lack of stocks. The hypothesis considered here is that, in case of need, a state A with excess stock could supply the products to state B with a lack of that same product, without the federal agency having to insert new products in the chain (Figure 17). The hypothesis considers that this exchange of vaccines between states can reduce transport costs, inventory costs and costs of unmet demand.

5.1.2 Model assumptions

Before presenting the model description it is important to understand the model's assumptions and justifications.

1. **States can exchange vaccines as long as they send at least the minimum:** The exchange of immunobiologicals involves costs. Thus, it would be very costly for the system that the vaccine transport effort be activated for a few units;
2. **The cost of transportation (in R$/km) between the states and the federal warehouse must be less than the cost of transportation between states:** The federative unit already has transportation infrastructure for sending immunobiologicals to States. And yet, it is the body responsible for the distribution of them. Therefore, if the states are going to exchange vaccines, they should trigger a less used infrastructure, consequently more expensive. The difference is defined in the model by α.;
3. **Demand:** The deterministic optimization model considers demand equal to the demand forecast provided by the machine learning model presented in Chapter 4. The stochastic optimization model considers demand to be uncertain. Thus, three possible scenarios are considered: one of low, medium and high demand (these are better described in the following sections);

The purpose of the model is to minimize system costs. The costs considered were as follows:

1. **Acquisition cost:** unit cost of each vaccine unit times the number of new vaccines arriving at the federal warehouse;
2. **Unmet demand cost:** cost incurred for each unmet demand unit;
3. **State holding cost:** cost incurred for each extra unit of product stored by the states;
4. **Transportation cost:** cost of transportation between the federal warehouse and the states;
5. **Transshipment cost:** cost of transportation between states;

6. **Federal holding cost:** cost incurred for each unit of product stored in the federal warehouse.

Each of the costs listed above is not public knowledge, being exclusively known by the Ministry of Health. However, this does not prevent an optimization model from being built. So that the model presented here could be built, an estimate of these values was performed.

Vaccine costs were considered as the internationally known average cost value. Transport costs were considered to be proportional to the distance between states. And the costs of surplus and unmet demand were defined in such a way that the cost of a not-administered vaccine was more expensive than a vaccine in stock (considering that the public health costs with a person who has the disease are significantly higher than the cost of the vaccine dose).

The three uncertain demand scenarios (low, medium and high) are presented below.

***i*) Low and *ii.*) High demand:** In order to define the low and high demand values of immunobiologicals, an analysis of historical data was performed. First, as vaccines and immunopreventable diseases were being dealt, it can be said that the demand is seasonal. Thus, the definition of the values was carried out for months separately (that is, to define the demand for January, it was analyzed only the historical demand for the months of January). The values considered as the low A and high amount was picked using randomness within the minimum ($Min \leq Demand\ minimum \leq A$) and maximum ($B \leq Demand\ maximum \leq Max$) intervals. That means, that the low demand will be a number, picked randomly in the interval between the lowest observation and A. And the high demand, in the interval between B and the highest demand observed in the period. The intervals were defined as illustrated in Figure 18, using the Equations 5.1 and 5.2.

$$A = Min + \frac{Max - Min}{4} \tag{5.1}$$

$$B = Max - \frac{Max - Min}{4} \tag{5.2}$$

***iii.*) Average demand:** The output data of the machine learning model presented in Chapter 4 was considered.

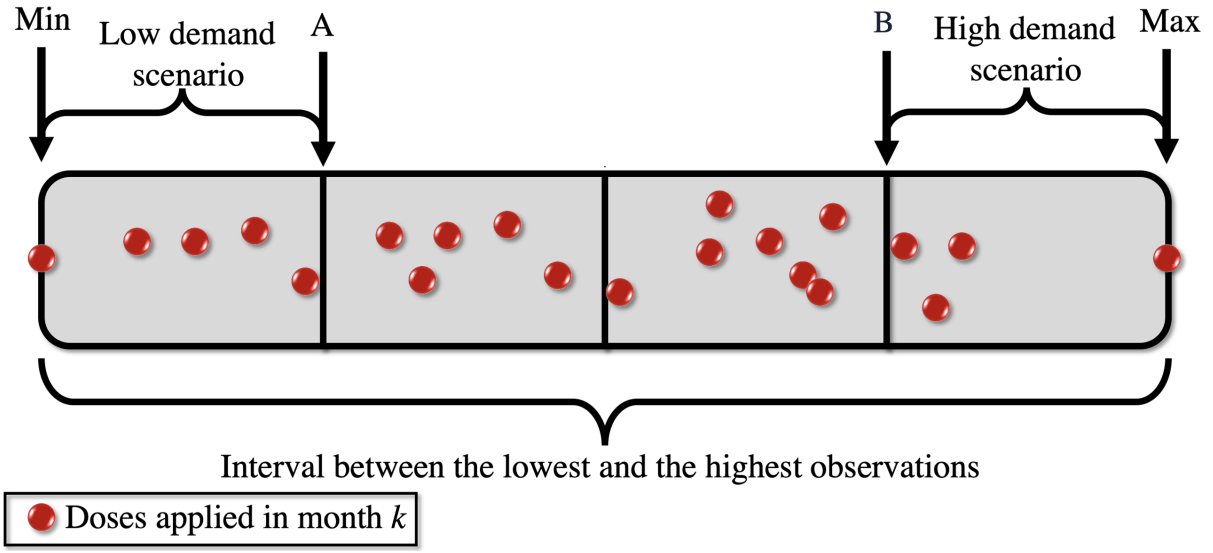


Figure 18: Interval between the lowest and the highest number of doses applied in a month in the historical series.

Source: Author

5.1.3 Stochastic model

This section presents the stochastic optimization model built. Appendix H presents codes written in the format that the CPLEX solver requires.

Sets:

I Set of states, indexed by i

K Set of months, indexed by k

Ω Set of scenarios, indexed by ω

Parameters:

p^{ω} Probability of scenario $\omega \in \Omega$

h_i Minimum amount of vaccines for interstate exchange of the state $i \in I$

c Cost of a vaccine dose

z_i Cost of unmet demand in state $i \in I$

b Holding cost for the federal government $(b < q_i)$

q_i Holding cost for state $i \in I$ $(b < q_i)$

t_i Cost of transportation from federal stock to state $i \in I$

r_{ij} Cost of transportation from state $i \in I$ to state $j \in I$

α Discount on cost of transportation from federal stock to states $(0 \leq \alpha \leq 1)$

β Manipulate percentage of unmet demand $(0 \leq \beta \leq 1)$

F^{ω} Initial stock of federal government under scenario $\omega \in \Omega$

l_i^ω Initial stock of state $i \in I$ under scenario $\omega \in \Omega$

g_i^ω Unmet demand of state $i \in I$ before first month under scenario $\omega \in \Omega$

d_{ik}^ω Predicted demand of vaccines of state i in month k under scenario $\omega \in \Omega$

First-stage decision variable:

v_k New vaccines in the federal stock in month $k \in K$

Second-stage decision variables:

x_{ik}^ω Number of new vaccines sent from federal stock to state i in the beginning of month k under scenario $\omega \in \Omega$

m_{ik}^ω Unmet demand of state i in the end of month k under scenario $\omega \in \Omega$

n_{ik}^ω Surplus of state i in the end of month k under scenario $\omega \in \Omega$

y_{ijk}^ω Number of vaccines to be sent from state ki to state j in the beginning of month k under scenario $\omega \in \Omega$

s_k^ω Surplus of federal stock at the end of month k under scenario $\omega \in \Omega$

u_{ijk}^ω Binary variable to decide if there will be transshipment from state i to state j in the end of month k under scenario $\omega \in \Omega$

Mathematical Formulation

Minimize:

$$\sum_{k \in K} cv_k + \mathbb{E}[f(v, \tilde{\omega})] \tag{5.3}$$

Subject to:

$$v_k \geq 0 \qquad \forall k \in K$$

where for each outcome (scenario) $\omega \in \Omega$ of $\tilde{\omega}$

$$minf(v, \tilde{\omega}) = \sum_{i \in I} \sum_{j \in I} \sum_{k \in K} (z_i m_{ik}^\omega + q_i n_{ik}^\omega + (1 - \alpha) t_i x_{ik}^\omega + r_{ij} y_{ijk}^\omega + b s_k^\omega) \tag{5.4}$$

Subject to:

$$x_{ik}^\omega - m_{ik-1}^\omega + n_{ik-1}^\omega - \sum_{j \in I, j \neq i} y_{ijk}^\omega + \sum_{j \in I, j \neq i} y_{jik}^\omega = d_{ik}^\omega - m_{ik}^\omega + n_{ik}^\omega \qquad \forall i, j \in I, k \in K, \omega \in \Omega$$

$$\sum_{i \in I} x_{ik}^\omega = v_k + s_{k-1}^\omega - s_k^\omega \qquad \forall k \in K, \omega \in \Omega$$

$$y_{ijk}^{\omega} \leq M u_{ijk}^{\omega} \qquad \forall i, j \in I, k \in K, \omega \in \Omega$$

$$y_{ijk}^{\omega} \geq h_i u_{ijk}^{\omega} \qquad \forall i, j \in I, k \in K, \omega \in \Omega$$

$$m_{ik}^{\omega} \leq (1-\beta) d_{ik}^{\omega} \qquad \forall i \in I, k \in K, \omega \in \Omega$$

$$m_{ik}^{\omega} = 0 \qquad \forall i \in I, \omega \in \Omega$$

$$m_{i0}^{\omega} = g_i^{\omega} \qquad \forall i \in I, \omega \in \Omega$$

$$s_0^{\omega} = F^{\omega} \qquad \forall \omega \in \Omega$$

$$n_{i0}^{\omega} = l_i^{\omega} \qquad \forall i \in I, \omega \in \Omega$$

$$x_{ik}^{\omega}, y_{ij}^{\omega}, m_{ik}^{\omega}, n_{ik}^{\omega}, s_k^{\omega} \geq 0 \qquad \forall i, j \in I, k \in K, \omega \in \Omega$$

$$u_{ik}^{\omega} \in \{0, 1\} \qquad \forall i \in I, k \in K, \omega \in \Omega$$

$$x_{ik}^{\omega}, y_{ij}^{\omega}, m_{ik}^{\omega}, n_{ik}^{\omega} \in \mathbb{Z}^{+} \qquad \forall i, j \in I, k \in K, \omega \in \Omega$$

$$i \in \{1, 2, \ldots, |I|\}$$

$$j \in \{1, 2, \ldots, |J|\}$$

$$k \in \{1, 2, \ldots, |K|\}$$

5.1.4 Stochastic model-Region based

This section presents the same stochastic model introduced before, but as if it were considering the possibility of optimizing vaccine distribution by region rather than by state.

Sets:

I Set of regions, indexed by i

K Set of months, indexed by k

Ω Set of scenarios, indexed by ω

First-stage decision variable:

v_k New vaccines in the federal stock in month $k \in K$

First-stage Parameters:

c Cost of the vaccine

Second-stage Parameters:

p^ω Probability of scenario $\omega \in \Omega$

h_i Minimum amount of vaccines for regional exchange $i \in I$

c Cost of vaccine

z_i Cost of unmet demand in region $i \in I$

b Holding cost for the federal government ($b < q_i$)

q_i Holding cost for region $i \in I$ ($b < q_i$)

t_i Cost of transportation from federal stock to region $i \in I$

r_{ij} Cost of transportation from region $i \in I$ to region $j \in I$

α Discount on cost of transportation from federal stock to any region ($0 \leq \alpha \leq 1$)

β Maximum percentage of demand to be unmet ($0 \leq \beta \leq 1$)

F Initial stock of federal government

l_i Initial stock of region $i \in I$

g_i Unmet demand of region $i \in I$ before first month ($k = 0$)

d_{ik}^ω Predicted demand of vaccines of region $i \in I$ in month $k \in K$ under scenario $\omega \in \Omega$

Second-stage decision variables:

x_{ik}^ω Number of new vaccines sent from federal stock to region $i \in I$ in the beginning of

month $k \in K$ under scenario $\omega \in \Omega$

m_{ik}^{ω} Unmet demand of region $i \in I$ in the end of month k under scenario $\omega \in \Omega$

n_{ik}^{ω} Surplus of region $i \in I$ in the end of month k under scenario $\omega \in \Omega$

y_{ijk}^{ω} Number of vaccines to be sent from region $i \in I$ to region $j \in I$ in the beginning of month $k \in K$ under scenario $\omega \in \Omega$

s_{k}^{ω} Surplus of federal stock at the end of month $k \in K$ under scenario $\omega \in \Omega$

u_{ijk}^{ω} Binary variable to decide if there will be transshipment from region $i \in I$ to region $j \in I$ in the end of month $k \in K$ under scenario $\omega \in \Omega$

Mathematical Formulation

Minimize:

$$\sum_{k \in K} cv_k + \mathbb{E}[f(v, \tilde{\omega})] \tag{5.5}$$

Subject to:

$$v_k \geq 0 \qquad \forall k \in K$$

where for each outcome (scenario) $\omega \in \Omega$ of $\tilde{\omega}$

$$minf(v, \tilde{\omega}) = \sum_{i \in I} \sum_{j \in I} \sum_{k \in K} (z_i m_{ik}^{\omega} + q_i n_{ik}^{\omega} + (1-\alpha) t_i x_{ik}^{\omega} + r_{ij} y_{ijk}^{\omega} + b s_k^{\omega}) \tag{5.6}$$

Subject to:

$$x_{ik}^{\omega} - m_{ik-1}^{\omega} + n_{ik-1}^{\omega} - \sum_{j \in I, j \neq i} y_{ijk}^{\omega} + \sum_{j \in I, j \neq i} y_{jik}^{\omega} = d_{ik}^{\omega} - m_{ik}^{\omega} + n_{ik}^{\omega} \qquad \forall i \in I, k \in K$$

$$\sum_{i \in I} x_{ik}^{\omega} = v_k + s_{k-1}^{\omega} - s_k^{\omega} \qquad \forall k \in K$$

$$y_{ijk}^{\omega} \leq M u_{ijk}^{\omega} \qquad \forall i, j \in I, k \in K$$

$$y_{ijk}^{\omega} \geq h_i u_{ijk}^{\omega} \qquad \forall i, j \in I, k \in K$$

$$m_{ik}^{\omega} \leq (1-\beta) d_{ik}^{\omega} \qquad \forall i \in I, k \in K$$

$$m_{iK}^{\omega} = 0 \qquad \forall i \in I$$

$$m_{i0}^{\omega} = g_i \qquad \forall i \in I$$

$$s_0^{\omega} = F$$

$$n_{i0}^{\omega} = l_i \qquad \forall i \in I$$

$$x_{ik}^{\omega}, y_{ij}^{\omega}, m_{ik}^{\omega}, n_{ik}^{\omega}, s_k^{\omega} \geq 0 \qquad \forall i, j \in I, k \in K$$

$$u_{ik}^{\omega} \in \{0,1\} \qquad \forall i \in I, k \in K$$

$$x_{ik}^{\omega}, y_{ij}^{\omega}, m_{ik}^{\omega}, n_{ik}^{\omega} \in \mathbb{Z}^{+} \qquad \forall i,j \in I, k \in K$$

$$i \in \{1,2,\ldots,|I|\}$$

$$j \in \{1,2,\ldots,|J|\}$$

$$k \in \{1,2,\ldots,|K|\}$$

5.1.5 Deterministic equivalent model

This section presents the deterministic optimization equivalent model developed. Its codes are presented in Appendix F.

Sets:

i index set of state regions, $i \in I$

j index set of all regions, $j \in I$

k index set of month, $k \in K$

Parameters:

d_{ik} predicted demand of vaccines of state i in month k

h_i minimum amount of vaccines for interstate exchange of the state i

c cost of the vaccine

z_i cost of unmet demand in state i

v holding cost for the federal government ($v < q_i$)

q_i holding cost for state i ($v < q_i$)

t_i cost of transportation from federal stock to state i

r_{ij} cost of transportation from state i to state j

α discount on cost of transportation from federal stock to states ($0 \leq \alpha \leq 1$)

β manipulate percentage of unmet demand ($0 \leq \beta \leq 1$)

Fi federal government initial stock

Is states initial stock

Decision variables:

f_k new vaccines in the federal stock in month k

x_{ik} number of new vaccines sent from federal stock to state i in the beginning of month k

m_{ik} unmet demand of state i in the end of month k

n_{ik} surplus of state i in the end of month k

y_{ijk} number of vaccines to be sent from state i to state j in the beginning of month k

s_k surplus of federal stock i in the end of month k

u_{ijk} binary variable to decide if there will be transshipment from state i to state j in the end of month k

Minimize:

$$\sum_{k\in K} cf_k + \sum_{i\in I}\sum_{k\in K} z_i m_{ik} + \sum_{i\in I}\sum_{k\in K} q_i n_{ik} + \sum_{i\in I}\sum_{k\in K}(1-\alpha)t_i x_{ik} + \sum_{i\in I}\sum_{j\in I, j\neq i}\sum_{k\in K} r_{ij} y_{ijk} + \sum_{k\in K} vs_k \tag{5.7}$$

Subject to:

$$x_{ik} - m_{ik-1} + n_{ik-1} - \sum_{j\in I, j\neq i} y_{ijk} + \sum_{j\in I, j\neq i} y_{jik} = d_{ik} - m_{ik} + n_{ik} \qquad i \in I, \forall k \in K$$

$$\sum_{i\in I} x_{ik} = f_k + s_{k-1} - s_k \qquad i \in I, \forall j \in I, \forall k \in K$$

$$y_{ijk} \leq M u_{ijk} \qquad i \in I, \forall j \in I, \forall k \in K$$

$$y_{ijk} \geq h_i u_{ijk} \qquad i \in I, \forall j \in I, \forall k \in K$$

$$m_{ik} \leq (1-\beta) d_{ik} \qquad i \in I, \forall k \in K$$

$$m_{iK=0} \qquad i \in I$$

$$s_0 = Fi \qquad \forall k \in K$$

$$n_{i0} = Is \qquad i \in I, \forall k \in K$$

$$x_i k, y_i j, m_i k, n_i k, f_k, s_k \geq 0 \qquad i \in I, \forall j \in I, \forall k \in K$$

$$u_{ik} \in \{0, 1\} \qquad i \in I, \forall k \in K$$

$$x_{ik}, y_{ij}, m_{ik}, n_{ik}, f_k \in \qquad i \in I, \forall j \in I, \forall k \in K$$

$$i = 1, 2, \ldots, |I|$$

$$j = 1, 2, \ldots, |J|$$

$$k = 1, 2, \ldots, |K|$$

5.2 Deterministic results

The results presented in Appendix G are the results of the equivalent deterministic optimization model. Because it is a very large model, the code with the deterministic optimization model, written in GAMS language, was submitted to the NEOS Server solver. It is important to remember that as the deterministic model considers a perfect model (that is, real demand is equal to the expected demand). Also, because of this, the model does not suggest the exchange of products between states. Therefore, the deterministic model allows the construction of the model itself to be validated. The model presented a suggestion to send exactly the same number of doses that the states presented as demand. This means that the model is suitable to be implemented stochastically.

5.3 Stochastic results

For the stochastic model, the main challenge was to run the codes with all possible scenarios, that is, considering the initial idea of the project to build a model to optimize the distribution among 27 states, during 12 months, and 3 scenario possibilities. This means that the number of possible scenarios for the model would be $3^{(12*27)}$ (3.9E+154). A number as high as this requires massive computational processing. In face of that, it was used an Sample Average Approximation (Monte Carlo Approximation) algorithm to help the stochastic model to deal with this number of scenarios. SAA é a very well known simulation-optimization method of solving otimization problems, for more information related to it check the work published by Kim, Pasupathy, and Henderson 2015.

The results presented here take into account the following scenario: 4 Brazilian states, 3 possible demand scenarios, and 3 months of decision making. The results obtained are shown in Table 8. The solution of the model itself (as the solver output format) is presented in Appendix I.

The result obtained by the model complies with the requirements assumed in the construction of the model. It is possible to observe that the model tried to avoid that a vaccine shortage could occur during the period.

The values presented in the Received column refer to the model result itself. That is, the number of doses that the model suggests that the federal warehouse sends to each of the 4 states, during the 3 months considered.

It should be remembered that the model made decisions on how many vaccines to

Table 8: Results for the stochastic optimization model considering 4 states and 3 months

State	*Month*	*Unmet demand*	*Initial Stock*	*Received*	*High demand*	*Medium demand*	*Low demand*	*Real demand*	*Final stock*
	0	200	1000	0	-	-	-	-	800
RO	1	-	-	2186	3008	2545	2186	2887	99
	2	-	-	1784	2681	2298	1784	1862	21
	3	-	-	2206	3808	2621	2206	2207	**20**
	0	0	1000	-	-	-	-	-	1000
AC	1	-	-	1060	2207	1626	1060	1543	517
	2	-	-	1039	2221	1594	1039	1002	554
	3	-	-	1148	2907	1762	1148	1698	**4**
	0	200	1000	-	-	-	-	-	800
AM	1	-	-	7281	8876	7877	6577	7346	735
	2	-	-	8519	8785	7515	5290	8697	557
	3	-	-	6460	8878	7670	5890	6261	**756**
	0	0	1000	-	-	-	-	-	1000
RR	1	-	-	906	1906	1168	746	759	1147
	2	-	-	1148	1751	1148	843	971	1324
	3	-	-	730	1778	1110	730	1499	**555**

Source: Author.

send to each state based on demand information that was estimated by the author. That is, average demand equal to the result of machine learning model predictions, and low and high demand based on the methodology presented earlier in this chapter.

The column with the actual data shows the number of doses that were actually administered in that period.

In order to test it, it was stipulated that each state starts with a stockpile of 1000 doses. And two states start the 3-month period with a prior unmet demand of 200 doses.

The final stock column presents a survey of how many doses would have been in stock if the model had been considered in the management of these 3 months (also considering that the initial scenario of unmet demand and initial stock were the same as those presented in the table).

As can be seen in the table, at the end of the last period, that is, at the end of the third month, the four states would have a positive stock. With this, it is possible to say that no vaccine had stopped being applied. This is due to the definition of costs defined in the study, in which the cost of keeping stock in each state is considered lower than the cost of an unapplied vaccine.

However, at the results of the RO and AC states it is possible to see that at the end of the period, despite the number of doses in stock being positive, they are very low.

In building the model, the minimum number of doses sent between one state and another was estimated. However, there was no definition of minimum stock in the states. The inclusion of this parameter can be a good alternative to prevent the stock of states from getting close to zero (the optimal scenario for the optimization model).

Despite the hypothesis that the stochastic optimization model could suggest exchange of vaccines between states, it cannot be confirmed. The model results did not suggest exchange of vaccines between states, but that does not mean that the hypothesis that this practice would optimize the distribution chain is not valid. This happens because, again, the model considers values that are estimates. Thus, this hypothesis would have to be reassessed after a possible adaptation of the model to real data from the operation of the vaccine supply chain considered in this study.

Due to the lack of access to the decision-making methodology used by the chain managers, it was not possible to compare the results of the model with what was actually decided at the time. Therefore, the model proposed here can be used as another tool to aid decision making. Its adoption as a single method is only suggested if an adaptation of

the assumptions is performed.

5.4 Discussion

The idea of developing an optimization model to improve the vaccine distribution chain came from the observation that the its losses are very high. Building an optimization model requires extensive work of translating a real-life problem into variables. An optimization model that aims to optimize a supply chain as complex as the distribution of vaccines in Brazil would obviously not be a small challenge.

The initial idea for the construction of this project considered a scenario where it would be possible to test the optimization model with proximity to the day-to-day operation of the chain. However this was not possible. The development of the model proposed here required researchers to make several assumptions that may differ from real numbers. This means that, if this model is adopted by managers in the future, the model needs to undergo some adjustments. However, it is important to emphasize that this is a standard procedure when taking an optimization model to real-time application.

An important step for the application of the model is also that the actual cost values are defined. Although it seems simple, this is not an easy task. Transport, inventory and unmet demand costs require in-depth analysis of chain costs. However, it is known that managers responsible for decision-making in relation to stock and demand currently do not consider all costs considered in this study.

The scope of this research needed to be revised frequently during its execution. The definition of the problem itself was a major challenge for researchers and MS technicians. Therefore, some stages of the research could not be carried out within the period of execution of the doctorate. In the section 5.5, suggestions for future work are presented, which could make this model better adapted to be used by chain managers.

However, it is important to emphasize that the simple construction of a model of this complexity that can be adapted to the operation must be considered as one of the great contributions of this research. As can be confirmed from the theoretical foundation of this dissertation, optimization is an approach that has a lot of space to be used in the management of the vaccine distribution chain. And unfortunately, despite this study having started in 2017, the surprise of a COVID-19 pandemic made it clear that improvements in the chain will be increasingly necessary. The scenario caused by the spread of this virus turned the eyes of the whole world to all areas of management of this distribution chain.

5.5 Future work

The model presented here has some limitations that can be overcome. One of them would be to increase the processing capacity of possible scenarios. The way in which the study was carried out model the regions are managed independently. Thus, if all states are considered in the management of the model at once, the model proposal can be more assertive. This step can happen in two ways, one that considers the use of a "super" data processor, where it is possible to leave the model running. And the other is from the continued use of Sample Average Approximation.

Some experiments can also be performed. For example, if it is possible to access the types of decision-making used by the chain managers, it would be possible to compare their solution with the solution of the model proposed here. Ideally, the model proposed here can be compared to different decision-making methods, whether used by technicians from the Brazilian Ministry of Health, or others available in the literature.

And last but not least, it is necessary to review the estimated costs. The costs involved in the chain (purchase, inventory, transport, and lack of vaccine) directly affect the results of the model. In this work, the estimation of these values allowed the model to be built, however, a review of the actual values is necessary before the model is implemented directly in the operation.

6 CONCLUSIONS

"It is necessary to choose a path that has no end, but, still, always walk in the expectation of finding it."

-- Geraldo Magela Amaral

This work was the result of a long journey to, initially, understand the problem that was being dealt with. The stage of the first year of the study, which mapped the processes of the Ministry of Health's vaccine distribution chain, made it possible to observe that:

- The vaccine distribution chain in Brazil is fraught with management challenges faced daily by public and health professionals;
- The management of the chain is basically all manual, depending on the knowledge of the technicians that make up the organization. This is observed both in the management part and in the operational part;
- Despite the Brazilian National Immunization Program being internationally recognized, its vaccination coverage has a cost to the public coffers that could be drastically reduced without necessarily reducing the quality of service provided to the population;
- Despite the vaccine losses due to chain management, it is important to emphasize that there are technical losses, which include loss of liquid in the syringes and loss of doses due to the difficulty of accessing the liquid inside the bottle;
- Although the subject of management is widely discussed here, it should be considered that investment in the infrastructure of the chain must also be considered. Refrigerators and vehicles for transporting vaccines are very poor in some parts of the country.

After the first year of this study, the objective was to look for ways to improve the vaccine distribution chain in Brazil as a whole. The decision to use machine learning came from the desire to embrace the challenge of using new technologies. This stage of the work led to the conclusion that:

- Despite being a technology that can reach unimaginable levels of complexity, machine learning can be used to solve linear supply chain management problems;
- The results obtained with the model presented in this study are of an acceptable magnitude for the proportions of vaccine loss that the vaccine distribution chain in Brazil currently faces;
- The proposed model could be used by technicians from the Ministry of Health to support the decision in the management of vaccine demand, as the model is currently found;
- The proposed vaccine prediction strategy has great potential to be expanded with more and more data from the chain.

Finally, the biggest challenge of this whole work was the construction of the stochastic optimization model. Translating a real-life problem into a mathematical equation requires that every detail be defined with precision. With the completion of the development of the optimization model, it can be concluded that:

- The optimization model fulfilled the objective of making a decision regarding the number of vaccines to be sent to each state. And yet, with the objective of avoiding that there is unmet demand;
- The model can be easily adapted to the operation, and has great potential to be an aid tool in decision making;
- Although it was not possible to confirm the hypothesis that the exchange of vaccines between states can benefit the chain, it was not refuted. It should be tested with new experiments.
- The model presented could integrate the systems used in the management of the chain. This would facilitate the use of the model, allowing technical experts in management not necessarily to have knowledge in optimization or programming to use it;
- The biggest challenge in building the optimization model is to be able to define all the costs involved in the operation. Although it was necessary to estimate many of the costs used in the model, it presents positive results;

- Optimization is a widely used field in the improvement of vaccine supply chains. However, it was possible to observe that most studies focus on optimizing the vaccination strategy;
- This study collaborated with the application of optimization in the management and logistics part of the vaccine supply chain.

REFERENCES

AGUSTO, F. B.; KHAN, M. A. Optimal control strategies for dengue transmission in pakistan. *Mathematical biosciences*, v. 305, p. 102–121, 2018. Compilation and indexing terms, Copyright 2019 Elsevier Inc.; undefined; undefined; undefined; undefined; undefined. Disponível em: ⟨http://dx.doi.org/10.1016/j.mbs.2018.09.007⟩.

ANPARASAN, A. A.; LEJEUNE, M. A. Data laboratory for supply chain response models during epidemic outbreaks. *Annals of Operations Research*, Springer, v. 270, n. 1, p. 53–64, 2018.

ASHOK, A.; BRISON, M.; LETALLEC, Y. Improving cold chain systems: challenges and solutions. *Vaccine*, Elsevier, v. 35, n. 17, p. 2217–2223, 2017.

BALLOU, R. *Business Logistics/supply Chain Management: Planning, Organizing, and Controlling the Supply Chain*. Pearson/Prentice Hall, 2004. ISBN 9780130661845. Disponível em: ⟨https://books.google.com/books?id=sgsdQAAACAAJ⟩.

BALLOU, R. H. *Gerenciamento da Cadeia de Suprimentos/ logística empresarial (Tradução Raul Rubenich)*. [S.l.]: Porto Alegre: Bookman, 2006.

BOECK, K. D.; DECOUTTERE, C.; VANDAELE, N. Vaccine distribution chains in low-and middle-income countries: A literature review. *Omega*, Elsevier, v. 97, p. 102097, 2020.

BRIAT, C.; VERRIEST, E. I. A new delay-sir model for pulse vaccination. *Biomedical Signal Processing and Control*, v. 4, n. 4, p. 272–277, 2009. Compilation and indexing terms, Copyright 2019 Elsevier Inc.; undefined; undefined; undefined; undefined; undefined; undefined; undefined; undefined. Disponível em: ⟨http://dx.doi.org/10.1016/j.bspc.2009.06.003⟩.

CHEN, H. et al. Next generation technology for epidemic prevention and control: Data-driven contact tracking. *IEEE Access*, IEEE, v. 7, p. 2633–2642, 2018.

CHEN, S.-I. et al. A planning model for the who-epi vaccine distribution network in developing countries. *IIE Transactions (Institute of Industrial Engineers)*, v. 46, n. 8, p. 853–865, 2014. Compilation and indexing terms, Copyright 2019 Elsevier Inc.; undefined; undefined; undefined; undefined; undefined; undefined; undefined; undefined. Disponível em: ⟨http://dx.doi.org/10.1080/0740817X.2013.813094⟩.

CHOPRA, S.; MEINDL, P.; GONÇALVES, M. A. Gestão da cadeia de suprimentos: estratégia, planejamento e operações. 2011.

CORRÊA, H. L. *Administração de cadeias de suprimento e logística*. [S.l.]: Editora Atlas SA, 2014.

CORRÊA, H. L.; GIANESI, I. G.; CAON, M. Planejamento, programação e controle da produção. *São Paulo: Atlas*, v. 1, 2001.

DAVID, G.; ANDRELINO, A.; BEGHIN, N. *Direito a Medicamentos: avaliação das despesas com medicamentos no âmbito federal do Sistema Único de Saúde entre 2008 e 2015*. Instituto de Estudos Socioeconômicos (Inesc), 2016. Disponível em: ⟨http://www.inesc.org.br/biblioteca/textos/direito-a-medicamentos-avaliacao-das-despesas-com-medicamentos-no-ambito-federal-do-sistema-unico-de-saude-entre-2008-e-2015/at_download/file⟩.

DEMARTEAU, N.; BREUER, T.; STANDAERT, B. Selecting a mix of prevention strategies against cervical cancer for maximum efficiency with an optimization program. *PharmacoEconomics*, v. 30, n. 4, p. 337–353, 2012.

DIMITROV, N. et al. Optimizing tactics for use of the u.s. antiviral strategic national stockpile for pandemic (h1n1) influenza, 2009. *PLoS Currents*, n. NOV, 2009.

DUIJZER, L. E.; JAARSVELD, W. V.; DEKKER, R. Literature review: The vaccine supply chain. *European Journal of Operational Research*, Elsevier, v. 268, n. 1, p. 174–192, 2018.

ENAYATI, S.; ÖZALTIN, O. Y. Optimal influenza vaccine distribution with equity. *European Journal of Operational Research*, Elsevier, v. 283, n. 2, p. 714–725, 2020.

ENGINEER, F. G.; KESKINOCAK, P.; PICKERING, L. K. Catch-up scheduling for childhood vaccination. *Operations research*, v. 57, n. 6, p. 1307–1319, 2009. Disponível em: ⟨http://dx.doi.org/10.1287/opre.1090.0756⟩.

FELIX, P. *Surto de febre amarela faz laboratório aumentar produção de vacina*. 2017. Disponível em: ⟨https://saude.estadao.com.br/noticias/geral,surto-de-febre-amarela-faz-laboratorio-aumentar-producao-de-vacina,70001649113⟩. Acesso em: 02 out. 2018.

FERREIRA, G. O.; ARRUDA, E. F.; MARUJO, L. G. Inventory management of perishable items in long-term humanitarian operations using markov decision processes. *International Journal of Disaster Risk Reduction*, v. 31, p. 460–469, October 2018 2018. ID: 282172.

GAGNON, M.-P.; LAMPRON, A.; BUYL, R. Implementation and adoption of an electronic information system for vaccine inventory management. In: IEEE. *2016 49th Hawaii International Conference on System Sciences (HICSS)*. [S.l.], 2016. p. 3172–3178.

GANANN, R.; CILISKA, D.; THOMAS, H. Expediting systematic reviews: methods and implications of rapid reviews. *Implementation Science*, Springer, v. 5, n. 1, p. 1–10, 2010.

GIERSING, B. K. et al. Challenges of vaccine presentation and delivery: How can we design vaccines to have optimal programmatic impact? *Vaccine*, Elsevier, v. 35, n. 49, p. 6793–6797, 2017.

GIRARD, D. Z. The distribution over time of costs and social net benefits for pertussis immunization programs. *International Journal of Health Care Finance and Economics*, v. 10, n. 1, p. 1–27, 2010.

GOLDSTEIN, E. et al. Distribution of vaccine/antivirals and the 'least spread line' in a stratified population. *Journal of the Royal Society Interface*, v. 7, n. 46, p. 755–764, 2010. Disponível em: ⟨http://dx.doi.org/10.1098/rsif.2009.0393⟩.

GUZMAN, T. Big pharma and big profits: The multibillion dollar vaccine market. 2018.

HARDT, K. et al. Vaccine strategies: Optimising outcomes. *Vaccine*, Elsevier, v. 34, n. 52, p. 6691–6699, 2016.

HARKER, J.; KLEIJNEN, J. What is a rapid review? a methodological exploration of rapid reviews in health technology assessments. *International Journal of Evidence-Based Healthcare*, Wiley Online Library, v. 10, n. 4, p. 397–410, 2012.

HARVEY, M. J. et al. Hitting the optimal vaccination percentage and the risks of error: Why to miss right. *PloS one*, Public Library of Science, v. 11, n. 6, p. e0156737, 2016.

HOTA, A. R.; SUNDARAM, S. Game-theoretic vaccination against networked sis epidemics and impacts of human decision-making. *IEEE Transactions on Control of Network Systems*, IEEE, v. 6, n. 4, p. 1461–1472, 2019.

HOVAV, S.; TSADIKOVICH, D. A network flow model for inventory management and distribution of influenza vaccines through a healthcare supply chain. *Operations Research for Health Care*, v. 5, p. 49–62, June 2015 2015. ID: 280863.

HUANG, H.-C. et al. Equalizing access to pandemic influenza vaccines through optimal allocation to public health distribution points. *PloS one*, Public Library of Science, v. 12, n. 8, p. e0182720, 2017.

KASONDE, M.; STEELE, P. The people factor: An analysis of the human resources landscape for immunization supply chain management. *Vaccine*, Elsevier, v. 35, n. 17, p. 2134–2140, 2017.

KHANGURA, S. et al. Evidence summaries: the evolution of a rapid review approach. *Systematic reviews*, BioMed Central, v. 1, n. 1, p. 1–9, 2012.

KIM, D. et al. On efficient vaccine distribution strategy to suppress pandemic using social relation. *Discrete Mathematics Algorithms and Applications*, v. 8, n. 1, p. UNSP 1650010, MAR 2016 2016.

KIM, S.; PASUPATHY, R.; HENDERSON, S. G. A guide to sample average approximation. *Handbook of simulation optimization*, Springer, p. 207–243, 2015.

KRESS, M. Policies for biodefense revisited: The prioritized vaccination process for smallpox. *Annals of Operations Research*, Springer, v. 148, n. 1, p. 5, 2006.

KUROSKY, S. K.; DAVIS, K. L.; KRISHNARAJAH, G. Completion and compliance of childhood vaccinations in the united states. *Vaccine*, Elsevier, v. 34, n. 3, p. 387–394, 2016.

LAUTON, F.; ROTHKOPF, A.; PIBERNIK, R. The value of entrant manufacturers: A study of competition and risk for donor-funded procurement of essential medicines. *European Journal of Operational Research*, v. 272, n. 1, p. 292–312, 1 January 2019 2019.

LEE, B. Y.; HAIDARI, L. A. The importance of vaccine supply chains to everyone in the vaccine world. *Vaccine*, Elsevier, v. 35, n. 35, p. 4475–4479, 2017.

LEE, B. Y. et al. Economic impact of thermostable vaccines. *Vaccine*, Elsevier, v. 35, n. 23, p. 3135–3142, 2017.

LEMMENS, S. et al. A review of integrated supply chain network design models: Key issues for vaccine supply chains. *Chemical Engineering Research and Design*, Elsevier, v. 109, p. 366–384, 2016.

LEMMENS, S. et al. A review of integrated supply chain network design models: Key issues for vaccine supply chains. *Chemical Engineering Research and Design*, Elsevier, v. 109, p. 366–384, 2016.

LIM, J.; NORMAN, B. A.; RAJGOPAL, J. Process redesign and simplified policies for more effective vaccine inventory management. *Engineering Management Journal*, Taylor & Francis, v. 29, n. 1, p. 17–25, 2017.

LLOYD, J. et al. Reducing the loss of vaccines from accidental freezing in the cold chain: the experience of continuous temperature monitoring in tunisia. *Vaccine*, Elsevier, v. 33, n. 7, p. 902–907, 2015.

LOPES, J. M. et al. Health 4.0: Challenges for an orderly and inclusive innovation [commentary]. *IEEE Technology and Society Magazine*, IEEE, v. 38, n. 3, p. 17–19, 2019.

LOZE, P. M. et al. Vaccines are different: A systematic review of budget impact analyses of vaccines. *Vaccine*, Elsevier, v. 35, n. 21, p. 2781–2793, 2017.

MEDLOCK, J.; GALVANI, A. P. Optimizing influenza vaccine distribution. *Science*, v. 325, n. 5948, p. 1705–1708, 2009.

MEYERS, L.; GALVANI, A.; MEDLOCK, J. Optimizing allocation for a delayed influenza vaccination campaign. *PLoS Currents*, n. DEC, 2009.

Ministério da Saúde. *Sobre o programa*. 2017. Available in: ⟨http://www.saude.gov.br/saude-de-a-z/vacinacao/sobre-o-programa⟩. Access on: 23 dec. 2019.

Ministério da Saúde. *Campanha de vacinação terá dose fracionada de febre amarela em três estados*. 2018. Available in: ⟨http://www.saude.gov.br/noticias/agencia-saude/42289-campanha-de-vacinacao-tera-dose-fracionada-de-febre-amarela-em-tres-estados⟩. Access on: 13 jan. 2020.

Ministério da Saúde. *Febre amarela: Ministério da Saúde atualiza casos no país*. 2018. Available in: ⟨http://www.saude.gov.br/noticias/agencia-saude/42655-febre-amarela-ministerio-da-saude-atualiza-casos-no-pais⟩. Access on: 13 jan. 2020.

Ministério da Saúde. *Informações de Saúde (TABNET)*. 2020. Available in: ⟨http://www2.datasus.gov.br/DATASUS/index.php?area=02⟩, note = Access on: 17 jan. 2020.

Ministério da Saúde. *Sobre o DATASUS*. 2020. Available in: ⟨http://datasus.saude.gov.br/sobre-o-datasus/⟩. Access on: 17 jan. 2020.

Ministério da Saúde. *Programa Nacional de Imunizações - Vacinação*. n.d. Available in: ⟨https://www.gov.br/saude/pt-br/acesso-a-informacao/acoes-e-programas/programa-nacional-de-imunizacoes-vacinacao⟩. Access on: 10 Jan. 2022.

MOHER, D. et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann. Intern. Med*, v. 151, p. W65–W94, 2009.

MOORE, S. M.; LESSLER, J. Optimal allocation of the limited oral cholera vaccine supply between endemic and epidemic settings. *Journal of The Royal Society Interface*, The Royal Society, v. 12, n. 111, p. 20150703, 2015.

MVUNDURA, M. et al. An economic evaluation of the controlled temperature chain approach for vaccine logistics: evidence from a study conducted during a meningitis a vaccine campaign in togo. *The Pan African medical journal*, African Field Epidemiology Network, v. 27, n. Suppl 3, 2017.

ONISHCHENKO, K. et al. Trends in vaccine investment in middle income countries. *Human vaccines & immunotherapeutics*, Taylor & Francis, p. 1–8, 2019.

PARMAR, D. et al. Impact of wastage on single and multi-dose vaccine vials: Implications for introducing pneumococcal vaccines in developing countries. *Human Vaccines*, Taylor Francis, v. 6, n. 3, p. 270–278, 2010. Disponível em: ⟨https://doi.org/10.4161/hv.6.3.10397⟩.

PATH. *Developing a Vision for Immunization Supply Systems in 2020*. 2011. ⟨https://path.azureedge.net/media/documents/TS_opt_vision_2020.pdf⟩.

PENG, X.-L. et al. An sis epidemic model with vaccination in a dynamical contact network of mobile individuals with heterogeneous spatial constraints. *Communications in Nonlinear Science and Numerical Simulation*, Elsevier, v. 73, p. 52–73, 2019.

PRECIADO, V. M. et al. Optimal resource allocation for network protection against spreading processes. *IEEE Transactions on Control of Network Systems*, v. 1, n. 1, p. 99–108, 2014. Disponível em: ⟨http://dx.doi.org/10.1109/TCNS.2014.2310911⟩.

RAEVEN, R. H. et al. Systems vaccinology and big data in the vaccine development chain. *Immunology*, Wiley Online Library, v. 156, n. 1, p. 33–46, 2019.

REN, Y.; ORDONEZ, F.; WU, S. Optimal resource allocation response to a smallpox outbreak. *Computers and Industrial Engineering*, v. 66, n. 2, p. 325–337, 2013. Disponível em: ⟨http://dx.doi.org/10.1016/j.cie.2013.07.002⟩.

RODRIGUES, H. S.; MONTEIRO, M. T.; TORRES, D. F. M. Vaccination models and optimal control strategies to dengue. *Mathematical biosciences*, v. 247, n. 1, p. 1–12, 2014. Disponível em: ⟨http://dx.doi.org/10.1016/j.mbs.2013.10.006⟩.

SAMII, A.-B. et al. Reservation and allocation policies for influenza vaccines. *European Journal of Operational Research*, v. 222, n. 3, p. 495–507, 1 November 2012 2012.

SAMUEL, A. L. Some studies in machine learning using the game of checkers. *IBM J. Res. Dev.*, IBM Corp., USA, v. 3, n. 3, p. 210–229, jul. 1959. ISSN 0018-8646. Disponível em: ⟨https://doi.org/10.1147/rd.33.0210⟩.

SANTOS, H. G. *Comparação da performance de algoritmos de machine learning para a análise preditiva em saúde pública e medicina.* Tese (Doutorado) — Universidade de São Paulo, São Paulo, 7 2018. Tese (Doutorado).

SATRIANO, N. *Inspeção acha mais 300 toneladas de remédio vencido em depósito no RJ.* 2016. Disponível em: ⟨http://g1.globo.com/rio-de-janeiro/noticia/2016/02/inspecao-acha-mais-300-toneladas-de-remedio-vencido-em-deposito-no-rj.html⟩. Acesso em: 02 out. 2018.

SATRIANO, N. *RJ pagará quase R$ 3 milhões para queimar medicamentos vencidos*. 2016. Disponível em: ⟨http://g1.globo.com/rio-de-janeiro/noticia/2016/03/rj-pagara-quase-r-3-milhoes-para-queimar-medicamentos-vencidos.html⟩. Acesso em: 02 out. 2018.

SAVACHKIN, A.; URIBE, A. Dynamic redistribution of mitigation resources during influenza pandemics. *Socio-economic planning sciences*, v. 46, n. 1, p. 33–45, 2012.

SHAROMI, O.; MALIK, T. Optimal control in epidemiology. *Annals of Operations Research*, Springer, v. 251, n. 1-2, p. 55–71, 2017.

SHOUKAT, A. et al. *How the interval between primary and booster vaccination affects long-term disease dynamics*. [S.l.]: World Scientific, 2016.

STANDAERT, B. et al. Constrained optimization for the selection of influenza vaccines to maximize the population benefit: a demonstration project. *Applied health economics and health policy*, Springer, v. 18, n. 4, p. 519–531, 2020.

TEBBENS, R. J. D. et al. Optimal vaccine stockpile design for an eradicated disease: Application to polio. *Vaccine*, v. 28, n. 26, p. 4312–4327, 11 June 2010 2010. ID: 271205.

THAKKAR, N. et al. Decreasing measles burden by optimizing campaign timing. *Proceedings of the National Academy of Sciences*, National Acad Sciences, v. 116, n. 22, p. 11069–11073, 2019.

TRICCO, A. C. et al. A scoping review of rapid review methods. *BMC medicine*, BioMed Central, v. 13, n. 1, p. 1–15, 2015.

UDDIN, M. J. et al. Use of mobile phones for improving vaccination coverage among children living in rural hard-to-reach areas and urban streets of bangladesh. *Vaccine*, Elsevier, v. 34, n. 2, p. 276–283, 2016.

Universidade Aberta do SUS. *Plano Nacional de Operacionalização da vacinação contra COVID-19*. 2021. Available in: ⟨https://www.gov.br/saude/pt-br/media/pdf/2021/janeiro/29/PlanoVacinaoCovid_ed4_15fev21_cgpni_18h05.pdf⟩. Access on: 10 Jan. 2022.

Universidade Aberta do SUS. *PNI faz 48 anos levando milhões de doses de vacinas aos brasileiros*. 2021. Available in: ⟨https://www.unasus.gov.br/noticia/pni-faz-48-anos-levando-milhoes-de-doses-de-vacinas-aos-brasileiros⟩. Access on: 10 Jan. 2022.

VEJA. *Governo do Rio queima 700 toneladas de medicamentos e material hospitalar*. 2016. Disponível em: ⟨https://veja.abril.com.br/politica/governo-do-rio-queima-700-toneladas-de-medicamentos-e-material-hospitalar/⟩. Acesso em: 02 out. 2018.

VENKATRAMANAN, S. et al. Optimizing spatial allocation of seasonal influenza vaccine under temporal constraints. *PLoS computational biology*, Public Library of Science San Francisco, CA USA, v. 15, n. 9, p. e1007111, 2019.

YUAN, E. C. et al. Optimal vaccination in a stochastic epidemic model of two non-interacting populations. *PloS one*, Public Library of Science, v. 10, n. 2, p. e0115826, 2015.

ZAFFRAN, M. et al. The imperative for stronger vaccine supply and logistics systems. *Vaccine*, Elsevier, v. 31, p. B73–B80, 2013.

APPENDIX A – STUDIES INCLUDED IN THE RAPID REVIEW

Tables A1 and A2 brings information about the studies included in the rapid review presented on Chapter 2.

Table A1: Main goal, supply chain part and vaccine or disease about the papers included in the rapid review.

#	*Authors*	*Main Goal*	*Supply Chain Part*	*Vaccine/ Disease*
1	(AGUSTO; KHAN, 2018)	Outbreak/ pandemics	Vaccination strategy	Dengue
2	(BRIAT; VERRIEST, 2009)	Outbreak/ pandemics	Vaccination strategy	General
3	(CHEN et al., 2014)	Optimal allocation/ availability	Logistics and Inventory management	General
4	(DEMARTEAU; BREUER; STANDAERT, 2012)	Budget	Vaccination strategy	HPV
5	(DIMITROV et al., 2009)	Outbreak/ pandemics	Logistics	H1N1
6	(TEBBENS et al., 2010)	Stockpile for eradicated disease	Inventory management	Polio

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Table A1 – *Continued from previous page*

#	*Authors*	*Main Goal*	*Supply Chain Part*	*Vaccine/ Disease*
7	(ENGINEER; KESKINOCAK; PICKERING, 2009)	Reduce impact of diseases	Vaccination strategy	Multiple vaccines
8	(FERREIRA; ARRUDA; MARUJO, 2018)	Reduce impact of diseases	Inventory management	General
9	(GIRARD, 2010)	Budget	Vaccination strategy	Pertussis
10	(GOLDSTEIN et al., 2010)	Outbreak/ pandemics	Vaccination strategy	Influenza
11	(HOVAV; TSADIKOVICH, 2015)	Budget	Logistics	Influeza
12	(KIM et al., 2016)	Outbreak/ pandemics	Vaccination strategy	General
13	(LAUTON; ROTHKOPF; PIBERNIK, 2019)	Impact of new manufacturers	Supply Chain Management	Vaccine and other products
14a	(MEDLOCK; GALVANI, 2009)	Reduce impact of diseases	Vaccination strategy	H1N1
14b	(MEYERS; GALVANI; MEDLOCK, 2009)	Reduce impact of diseases	Vaccination strategy	H1N1
15	(PRECIADO et al., 2014)	Optimal allocation/ availability	Logistics	Vaccine and other products

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Table A1 – *Continued from previous page*

#	*Authors*	*Main Goal*	*Supply Chain Part*	*Vaccine/ Disease*
16	(REN; ORDONEZ; WU, 2013)	Outbreak/ pandemics	Vaccination strategy	H1N1
17	(RODRIGUES; MONTEIRO; TORRES, 2014)	Budget	Vaccination strategy	Dengue
18	(SAMII et al., 2012)	Optimal allocation/ availability	Inventory management	Influeza
19	(SAVACHKIN; URIBE, 2012)	Outbreak/ pandemics	Vaccination strategy	Influeza
20	(PENG et al., 2019)	Reduce impact of diseases	Vaccination strategy	General
21	(STANDAERT et al., 2020)	Budget	Vaccination strategy	Influenza
22	(THAKKAR et al., 2019)	Reduce impact of diseases	Vaccination strategy	Measles
23	(HOTA; SUNDARAM, 2019)	Reduce impact of diseases	Vaccination strategy	General
24	(ENAYATI; ÖZALTIN, 2020)	Optimal allocation	Vaccination strategy	Influenza
25	(VENKATRAMANAN et al., 2019)	Optimal allocation	Inventory and logistics	Influenza

Source: Author

Table A2: Optimization approach and solution applied in the papers included in the rapid review and whether they consider outbreak scenarios, uncertainty, and as network problem.

#	*Authors*	*Optimization approach*	*Solution Applied*	*Outbreak*	*Uncertainty*	*Network*
1	(AGUSTO; KHAN, 2018)	Optimal Control	No	Yes	Yes	No
2	(BRIAT; VERRIEST, 2009)	Epidemiological Model	No	Yes	No	No
3	(CHEN et al., 2014)	Linear Programming	Yes	No	No	Yes
4	(DEMARTEAU; BREUER; STANDAERT, 2012)	Markov Model and Linear programming	No	No	No	No
5	(DIMITROV et al., 2009)	Network Optimization	No	Yes	Yes	Yes
6	(TEBBENS et al., 2010)	Linear Programming	No	Yes	Yes	Yes
7	(ENGINEER; KESKINOCAK; PICKERING, 2009)	Dynamic Programming	Yes	No	No	No
8	(FERREIRA; ARRUDA; MARUJO, 2018)	Markov Decision Processes	No	No	Yes	No
9	(GIRARD, 2010)	Cost analysis, forecasting	Yes	No	No	No
10	(GOLDSTEIN et al., 2010)	Simulation	Yes	Yes	Yes	Yes

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Table A2 – *Continued from previous page*

#	*Authors*	*Optimization approach*	*Solution Applied*	*Outbreak*	*Uncertainty*	*Network*
11	(HOVAV; TSADIKOVICH, 2015)	Linear Programming + Network	Yes	No	No	Yes
12	(KIM et al., 2016)	Network Optimization	No	Yes	No	Yes
13	(LAUTON; ROTHKOPF; PIBERNIK, 2019)	Game Theory	Yes	No	Yes	No
14a	(MEDLOCK; GALVANI, 2009)	Epidemiological Model	Yes	Yes	No	No
14b	(MEYERS; GALVANI; MEDLOCK, 2009)	Epidemiological Model	Yes	Yes	No	No
15	(PRECIADO et al., 2014)	Geometric Programming	Yes	Yes	Yes	Yes
16	(REN; ORDONEZ; WU, 2013)	Optimal Control + Mixed integer programming (MIP)	No	Yes	No	No
17	(RODRIGUES; MONTEIRO; TORRES, 2014)	Optimal Control	No	Yes	No	No
18	(SAMII et al., 2012)	Revenue Management	No	No	Yes	Yes

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Table A2 – *Continued from previous page*

#	*Authors*	*Optimization approach*	*Solution Applied*	*Outbreak*	*Uncertainty*	*Network*
19	(SAVACHKIN; URIBE, 2012)	Simulation	Yes	Yes	No	Yes
20	(PENG et al., 2019)	Epidemiological Model	No	Yes	Yes	Yes
21	(STANDAERT et al., 2020)	Constrained Optimization	Yes	No	No	No
22	(THAKKAR et al., 2019)	Epidemiological Model	No	No	Yes	No
23	(HOTA; SUNDARAM, 2019)	Game Theory applied to Epidemiological Model	No	Yes	Yes	Yes
24	(ENAYATI; ÖZALTIN, 2020)	Epidemiological Model, Mixed-integer programming (MIP)	No	Yes	No	No
25	(VENKATRAMANAN et al., 2019)	Epidemiological Model	No	No	No	Yes

Source: Author

APPENDIX B – SUMMARY OF STUDIES INCLUDED IN THE RAPID REVIEW

Appendix B presents a summary of each of the manuscripts included in the rapid review.

Table B1: Manuscripts included in the rapid review.

Authors	*Overview of the problem description*
(AGUSTO; KHAN, 2018)	This paper investigates the transmission dynamic of dengue and studies the impact of imperfect vaccine in the bid to control the dengue. Their approach is to write and solve the optimal control theory model and then using sensitivity analysis to test and develop control strategies that reduce transmission. Specifically, they focus on the use of insectiside and the use of vaccination. Results showed that the use of both significantly reduce transmission; also, as the cost of one increases, the use of the other increases as well.

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Table B1 – *Continued from previous page*

Authors	*Main Goal*
(BRIAT; VERRIEST, 2009)	This work presents a modified SIR model that includes a distribute delay when modeling the rate at which infected people recover. The model is validated with data from an influenza epidemic in a school and was used to develop an optimal vaccination strategy (control theory application) by measuring the cost of campaign and the time spent by the population being sick. The model is run through a numerical example.
(CHEN et al., 2014)	This paper develops a linear programming model for the distribution networks of generic WHOEPI vaccines in developing countries. They run 4 different scenarios in addition to the baseline model. The model was applied to the supply chains of 3 countries, making it easy to adapt it to different environments and use it as a planning and evaluation tool.
(DEMARTEAU; BREUER; STANDAERT, 2012)	This paper presents two model: a markov decision model and a linear program. The markov model estimates the cost and the number of cervical cancer cases for a population of 100 000 women at prevention steady state level, for each prevention strategy analysed separately. Then, using this as input, the Linear Program finds the optimal mix of cervical cancer prevention strategies to minimize the expected cervical cancer incidence rate within a fixed budget, with additional constraints on screening and vaccination coverage. It was applied in UK and Brazil data and resulted in a reduction of cancer cases.

Continued on next page

Table B1 – *Continued from previous page*

Authors	*Main Goal*
(DIMITROV et al., 2009)	This paper presents an optimization model for distributing a stockpile for treatment of infected cases during the early stages of a pandemic, prior to the wide availability of vaccines. The optimization method efficiently searches large sets of intervention strategies applied to a stochastic network model of pandemic influenza transmission within U.S. cities. Two main results arise: 1) for mildly transmissible strains, an aggressive community-based antiviral treatment strategy involving early, widespread, pro-rata distribution of antivirals to States can contribute to slowing the transmission, and 2) For more highly transmissible strains, outcomes of antiviral use are more heavily impacted by choice of distribution intervals, quantities per shipment, and timing of shipments in relation to pandemic spread. The results provide support for the management of future influenza pandemics.
(TEBBENS et al., 2010)	This paper develops a framework for determining the optimal management of a vaccine stockpile over time. It is applied to the polio vaccine stockpile for the post-eradication era. The framework includes a Linear Progam and is used to discuss issues on the development and use of the polio vaccine stockpile. This serves as context in discussions among decision makers by demonstrating how optimization may lead to useful results in terms of the ordering strategy that minimizes the present value of public health and vaccine costs.

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Table B1 – *Continued from previous page*

Authors	*Main Goal*
(ENGINEER; KESKINOCAK; PICKERING, 2009)	The authors examine the complicating characteristics of the catch-up scheduling problem and design a Dynamic Programming algorithm that constructs a schedule for a child based on their vaccination history and current age that are optimal with respect to the potential coverage provided to the child .The paper presents four solutions obtained for two different real-life scenarios for children requiring catch-up schedules.
(FERREIRA; ARRUDA; MARUJO, 2018)	This paper aims to build a Markov decision-making model to find the optimal ordering (collecting) policy and inventory management of perishable items for humanitarian organizations in continuous aid operations, considering uncertain (stochastic) demands and donations and deterministic deterioration rate. Different experiments are presented to show the different optimal ordering policies for different shelf lives of critical perishable goods. The outputs of the model are the actions that must be executed at each decision period, as a function of the inventory level at the onset of the current decision period.
(GIRARD, 2010)	This paper performs a cost analysis that compares the total costs and benefits among different immunaztion programs with varying percentages of vaccination coverage. Data from England and Wales is used. When minimizing the total social costs, they find that the program with 90% coverage maintained over time is best since the social benefits outweigh the costs.

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Table B1 – *Continued from previous page*

Authors	*Main Goal*
(GOLDSTEIN et al., 2010)	This paper develops a stratified mass-action model and tests different influenza vaccination strategies on a population in Utah using simulation and representing the dynamics as a network. Considering age as the stratification, they found that the top priority in an allocation of a sizeable quantity of seasonal influenza vaccinations goes to young children (0–6), followed by teens (14–18), then children (7–13), with the adult share being quite low. They compare the results with influenza vaccination coverage in the US.
(HOVAV; TSADIKOVICH, 2015)	In this work, the authors aimed to reduce the costs of vaccine distribution without reducing the effectiveness of the existing vaccination campaign. They consider the number of manufacturers, distributing to distribution centres and clinics. The developed Mixed Integer Programming Model is applied to simulate several different scenarios of demand and supplier numbers. They achieved a 12% reduction in costs in a simulated scenario.
(KIM et al., 2016)	This work aims to improve the distribution of vaccines based on the concept of minimal flow, and thus reduce the number of infected people until a cure emerges. They introduce the problem as the social-relation-based vaccine distribution planning problem (SVDP). Based on simulations, their model presents a better distribution strategy than a random distribution.

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Table B1 – *Continued from previous page*

Authors	*Main Goal*
(LAUTON; ROTHKOPF; PIBERNIK, 2019)	The work aims to understand the impacts faced by a non-for-profit buyer related to the inclusion of a new manufacturer. It is understood that the entry of a new generic supplier can help to reduce the cost of the product but contributes to an increase in supply chain risk. The work divides a buyer's performance into two stages: negotiation and coordination. For the bilateral negotiation model, the Nash Bargaining Model is used, and in the coordination model, a Mathematical Model is used.
(MEDLOCK; GALVANI, 2009)	This paper focused on determining optimal vaccine allocation for influenza considering five outcome measures: deaths, infections, years of life lost, contingent valuation, and economic costs. The model tracks 17 age groups and tests all possible age-based vaccination policies. They found that optimal vaccination is achieved by prioritizing schoolchildren and adults aged 30 to 39 years. An explanation for this is that children are most responsible for transmission, and their parents serve as bridges to the rest of the population. Therefore, age-specific transmission dynamics is paramount to the optimal allocation of influenza vaccines.

Continued on next page

Table B1 – *Continued from previous page*

Authors	*Main Goal*
(MEYERS; GALVANI; MEDLOCK, 2009)	On this ocassion, the authors focused on determining optimal vaccine allocation for influenza considering three outcome measures: deaths, infections and hospitalizations. It was found that optimal allocations of vaccine among people in different age groups and peoplewith high-risk conditions depends on the schedule of vaccine availability relative to the progress of theepidemic. For the projected schedule of H1N1 vaccine availability, the optimal strategy to reduceinfluenza-related deaths is to initial target high-risk people, followed by school-aged children (5–17) andthen young adults (18–44). The optimal strategy to minimize hospitalizations, however, is to target ages 5–44 throughout the vaccination campaign, with only a tiny amount of vaccine used on high-risk people. Optimizing at each vaccine release time independently does not give the overall optimal strategy.
(PRECIADO et al., 2014)	This work, in addition to considering the existence of vaccines, takes into account the existence of drugs that can prevent the continuation of a disease, such as an antidote. The objective then was to find the optimal distribution of both limited-budget and unlimited-budget products. The problem is solved in polynomial time using geometric programming (GP). They illustrate the solution applied to a real aerial network.

Continued on next page

Table B1 – *Continued from previous page*

Authors	*Main Goal*
(REN; ORDONEZ; WU, 2013)	This work presents a multi-city resource allocation model to distribute a limited amount of vaccine in order to minimize the total number of fatalities due to a smallpox outbreak. The model decides the amount of limited supplies to deliver and which infection control measure (isolation, ring, or mass vaccination) to use in each location in order to decrease the number of fatalities. The proposed model approximates the disease propagation dynamics in order to represent the problem as a mixed integer programming problem. The model is applied to a case study in planning an emergency response to a hypothetical national smallpox outbreak, which shows the possibility of saving a significant number of lives compared with a prorated allocation policy.
(RODRIGUES; MONTEIRO; TORRES, 2014)	This work considers a scenario where a vaccine for dengue is existent. Thus, the objective is to simulate the optimization of disease control according to vaccine efficacy and vaccine coverage. Also, the scenario where the pediatric population would be vaccinated, and the scenario where the entire population would be randomly vaccinated are simulated. They perform an analysis with an optimal control approach to understand the impact of introducing a vaccine.
(SAMII et al., 2012)	This work addresses the optimization of vaccine distribution and management of reserved stocks when there are two classes of the population. It is common for a vaccination to be carried out with priority for a portion of the population, such as health professionals. They perform numerical simulations to sense the impact of the model on the actions of different decision-makers. They conclude that in some scenarios the allocation of vaccines outweighs or impacts the reserve of vaccines for a specific population.

Continued on next page

Table B1 – *Continued from previous page*

Authors	*Main Goal*
(SAVACHKIN; URIBE, 2012)	This work uses simulation-optimization to create a dynamic vaccine allocation model. The study presents a simulation using data from 4 counties in Florida. The presented model has the capacity to redistribute resources in face of the changes that occurred during the outbreak situation. The main contribution of the study is that it gives the decision maker a model that allows him to modify the parameters as the situation of an epidemic changes.
(PENG et al., 2019)	This work presents a susceptible-infected-susceptible model. The model considers the probability of individuals becoming infected with heterogeneous spatial conditions. The study takes into account the impact of infections by individuals who move and with heterogeneous conditions of proximity. The study confirmed that the distance radius in individuals directly impacts the agility with which an epidemic is fought. The results obtained were observed through simulations.
(STANDAERT et al., 2020)	This study proposes a constrained optimization model to test influenza vaccination strategies in the American scenario. The study considers the existence of multiple vaccines and tests multiple vaccination strategies with US data. The objective was to confirm that the model can determine an optimal vaccination strategy based on different age groups when the scenario is of a limited budget.
(THAKKAR et al., 2019)	This study considers the scenario of vaccination campaigns against measles in Pakistan, and its results were used in the 2018 vaccination campaign. One of the main contributions of this study is that it considers scenarios where the supply chain infrastructure is not perfectly adequate, which matches the reality of many developing countries.

Continued on next page

Table B1 – *Continued from previous page*

Authors	*Main Goal*
(HOTA; SUNDARAM, 2019)	This study considers the scenario of decisions regarding vaccination in the face of different possibilities of human behaviour (perspection). They investigated "decentralized vaccination decisions by human decision-makers against networked SIS epidemics in a population game framework".
(ENAYATI; ÖZALTIN, 2020)	This study focuses on optimizing the vaccination strategy to halt the advance of an early-stage epidemic. The study proposes separating vaccine distribution for different age groups and regions to find the best distribution strategy. The study is composed of epidemic model models with a nonlinear mathematical program and a global optimization algorithm.
(VENKATRAMANAN et al., 2019)	This study considers the US scenario regarding seasonal Influenza. Through simulation, the study seeks to find the best way to distribute vaccines to American states, in order to reduce the risk of an epidemic. The study found that sending vaccines in advance to regions that start epidemics can reduce vaccination campaign size by 17%.

APPENDIX C – MAP OF INFORMATION SYSTEMS BEING USED BY PNI

Figure C1 shows a mapping of the information systems in use in the logistics chain of the National Immunization Program (PNI). The different systems are identified by colors, and the pools separate the departments.

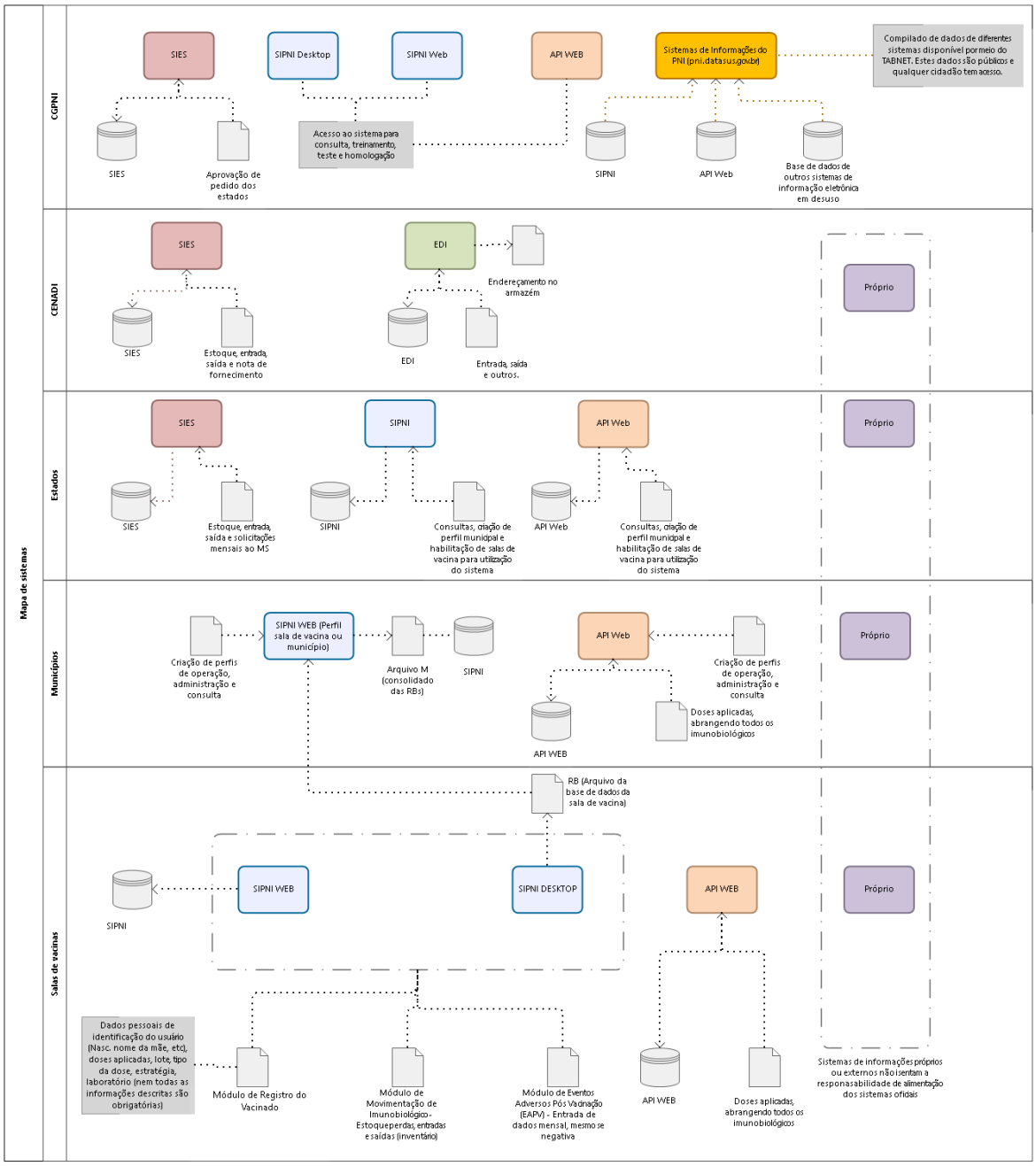

Figure C1: Illustration of the information systems in use at different instances in PNI
Source: Author

APPENDIX D – MACHINE LEARNING CODES

Below the code in Python with the three machine learning models introduced in Chapter 4 is presented.

```
import pandas as pd
import numpy as np
import matplotlib.pyplot as plt
#from sklearn import linear_model
from sklearn import ensemble

data_raw = pd.read_csv('working_data_diff.csv')
data = data_raw.iloc[1:,:] # removing first row with nan
    ↪ value

train_test_cutoff = 130

# calculating normalization factors for  delta_dosis
#m = data.iloc[:train_test_cutoff ,:].delta_dosis.mean() #
    ↪ mean
#s = data.iloc[:train_test_cutoff ,:].delta_dosis.std() #
    ↪ standard deviation
m=0
s=1

# creating a normalized delta_dosis column
data['delta_dosis_norm'] = (data.delta_dosis - m)/s

```

```
21 # creating lags
22 for i in range(1, 6):
23     data["lag_{}".format(i)] = data.delta_dosis_norm.shift(i)
24
25 # removing nans resulting from shifting
26 data = data.iloc[5:,:]
27
28 # test set
29 data_test = data.iloc[130:,:]
30
31 # train set
32 data_train = data.iloc[:130,:]
33
34 #regression column names
35 cols = [z for z in data_train if 'lag_' in z]
36
37 # fitting regression
38 #R = linear_model.Ridge(alpha=0.05)
39 R = ensemble.GradientBoostingRegressor()
40 R.fit(data[cols], data.delta_dosis_norm)
41
42 R2 = ensemble.RandomForestRegressor()
43 R2.fit(data[cols], data.delta_dosis_norm)
44
45 # in-sample prediction
46 in_sample_preds = R.predict(data_train[cols])
47 in_sample_preds2 = R2.predict(data_train[cols]) #Juliano
48
49 # stacking real data and predictions
50 w = np.vstack([np.array(data_train.delta_dosis_norm),
    ↪ in_sample_preds ]).T
51 w2 = np.vstack([np.array(data_train.delta_dosis_norm),
    ↪ in_sample_preds2 ]).T #Juliano
52
53 # plotting prediction and real in-sample data
54 plt.figure(1, figsize=(13, 6))
```

```
55 plt.plot(np.array(data_train.delta_dosis_norm),'r-o',label='
   ↪ Real data')
56 plt.plot(in_sample_preds ,'b-o', label='Predictions')
57 plt.xlabel('Number of months of training data')
58 plt.ylabel('Normalized delta')
59 plt.title('Gadient Boosting prediction and real in-train data
   ↪ ')
60 plt.legend()
61 plt.savefig('BR_BCG_01_GB_NORM_TRAIN.png')
62
63 #Juliano
64 plt.figure(2, figsize=(13, 6))
65 plt.plot(np.array(data_train.delta_dosis_norm),'r-o', label='
   ↪ Real data')
66 plt.plot(in_sample_preds2 ,'b-o', label='Predictions')
67 plt.xlabel('Number of months of training data')
68 plt.ylabel('Normalized delta')
69 plt.title('Random Forest Regresssor prediction and real in-
   ↪ train data')
70 plt.legend()
71 plt.savefig('BR_BCG_02_RFR_NORM_TRAIN.png')
72
73 # calculating MSE
74 in_sample_err = np.sqrt(1/float(len(w))*np.dot((w[:,0]-w
   ↪ [:,1]), (w[:,0]-w[:,1])))
75 in_sample_err2 = np.sqrt(1/float(len(w2))*np.dot((w2[:,0]-w2
   ↪ [:,1]), (w2[:,0]-w2[:,1])))
76
77 # out-sample predictions
78 out_sample_preds = R.predict(data_test[cols])
79 out_sample_preds2 = R2.predict(data_test[cols])
80
81 out_sample_preds_ens = (out_sample_preds+out_sample_preds2)
   ↪ *0.5
82
83 # stacking real data and predictions
```

```
84 out_sample_w = np.vstack([np.array(data_test.delta_dosis_norm
     ↪ ), out_sample_preds]).T
85
86 # stacking real data and predictions
87 out_sample_w2 = np.vstack([np.array(data_test.
     ↪ delta_dosis_norm), out_sample_preds2]).T
88
89 # stacking real data and predictions
90 out_sample_w_ens = np.vstack([np.array(data_test.
     ↪ delta_dosis_norm), out_sample_preds_ens]).T
91
92 # plotting prediction and real in-sample data
93 plt.figure(3, figsize=(13, 6))
94 plt.plot(np.array(data_test.delta_dosis_norm),'r-o',label='
     ↪ Real data')
95 plt.plot(out_sample_preds,'b-o', label='Predictions')
96 plt.xlabel('Number of months of test data')
97 plt.title('Gadient Boosting predictions and real in-test data
     ↪ ')
98 plt.legend()
99 plt.savefig('BR_BCG_03_GB_NORM_TEST.png')
100
101 plt.figure(4, figsize=(13, 6))
102 plt.plot(np.array(data_test.delta_dosis_norm),'r-o',label='
     ↪ Real data')
103 plt.plot(out_sample_preds2,'b-o',label='Predictions')
104 plt.xlabel('Number of months of test data')
105 plt.title('Random Forest Regresssor predictions and real in-
     ↪ test data')
106 plt.legend()
107 plt.savefig('BR_BCG_04_RFR_NORM_TEST.png')
108
109 # calculating MSE
110 out_sample_err = np.sqrt(1/float(len(out_sample_w))*np.dot((
     ↪ out_sample_w[:,0]-out_sample_w[:,1]), (out_sample_w
     ↪ [:,0]-out_sample_w[:,1])))
```

```
111
112 # calculating MSE
113 out_sample_err2 = np.sqrt(1/float(len(out_sample_w2))*np.dot
    ↪ ((out_sample_w2[:,0]-out_sample_w2[:,1]), (
    ↪ out_sample_w2[:,0]-out_sample_w2[:,1])))
114
115 # calculating MSE
116 out_sample_err_ens = np.sqrt(1/float(len(out_sample_w_ens))*
    ↪ np.dot((out_sample_w_ens[:,0]-out_sample_w_ens[:,1]), (
    ↪ out_sample_w_ens[:,0]-out_sample_w_ens[:,1])))
117
118 # recreating dosis values from dosis diff
119 # 6/1/2004  1788079
120
121 # in-sample dosis preds
122 d_pred_in_sample = []
123 dosis = 1788079
124 for i,x in enumerate(in_sample_preds):
125     # rescaling
126     x_hat = (x+m)*s
127     d_pred_in_sample.append(dosis+x)
128     dosis = data_train.iloc[i,:].dosis_applied
129
130 d_pred_in_sample = np.array(d_pred_in_sample)
131
132 plt.figure(5, figsize=(13, 6))
133 plt.plot(np.array(data_train.dosis_applied),'r-o',label='Real
    ↪  data')
134 plt.plot(d_pred_in_sample, 'b-o', label='Predictions')
135 plt.xlabel('Number of months of train data')
136 plt.ylabel('Number of dosis')
137 plt.title('Gradient Boosting and Random Forest Regression
    ↪ predictions and real train data')
138 plt.legend()
139 plt.savefig('BR_BCG_05_GBRFR_REAL_TRAIN.png')
140
```

```
141 # out-sample dosis preds
142 d_pred_out_sample = []
143 dosis = 1314352
144 for i,x in enumerate(out_sample_preds):
145     # rescaling
146     x_hat = (x+m)*s
147     d_pred_out_sample.append(dosis+x)
148     dosis = data_test.iloc[i,:].dosis_applied
149 
150 d_pred_out_sample = np.array(d_pred_out_sample)
151 
152 plt.figure(6, figsize=(13, 6))
153 plt.plot(np.array(data_test.dosis_applied),'r-o', label='Real
      ↪  data')
154 plt.plot(d_pred_out_sample, 'b-o',label='Predictions')
155 plt.xlabel('Number of months of test data')
156 plt.ylabel('Number of dosis')
157 plt.title('Gradient Boosting and Random Forest Regression
      ↪ predictions and real test data')
158 plt.legend()
159 plt.savefig('BR_BCG_06_GBRFR_REAL_TEST.png')
```

APPENDIX E – MACHINE LEARNING OUTPUT GRAPHS

This session presents the prediction curves generated by the model developed. The following figures were generated by applying the model to the data compiled from Brazil and also from some states for comparison purposes.

The following sections provide graphical representations of actual historical data and model forecasts.

E.1 Gradient Boosting preliminary results

Figures E1 and E2 illustrate the comparison between the output data of the Gradient Boosting model and the real Brazil's historical data in the training and test data, respectively.

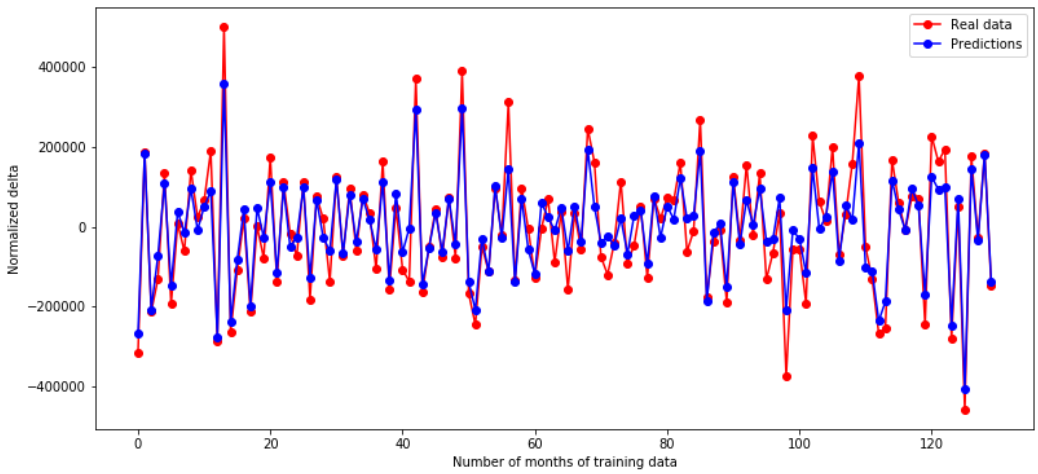

Figure E1: Gadient Boosting prediction and real in-train data for Brazil.

Source: Author.

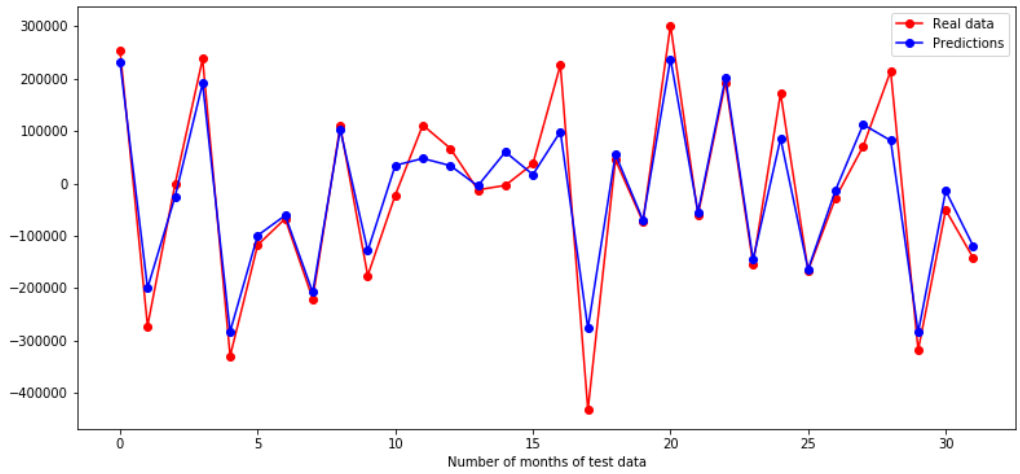

Figure E2: Gadient Boosting prediction and real in-test data for Brazil.

Source: Author.

E.2 Random Forest Regressor preliminary results

Figures E3 and E4 illustrate the comparison between the output data of the Random Forest Regressor model and the real Brazil's historical data in the training and test data, respectively.

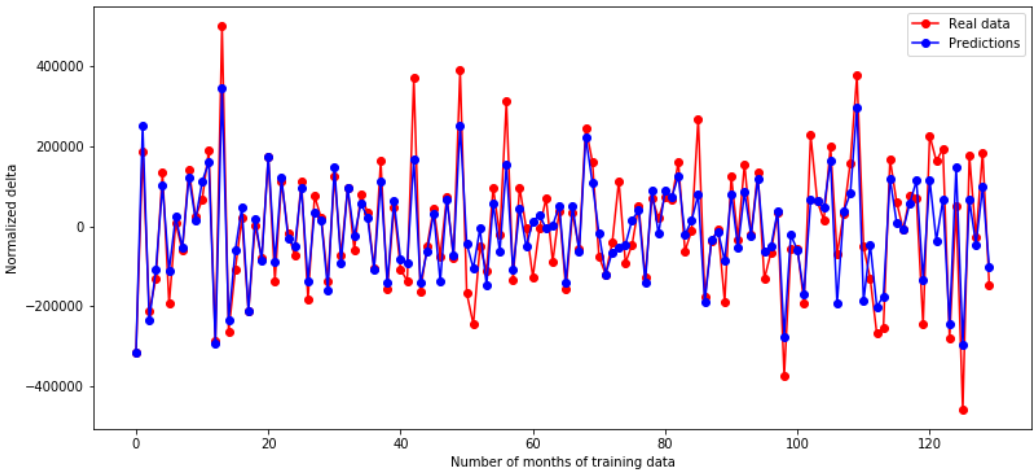

Figure E3: Random Forest Regressor prediction and real in-train data for Brazil.

Source: Author.

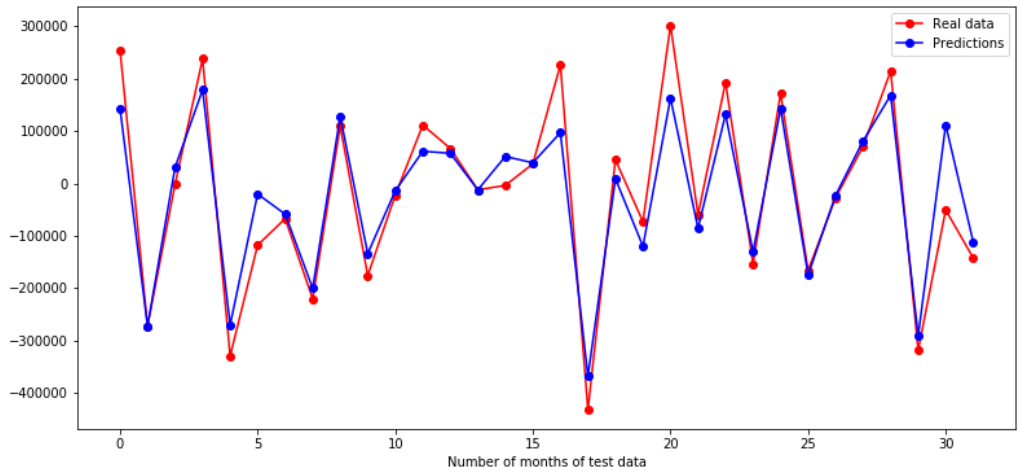

Figure E4: Random Forest Regressor prediction and real in-test data for Brazil.

Source: Author.

E.3 Gradient Boosting and Random Forest Regressor preliminary results for Brazil

Figures E5 and E6 illustrate the comparison between the output data of the Random Forest Regressor model with in addition to the Gradient Boosting model with the real Brazil's historical data in the training and test data, respectively. The data presented here present real numbers of doses, that is, they are non-normalized data.

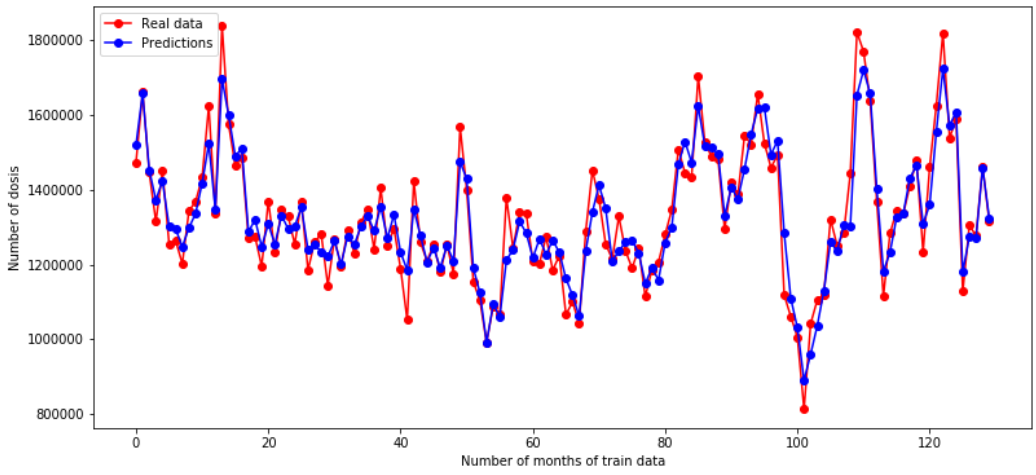

Figure E5: Gadient Boosting and Random Forest Regressor prediction and real in-train data for Brazil

Source: Author.

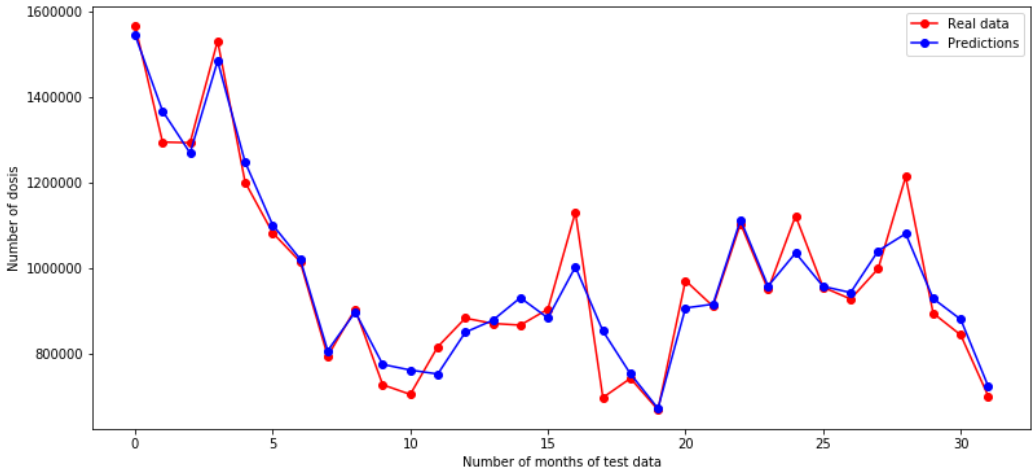

Figure E6: Gadient Boosting and Random Forest Regressor prediction and real in-test data for Brazil.

Source: Author.

E.4 Scenario: States

In this section, the model is applied in forecasting exclusive demand for states. As it is still in the development and adaptation phase, it is being tested with data from São Paulo state. The final version of this study should include other Brazilian states.

E.4.1 Scenario: São Paulo

This section presents the application of the machine learning model in the historical data of São Paulo.

Gradient Boosting preliminary results: Figures E7 and E8 illustrate the comparison between the output data of the Gradient Boosting model and the real São Paulo's historical data in the training and test data, respectively.

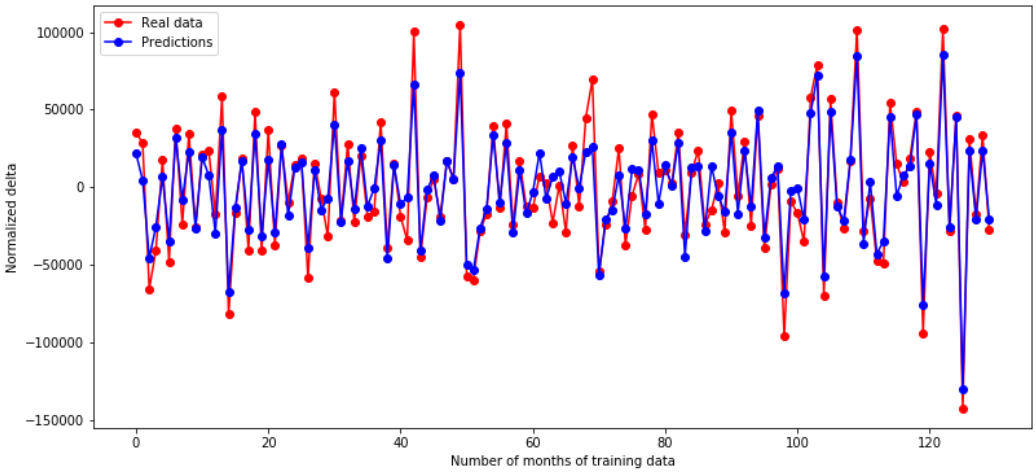

Figure E7: Gadient Boosting prediction and real in-train data for São Paulo State.

Source: Author.

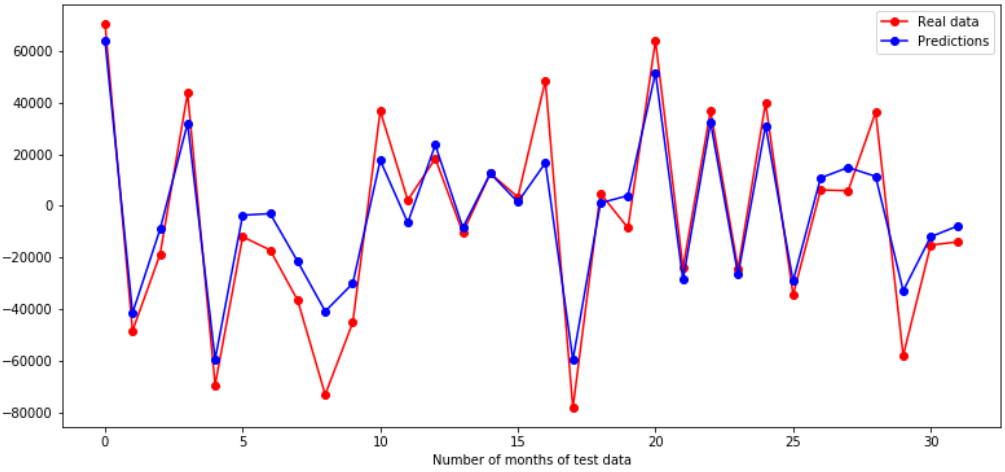

Figure E8: Gadient Boosting prediction and real in-test data for São Paulo State.

Source: Author.

Random Forest Regressor preliminary results for São Paulo State: Figures E9 and E10 illustrate the comparison between the output data of the Random Forest Regressor model and the real São Paulo's historical data in the training and test data, respectively.

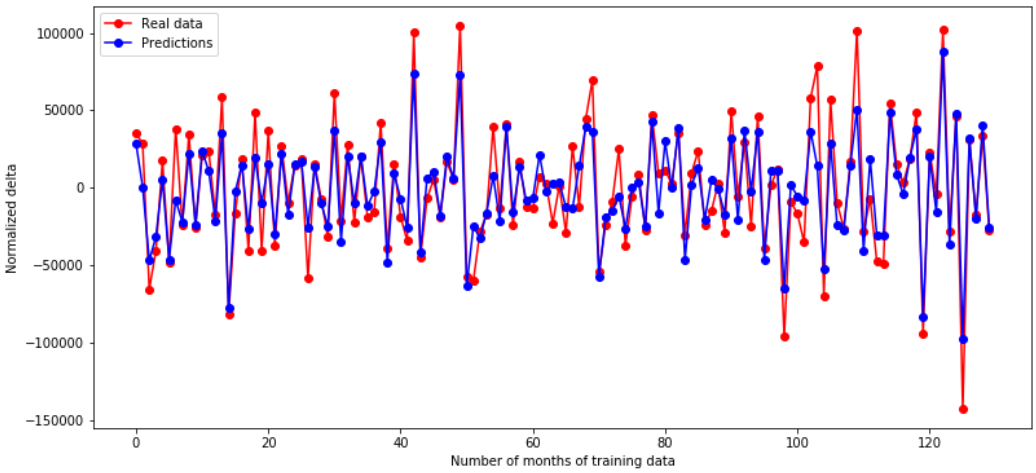

Figure E9: Random Forest Regressor prediction and real in-train data for São Paulo State.

Source: Author.

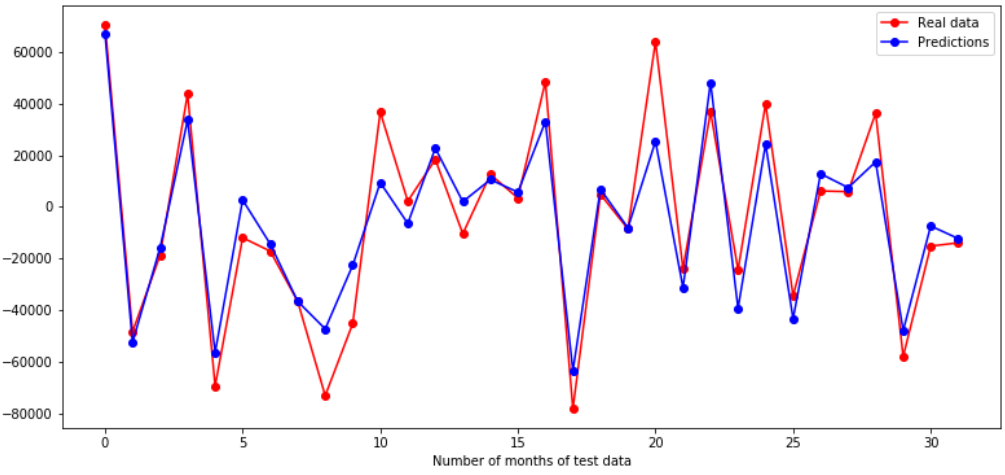

Figure E10: Random Forest Regressor prediction and real in-test data for São Paulo State.

Source: Author.

Gradient Boosting and Random Forest Regressor preliminary results: Figures E11 and E12 illustrate the comparison between the output data of the Random Forest Regressor model with in addition to the Gradient Boosting model with the real São Paulo's historical data in the training and test data, respectively.

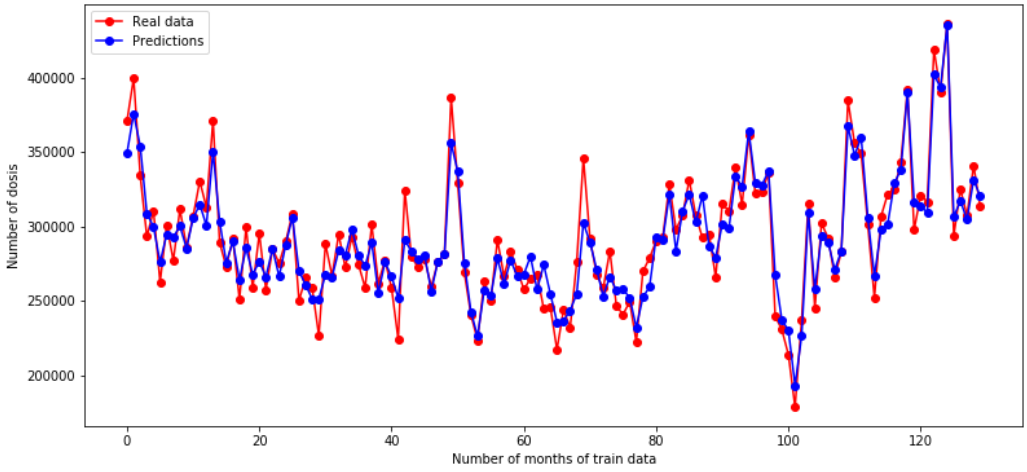

Figure E11: Gadient Boosting and Random Forest Regressor prediction and real in-train data for São Paulo State.

Source: Author.

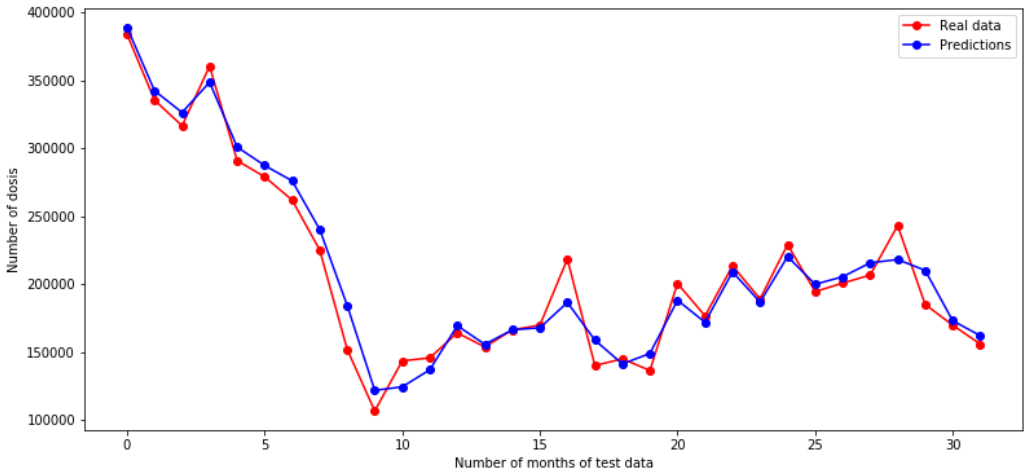

Figure E12: Gadient Boosting and Random Forest Regressor prediction and real in-test data.

Source: Author.

APPENDIX F – DETERMINISTIC OPTIMIZATION MODEL

The deterministic optimization model first introduced in Chapter 5 is presented below written in GAMS language. The model below is considering 4 states and 3 months, so it is easier to understand its write.

```
1
2  $title vaccine allocation
3  Set
4       i 'states'   /RO,AC,AM,RR/
5       k 'month'    /1*3/;
6  Alias (i, j);
7  Parameter
8       is(i) 'initial stock of each state'
9           /RO   1000
10    AC   1000
11    AM   1000
12    RR   1000/
13
14      iud(i) 'initial unmet demand'
15          /RO   200
16    AC   0
17    AM   200
18    RR   0/
19
20      fi 'initial stock of federal government'
21          /10000/
22
```

```
23      h(i) 'minimum amount of vaccines for interstate exchange
    ↪ of the state i'
24          /RO       1000
25           AC       1000
26           AM       1000
27           RR       1000/
28
29      c 'cost of the vaccine'
30           /1/
31
32      p(i) 'cost of unmet demand in state i'
33          /RO  0.9
34    AC  0.4
35    AM  1.9
36    RR  0.2/
37
38      v   'holding cost for federal government'
39           /0.2/
40
41      q(i) 'holding cost for state i'
42          /RO  0.099
43    AC  0.1
44    AM  0.098
45    RR  0.1/
46
47      t(i) 'cost of transportation from federal stock to state
    ↪ i'
48           /RO  3.473
49    AC  4.007
50    AM  4.374
51    RR  5.159/
52
53      BigM   'big M'
54      /10000000000/
55
56      a   'alpha'
```

```
57      /0.70/
58
59      b    'beta'
60      /0.0/;
61
62  Table d(i,k)      'predicted demand of vaccines of state i in
    ↪ month k'
63              1  2  3
64    RO   2186   1784   2206
65    AC   1060   1039   1148
66    AM   6577   5290   5890
67    RR   746      843      730;
68
69  Table r(i,j)      'cost of transportation from state i to state
    ↪  j'
70              RO   AC   AM   RR
71    RO   1000   0.544  0.901  1.686
72    AC   0.544  1000   1.445  2.23
73    AM   0.901  1.445  1000   0.785
74    RR   1.686  2.23   0.785  1000;
75
76  Positive Variables
77
78      f(k)          'new vaccines in the federal stock in month k
    ↪ '
79      m(i,k)        'unmet demand of state i in the end of month
    ↪ k'
80      n(i,k)        'surplus of state i in the end of month k'
81      y(i,j,k)      'number of vaccines to be sent from state i
    ↪ to state j in the beginning of month k'
82      x(i,k)        'number of new vaccines sent from federal
    ↪ stock to state i in the beginning of month k'
83      s(k)          'surplus of federal in the end of month k';
84
85  Variable
86      z                        'total cost of vaccine allocation';
```

```
87
88 Binary Variable u(i,j,k)    'it will help to define if there
   ↪ will be vaccines sent from the state i to state j in
   ↪ the month k';
89
90
91 Equation
92     cost                  'objective function'
93     demand(i,k)           'observe relation demand x order'
94     federalbalance(k)     'update federal stock'
95     excapacity(i,j,k)     'used to determine a maximum amount
   ↪ of ZERO or M vaccines permitted to be send to other
   ↪ state.'
96     minamount(i,j,k)      'check if the state can send vaccine
   ↪ and, if yes, the minimum amount allowed'
97     percentage(i,k)       'check percentage of unmet demand'
98     unmetattheend(i,k)    'guarantee that all demand is
   ↪ satisfied in the last month';
99
100
101
102 cost..                   z =e= sum((k), c*f(k)) + sum((i,k), p
   ↪ (i)*m(i,k)) + sum((i,k), q(i)*n(i,k)) + sum((i,k), (1-a
   ↪ )*t(i)*x(i,k)) + sum((i,j,k), r(i,j)*y(i,j,k)) + sum((k
   ↪ ), v*s(k));
103
104 demand(i,k)..            x(i,k) - m(i,k-1) + is(i)$(ord(k)=1)
   ↪ - iud(i) + n(i,k-1) - sum(j, y(i,j,k)) + sum(j, y(j,i,k
   ↪ )) =e= d(i,k) - m(i,k) + n(i,k);
105
106 federalbalance(k)..     f(k)+ fi$(ord(k)=1) + s(k-1) -s(k) =e
   ↪ = sum(i, x(i,k));
107
108 excapacity(i,j,k)..     y(i,j,k) =l= BigM*u(i,j,k);
109
110 minamount(i,j,k)..      y(i,j,k) =g= h(i)*u(i,j,k);
```

```
111
112 percentage(i,k)..        m(i,k) =l= (1-b)*d(i,k);
113
114 unmetattheend(i,k)..     m(i,'3') =e= 0;
115
116
117
118 model vaccineallocation /all/;
119 solve vaccineallocation using mip minimizing z;
```

APPENDIX G – DETERMINISTIC OPTIMIZATION MODEL OUTPUT

The following file is a version of the output file of the deterministic optimization model issued by NEOS Server. To get the results the model was fed with data from 4 states and 3 months, so it is easier to understand its results.

NEOS Server Deterministic Optimization Model Output.txt

```
NEOS Server Home


   NEOS Server Version 5.0
   Job#     : 8059300
   Password : GEeMIqQC
   User     : None
   Solver   : go:ANTIGONE:GAMS
   Start    : 2020-04-03 17:41:47
   End      : 2020-04-03 17:42:06
   Host     : NEOS HTCondor Pool

   Disclaimer:

   This information is provided without any express or
   implied warranty. In particular, there is no warranty
   of any kind concerning the fitness of this
   information  for any particular purpose.
Executed on prod-exec-5.neos-server.org
GAMS 30.1.0  re01a340 Released Jan 10, 2020 LEX-LEG x86 64bit/Linux 04/03/20 17:42:05 Page 1
```

```
vaccine allocation
C o m p i l a t i o n



COMPILATION TIME     =        0.000 SECONDS      3 MB  30.1.0 re01a340 LEX-LEG
GAMS 30.1.0  re01a340 Released Jan 10, 2020 LEX-LEG x86 64bit/Linux 04/03/20 17:42:05 Page 2
vaccine allocation
Model Statistics    SOLVE vaccineallocation Using MIP From line 115


MODEL STATISTICS

BLOCKS OF EQUATIONS           6     SINGLE EQUATIONS          124
BLOCKS OF VARIABLES           8     SINGLE VARIABLES          139
NON ZERO ELEMENTS           439     DISCRETE VARIABLES         48


GENERATION TIME      =        0.003 SECONDS      4 MB  30.1.0 re01a340 LEX-LEG


EXECUTION TIME       =        0.004 SECONDS      4 MB  30.1.0 re01a340 LEX-LEG
GAMS 30.1.0  re01a340 Released Jan 10, 2020 LEX-LEG x86 64bit/Linux 04/03/20 17:42:05 Page 3
vaccine allocation
Solution Report     SOLVE vaccineallocation Using MIP From line 115


               S O L V E      S U M M A R Y

     MODEL   vaccineallocation   OBJECTIVE  z
     TYPE    MIP                 DIRECTION  MINIMIZE
     SOLVER  XPRESS              FROM LINE  115


 RESOURCE USAGE, LIMIT          0.028      1000.000
 ITERATION COUNT, LIMIT        30    2000000000

FICO-Xpress      30.1.0 re01a340 Released Jan 10, 2020 LEG x86 64bit/Linux

Xpress Optimizer 33.01
Xpress Solver 64bit v8.5.8 Nov 14 2018
fixing discrete vars and re-solving as an LP.
```

```
fixed LP solved successfully, objective = 39230.1696.
Integer solution proven optimal.
MIP solution  :      39230.169600
Best possible :      39230.169600
Absolute gap  :          0.000000     optca :          0.000000
Relative gap  :          0.000000     optcr :          0.100000


                       LOWER     LEVEL     UPPER    MARGINAL

---- EQU cost            .         .         .        1.000

  cost  objective function

---- EQU demand  observe relation demand x order

        LOWER     LEVEL     UPPER    MARGINAL

RO.1  1186.000  1186.000  1186.000     1.944
RO.2  1784.000  1784.000  1784.000     2.042
RO.3  2206.000  2206.000  2206.000     1.142
AC.1    60.000    60.000    60.000     2.104
AC.2  1039.000  1039.000  1039.000     2.202
AC.3  1148.000  1148.000  1148.000     1.802
AM.1  5577.000  5577.000  5577.000     2.214
AM.2  5290.000  5290.000  5290.000     2.312
AM.3  5890.000  5890.000  5890.000     1.900
RR.1  -254.000  -254.000  -254.000     2.448
RR.2   843.000   843.000   843.000     2.548
RR.3   730.000   730.000   730.000     2.348

---- EQU federalbalance  update federal stock

     LOWER     LEVEL     UPPER    MARGINAL

1 -1.000E+4 -1.000E+4 -1.000E+4     0.902
2      .         .         .        1.000
3      .         .         .        0.800

---- EQU excapacity  used to determine a maximum amount of ZERO or M vaccines p
                     ermitted to be send to other state.

           LOWER     LEVEL     UPPER    MARGINAL
```

```
RO.RO.1     -INF       .          .          .
RO.RO.2     -INF       .          .          .
RO.RO.3     -INF       .          .          .
RO.AC.1     -INF       .          .          .
RO.AC.2     -INF       .          .          .
RO.AC.3     -INF       .          .       -0.116
RO.AM.1     -INF       .          .          .
RO.AM.2     -INF       .          .          .
RO.AM.3     -INF       .          .          .
RO.RR.1     -INF       .          .          .
RO.RR.2     -INF       .          .          .
RO.RR.3     -INF       .          .          .
AC.RO.1     -INF       .          .          .
AC.RO.2     -INF       .          .          .
AC.RO.3     -INF       .          .          .
AC.AC.1     -INF       .          .          .
AC.AC.2     -INF       .          .          .
AC.AC.3     -INF       .          .          .
AC.AM.1     -INF       .          .          .
AC.AM.2     -INF       .          .          .
AC.AM.3     -INF       .          .          .
AC.RR.1     -INF       .          .          .
AC.RR.2     -INF       .          .          .
AC.RR.3     -INF       .          .          .
AM.RO.1     -INF       .          .          .
AM.RO.2     -INF       .          .          .
AM.RO.3     -INF       .          .          .
AM.AC.1     -INF       .          .          .
AM.AC.2     -INF       .          .          .
AM.AC.3     -INF       .          .          .
AM.AM.1     -INF       .          .          .
AM.AM.2     -INF       .          .          .
AM.AM.3     -INF       .          .          .
AM.RR.1     -INF       .          .          .
AM.RR.2     -INF       .          .          .
AM.RR.3     -INF       .          .          .
RR.RO.1     -INF       .          .          .
RR.RO.2     -INF       .          .          .
RR.RO.3     -INF       .          .          .
RR.AC.1     -INF       .          .          .
RR.AC.2     -INF       .          .          .
RR.AC.3     -INF       .          .          .
```

```
RR.AM.1     -INF        .          .          .
RR.AM.2     -INF        .          .          .
RR.AM.3     -INF        .          .          .
RR.RR.1     -INF        .          .          .
RR.RR.2     -INF        .          .          .
RR.RR.3     -INF        .          .          .

---- EQU minamount  check if the state can send vaccine and, if yes, the minimu
                    m amount allowed

            LOWER      LEVEL      UPPER     MARGINAL

RO.RO.1       .          .         +INF        .
RO.RO.2       .          .         +INF        .
RO.RO.3       .          .         +INF        .
RO.AC.1       .          .         +INF        .
RO.AC.2       .          .         +INF        .
RO.AC.3       .          .         +INF        .
RO.AM.1       .          .         +INF        .
RO.AM.2       .          .         +INF        .
RO.AM.3       .          .         +INF        .
RO.RR.1       .          .         +INF        .
RO.RR.2       .          .         +INF        .
RO.RR.3       .          .         +INF        .
AC.RO.1       .          .         +INF        .
AC.RO.2       .          .         +INF        .
AC.RO.3       .          .         +INF        .
AC.AC.1       .          .         +INF        .
AC.AC.2       .          .         +INF        .
AC.AC.3       .          .         +INF        .
AC.AM.1       .          .         +INF        .
AC.AM.2       .          .         +INF        .
AC.AM.3       .          .         +INF        .
AC.RR.1       .          .         +INF        .
AC.RR.2       .          .         +INF        .
AC.RR.3       .          .         +INF        .
AM.RO.1       .          .         +INF        .
AM.RO.2       .          .         +INF        .
AM.RO.3       .          .         +INF        .
AM.AC.1       .          .         +INF        .
AM.AC.2       .          .         +INF        .
AM.AC.3       .          .         +INF        .
AM.AM.1       .          .         +INF        .
```

```
AM.AM.2      .          .        +INF       .
AM.AM.3      .          .        +INF       .
AM.RR.1      .          .        +INF       .
AM.RR.2      .          .        +INF       .
AM.RR.3      .          .        +INF       .
RR.RO.1      .          .        +INF       .
RR.RO.2      .          .        +INF       .
RR.RO.3      .          .        +INF       .
RR.AC.1      .          .        +INF       .
RR.AC.2      .          .        +INF       .
RR.AC.3      .          .        +INF       .
RR.AM.1      .          .        +INF       .
RR.AM.2      .          .        +INF       .
RR.AM.3      .          .        +INF       .
RR.RR.1      .          .        +INF       .
RR.RR.2      .          .        +INF       .
RR.RR.3      .          .        +INF       .

---- EQU percentage  check percentage of unmet demand

        LOWER     LEVEL     UPPER    MARGINAL

RO.1     -INF       .     2186.000      .
RO.2     -INF       .     1784.000      .
RO.3     -INF   2206.000  2206.000    -0.242
AC.1     -INF       .     1060.000      .
AC.2     -INF       .     1039.000      .
AC.3     -INF   1148.000  1148.000    -1.402
AM.1     -INF       .     6577.000      .
AM.2     -INF       .     5290.000      .
AM.3     -INF   5890.000  5890.000      .
RR.1     -INF       .      746.000      .
RR.2     -INF       .      843.000      .
RR.3     -INF    730.000   730.000    -2.148

---- VAR f  new vaccines in the federal stock in month k

     LOWER     LEVEL     UPPER    MARGINAL

1      .          .        +INF      0.098
2      .     5525.000      +INF       .
3      .          .        +INF      0.200
```

---- VAR m unmet demand of state i in the end of month k

	LOWER	LEVEL	UPPER	MARGINAL
RO.1	.	.	+INF	0.998
RO.2	.	.	+INF	.
RO.3	.	2206.000	+INF	.
AC.1	.	.	+INF	0.498
AC.2	.	.	+INF	.
AC.3	.	1148.000	+INF	.
AM.1	.	.	+INF	1.998
AM.2	.	.	+INF	1.488
AM.3	.	5890.000	+INF	.
RR.1	.	.	+INF	0.300
RR.2	.	.	+INF	.
RR.3	.	730.000	+INF	.

---- VAR n surplus of state i in the end of month k

	LOWER	LEVEL	UPPER	MARGINAL
RO.1	.	.	+INF	1.0000E-3
RO.2	.	.	+INF	0.999
RO.3	.	.	+INF	1.241
AC.1	.	.	+INF	0.002
AC.2	.	.	+INF	0.500
AC.3	.	.	+INF	1.902
AM.1	.	3177.000	+INF	.
AM.2	.	.	+INF	0.510
AM.3	.	.	+INF	1.998
RR.1	.	254.000	+INF	.
RR.2	.	.	+INF	0.300
RR.3	.	.	+INF	2.448

---- VAR y number of vaccines to be sent from state i to state j in the beginning of month k

	LOWER	LEVEL	UPPER	MARGINAL
RO.RO.1	.	.	+INF	1000.000
RO.RO.2	.	.	+INF	1000.000
RO.RO.3	.	.	+INF	1000.000
RO.AC.1	.	.	+INF	0.384

RO.AC.2	.	.	+INF	0.384
RO.AC.3	.	.	+INF	.
RO.AM.1	.	.	+INF	0.631
RO.AM.2	.	.	+INF	0.631
RO.AM.3	.	.	+INF	0.143
RO.RR.1	.	.	+INF	1.182
RO.RR.2	.	.	+INF	1.180
RO.RR.3	.	.	+INF	0.480
AC.RO.1	.	.	+INF	0.704
AC.RO.2	.	.	+INF	0.704
AC.RO.3	.	.	+INF	1.204
AC.AC.1	.	.	+INF	1000.000
AC.AC.2	.	.	+INF	1000.000
AC.AC.3	.	.	+INF	1000.000
AC.AM.1	.	.	+INF	1.335
AC.AM.2	.	.	+INF	1.335
AC.AM.3	.	.	+INF	1.347
AC.RR.1	.	.	+INF	1.886
AC.RR.2	.	.	+INF	1.884
AC.RR.3	.	.	+INF	1.684
AM.RO.1	.	.	+INF	1.171
AM.RO.2	.	.	+INF	1.171
AM.RO.3	.	.	+INF	1.659
AM.AC.1	.	.	+INF	1.555
AM.AC.2	.	.	+INF	1.555
AM.AC.3	.	.	+INF	1.543
AM.AM.1	.	.	+INF	1000.000
AM.AM.2	.	.	+INF	1000.000
AM.AM.3	.	.	+INF	1000.000
AM.RR.1	.	.	+INF	0.552
AM.RR.2	.	.	+INF	0.550
AM.RR.3	.	.	+INF	0.337
RR.RO.1	.	.	+INF	2.190
RR.RO.2	.	.	+INF	2.192
RR.RO.3	.	.	+INF	2.892
RR.AC.1	.	.	+INF	2.574
RR.AC.2	.	.	+INF	2.576
RR.AC.3	.	.	+INF	2.776
RR.AM.1	.	.	+INF	1.018
RR.AM.2	.	.	+INF	1.021
RR.AM.3	.	.	+INF	1.233
RR.RR.1	.	.	+INF	1000.000
RR.RR.2	.	.	+INF	1000.000

```
RR.RR.3      .          .        +INF   1000.000

---- VAR x  number of new vaccines sent from federal stock to state i in the be
            ginning of month k

        LOWER     LEVEL     UPPER    MARGINAL

RO.1      .     1186.000     +INF       .
RO.2      .     1784.000     +INF       .
RO.3      .          .       +INF     0.700
AC.1      .       60.000     +INF       .
AC.2      .     1039.000     +INF       .
AC.3      .          .       +INF     0.200
AM.1      .     8754.000     +INF       .
AM.2      .     2113.000     +INF       .
AM.3      .          .       +INF     0.212
RR.1      .          .       +INF     0.002
RR.2      .      589.000     +INF       .
RR.3      .          .       +INF       .

---- VAR s  surplus of federal in the end of month k

     LOWER     LEVEL     UPPER    MARGINAL

1      .         .        +INF     0.102
2      .         .        +INF     0.400
3      .         .        +INF     1.000

                      LOWER     LEVEL     UPPER    MARGINAL

---- VAR z              -INF  39230.170     +INF       .

  z  total cost of vaccine allocation

---- VAR u  it will help to define if there will be vaccines sent from the stat
            e i to state j in the month k

           LOWER     LEVEL     UPPER    MARGINAL

RO.RO.1      .         .        1.000      EPS
RO.RO.2      .         .        1.000      EPS
RO.RO.3      .         .        1.000      EPS
RO.AC.1      .         .        1.000      EPS
```

RO.AC.2	.	.	1.000	EPS
RO.AC.3	.	.	1.000	-1.162E+9
RO.AM.1	.	.	1.000	EPS
RO.AM.2	.	.	1.000	EPS
RO.AM.3	.	.	1.000	EPS
RO.RR.1	.	.	1.000	EPS
RO.RR.2	.	.	1.000	EPS
RO.RR.3	.	.	1.000	EPS
AC.RO.1	.	.	1.000	EPS
AC.RO.2	.	.	1.000	EPS
AC.RO.3	.	.	1.000	EPS
AC.AC.1	.	.	1.000	EPS
AC.AC.2	.	.	1.000	EPS
AC.AC.3	.	.	1.000	EPS
AC.AM.1	.	.	1.000	EPS
AC.AM.2	.	.	1.000	EPS
AC.AM.3	.	.	1.000	EPS
AC.RR.1	.	.	1.000	EPS
AC.RR.2	.	.	1.000	EPS
AC.RR.3	.	.	1.000	EPS
AM.RO.1	.	.	1.000	EPS
AM.RO.2	.	.	1.000	EPS
AM.RO.3	.	.	1.000	EPS
AM.AC.1	.	.	1.000	EPS
AM.AC.2	.	.	1.000	EPS
AM.AC.3	.	.	1.000	EPS
AM.AM.1	.	.	1.000	EPS
AM.AM.2	.	.	1.000	EPS
AM.AM.3	.	.	1.000	EPS
AM.RR.1	.	.	1.000	EPS
AM.RR.2	.	.	1.000	EPS
AM.RR.3	.	.	1.000	EPS
RR.RO.1	.	.	1.000	EPS
RR.RO.2	.	.	1.000	EPS
RR.RO.3	.	.	1.000	EPS
RR.AC.1	.	.	1.000	EPS
RR.AC.2	.	.	1.000	EPS
RR.AC.3	.	.	1.000	EPS
RR.AM.1	.	.	1.000	EPS
RR.AM.2	.	.	1.000	EPS
RR.AM.3	.	.	1.000	EPS
RR.RR.1	.	.	1.000	EPS
RR.RR.2	.	.	1.000	EPS

```
RR.RR.3      .          .        1.000      EPS


                              0 INFEASIBLE
                              0  UNBOUNDED


EXECUTION TIME       =        0.003 SECONDS      2 MB  30.1.0 re01a340 LEX-LEG


USER: NEOS server license                                G181108/0001AS-LNX
      University of Wisconsin-Madison, Computer Sciences Dept.   DC8499
      License for teaching and research at degree granting institutions



Input      /var/lib/condor/execute/dir_45218/MODEL.gms
Output     /var/lib/condor/execute/dir_45218/solve.out

 NEOS Server
```

APPENDIX H – STOCHASTIC OPTIMIZATION MODEL

The stochastic optimization model first introduced in Chapter 5 is presented below written in C, and it was fed to CPLEX Solver Software.

Linear programming file

```
\ENCODING=ISO-8859-1
\Problem name: vaccine.mps

Minimize
 R0125: C0001 + C0002 + C0003 + 2.4311 C0076 + 2.4311 C0077 + 2.4311 C0078
      + 2.8049 C0079 + 2.8049 C0080 + 2.8049 C0081 + 3.0618 C0082
      + 3.0618 C0083 + 3.0618 C0084 + 3.6113 C0085 + 3.6113 C0086
      + 3.6113 C0087 + 0.2 C0088 + 0.2 C0089 + 0.2 C0090 + 0.9 C0004 + 0.9 C0005 + 0.9 C0006 + 0.4 C0007
      + 0.4 C0008 + 0.4 C0009 + 1.9 C0010 + 1.9 C0011 + 1.9 C0012 + 0.2 C0013
      + 0.2 C0014 + 0.2 C0015 + 0.099 C0016 + 0.099 C0017 + 0.099 C0018
      + 0.1 C0019 + 0.1 C0020 + 0.1 C0021 + 0.098 C0022 + 0.098 C0023
      + 0.098 C0024 + 0.1 C0025 + 0.1 C0026 + 0.1 C0027 + 1000 C0028
      + 1000 C0029 + 1000 C0030 + 0.544 C0031 + 0.544 C0032 + 0.544 C0033
```

```
14          + 0.901 C0034 + 0.901 C0035 + 0.901 C0036 + 1.686
    ↪ C0037 + 1.686 C0038
15          + 1.686 C0039 + 0.544 C0040 + 0.544 C0041 + 0.544
    ↪ C0042 + 1000 C0043
16          + 1000 C0044 + 1000 C0045 + 1.445 C0046 + 1.445 C0047
    ↪  + 1.445 C0048
17          + 2.23 C0049 + 2.23 C0050 + 2.23 C0051 + 0.901 C0052
    ↪ + 0.901 C0053
18          + 0.901 C0054 + 1.445 C0055 + 1.445 C0056 + 1.445
    ↪ C0057 + 1000 C0058
19          + 1000 C0059 + 1000 C0060 + 0.785 C0061 + 0.785 C0062
    ↪  + 0.785 C0063
20          + 1.686 C0064 + 1.686 C0065 + 1.686 C0066 + 2.23
    ↪ C0067 + 2.23 C0068
21          + 2.23 C0069 + 0.785 C0070 + 0.785 C0071 + 0.785
    ↪ C0072 + 1000 C0073
22          + 1000 C0074 + 1000 C0075
23 Subject To
24  R0001: C0001 + C0002 + C0003 >= 0
25  R0001a: C0001 <= 50000
26  R0001b: C0002 <= 50000
27  R0001c: C0003 <= 50000
28  R0014: - C0001 + C0076 + C0079 + C0082 + C0085 + C0088  =
    ↪ 10000
29  R0015: C0002 - C0077 - C0080 - C0083 - C0086 + C0088 - C0089
    ↪   = 0
30  R0016: C0003 - C0078 - C0081 - C0084 - C0087 + C0089 - C0090
    ↪   = 0
31  R0002: C0004 - C0016 - C0031 - C0034 - C0037 + C0040 + C0052
    ↪  + C0064 + C0076
32           = 1386
33  R0003: C0007 - C0019 + C0031 - C0040 - C0046 - C0049 + C0055
    ↪  + C0067 + C0079
34           = 60
35  R0004: C0010 - C0022 + C0034 + C0046 - C0052 - C0055 - C0061
    ↪  + C0070 + C0082
```

```
          = 5777
R0005: C0013 - C0025 + C0037 + C0049 + C0061 - C0064 - C0067
  ↪  - C0070 + C0085
          = -254
R0006: - C0005 + C0017 - C0018 - C0033 - C0036 - C0039 +
  ↪ C0042 + C0054 + C0066
        + C0078  = 2206
R0007: - C0008 + C0020 - C0021 + C0033 - C0042 - C0048 -
  ↪ C0051 + C0057 + C0069
        + C0081  = 1148
R0008: - C0011 + C0023 - C0024 + C0036 + C0048 - C0054 -
  ↪ C0057 - C0063 + C0072
        + C0084  = 5890
R0009: - C0014 + C0026 - C0027 + C0039 + C0051 + C0063 -
  ↪ C0066 - C0069 - C0072
        + C0087  = 730
R0010: - C0004 + C0005 + C0016 - C0017 - C0032 - C0035 -
  ↪ C0038 + C0041 + C0053
        + C0065 + C0077  = 1784
R0011: - C0007 + C0008 + C0019 - C0020 + C0032 - C0041 -
  ↪ C0047 - C0050 + C0056
        + C0068 + C0080  = 1039
R0012: - C0010 + C0011 + C0022 - C0023 + C0035 + C0047 -
  ↪ C0053 - C0056 - C0062
        + C0071 + C0083  = 5290
R0013: - C0013 + C0014 + C0025 - C0026 + C0038 + C0050 +
  ↪ C0062 - C0065 - C0068
        - C0071 + C0086  = 843
R0017: C0028 - 10000000000 C0091 <= 0
R0018: C0029 - 10000000000 C0092 <= 0
R0019: C0030 - 10000000000 C0093 <= 0
R0020: C0031 - 10000000000 C0094 <= 0
R0021: C0032 - 10000000000 C0095 <= 0
R0022: C0033 - 10000000000 C0096 <= 0
R0023: C0034 - 10000000000 C0097 <= 0
R0024: C0035 - 10000000000 C0098 <= 0
```

```
63 R0025: C0036 - 10000000000 C0099 <= 0
64 R0026: C0037 - 10000000000 C0100 <= 0
65 R0027: C0038 - 10000000000 C0101 <= 0
66 R0028: C0039 - 10000000000 C0102 <= 0
67 R0029: C0040 - 10000000000 C0103 <= 0
68 R0030: C0041 - 10000000000 C0104 <= 0
69 R0031: C0042 - 10000000000 C0105 <= 0
70 R0032: C0043 - 10000000000 C0106 <= 0
71 R0033: C0044 - 10000000000 C0107 <= 0
72 R0034: C0045 - 10000000000 C0108 <= 0
73 R0035: C0046 - 10000000000 C0109 <= 0
74 R0036: C0047 - 10000000000 C0110 <= 0
75 R0037: C0048 - 10000000000 C0111 <= 0
76 R0038: C0049 - 10000000000 C0112 <= 0
77 R0039: C0050 - 10000000000 C0113 <= 0
78 R0040: C0051 - 10000000000 C0114 <= 0
79 R0041: C0052 - 10000000000 C0115 <= 0
80 R0042: C0053 - 10000000000 C0116 <= 0
81 R0043: C0054 - 10000000000 C0117 <= 0
82 R0044: C0055 - 10000000000 C0118 <= 0
83 R0045: C0056 - 10000000000 C0119 <= 0
84 R0046: C0057 - 10000000000 C0120 <= 0
85 R0047: C0058 - 10000000000 C0121 <= 0
86 R0048: C0059 - 10000000000 C0122 <= 0
87 R0049: C0060 - 10000000000 C0123 <= 0
88 R0050: C0061 - 10000000000 C0124 <= 0
89 R0051: C0062 - 10000000000 C0125 <= 0
90 R0052: C0063 - 10000000000 C0126 <= 0
91 R0053: C0064 - 10000000000 C0127 <= 0
92 R0054: C0065 - 10000000000 C0128 <= 0
93 R0055: C0066 - 10000000000 C0129 <= 0
94 R0056: C0067 - 10000000000 C0130 <= 0
95 R0057: C0068 - 10000000000 C0131 <= 0
96 R0058: C0069 - 10000000000 C0132 <= 0
97 R0059: C0070 - 10000000000 C0133 <= 0
98 R0060: C0071 - 10000000000 C0134 <= 0
```

```
R0061: C0072 - 10000000000 C0135 <= 0
R0062: C0073 - 10000000000 C0136 <= 0
R0063: C0074 - 10000000000 C0137 <= 0
R0064: C0075 - 10000000000 C0138 <= 0
R0065: C0028 - 1000 C0091 >= 0
R0066: C0029 - 1000 C0092 >= 0
R0067: C0030 - 1000 C0093 >= 0
R0068: C0031 - 1000 C0094 >= 0
R0069: C0032 - 1000 C0095 >= 0
R0070: C0033 - 1000 C0096 >= 0
R0071: C0034 - 1000 C0097 >= 0
R0072: C0035 - 1000 C0098 >= 0
R0073: C0036 - 1000 C0099 >= 0
R0074: C0037 - 1000 C0100 >= 0
R0075: C0038 - 1000 C0101 >= 0
R0076: C0039 - 1000 C0102 >= 0
R0077: C0040 - 1000 C0103 >= 0
R0078: C0041 - 1000 C0104 >= 0
R0079: C0042 - 1000 C0105 >= 0
R0080: C0043 - 1000 C0106 >= 0
R0081: C0044 - 1000 C0107 >= 0
R0082: C0045 - 1000 C0108 >= 0
R0083: C0046 - 1000 C0109 >= 0
R0084: C0047 - 1000 C0110 >= 0
R0085: C0048 - 1000 C0111 >= 0
R0086: C0049 - 1000 C0112 >= 0
R0087: C0050 - 1000 C0113 >= 0
R0088: C0051 - 1000 C0114 >= 0
R0089: C0052 - 1000 C0115 >= 0
R0090: C0053 - 1000 C0116 >= 0
R0091: C0054 - 1000 C0117 >= 0
R0092: C0055 - 1000 C0118 >= 0
R0093: C0056 - 1000 C0119 >= 0
R0094: C0057 - 1000 C0120 >= 0
R0095: C0058 - 1000 C0121 >= 0
R0096: C0059 - 1000 C0122 >= 0
```

```
R0097: C0060 - 1000 C0123 >= 0
R0098: C0061 - 1000 C0124 >= 0
R0099: C0062 - 1000 C0125 >= 0
R0100: C0063 - 1000 C0126 >= 0
R0101: C0064 - 1000 C0127 >= 0
R0102: C0065 - 1000 C0128 >= 0
R0103: C0066 - 1000 C0129 >= 0
R0104: C0067 - 1000 C0130 >= 0
R0105: C0068 - 1000 C0131 >= 0
R0106: C0069 - 1000 C0132 >= 0
R0107: C0070 - 1000 C0133 >= 0
R0108: C0071 - 1000 C0134 >= 0
R0109: C0072 - 1000 C0135 >= 0
R0110: C0073 - 1000 C0136 >= 0
R0111: C0074 - 1000 C0137 >= 0
R0112: C0075 - 1000 C0138 >= 0
R0113: C0004 <= 2186
R0114: C0005 <= 1784
R0115: C0006 <= 2206
R0116: C0007 <= 1060
R0117: C0008 <= 1039
R0118: C0009 <= 1148
R0119: C0010 <= 6577
R0120: C0011 <= 5290
R0121: C0012 <= 5890
R0122: C0013 <= 746
R0123: C0014 <= 843
R0124: C0015 <= 730
B1: C0091 <= 1
B2: C0092 <= 1
B3:  C0093 <= 1
B4:  C0094 <= 1
B5:  C0095 <= 1
B6:  C0096 <= 1
B7:  C0097 <= 1
B8:  C0098 <= 1
```

```
171 B9:  C0099 <= 1
172 B10:  C0100 <= 1
173 B11:  C0101 <= 1
174 B12:  C0102 <= 1
175 B13:  C0103 <= 1
176 B14:  C0104 <= 1
177 B15:  C0105 <= 1
178 B16:  C0106 <= 1
179 B17:  C0107 <= 1
180 B18:  C0108 <= 1
181 B19:  C0109 <= 1
182 B20:  C0110 <= 1
183 B21:  C0111 <= 1
184 B22:  C0112 <= 1
185 B23:  C0113 <= 1
186 B24:  C0114 <= 1
187 B25:  C0115 <= 1
188 B26:  C0116 <= 1
189 B27:  C0117 <= 1
190 B28:  C0118 <= 1
191 B29:  C0119 <= 1
192 B30:  C0120 <= 1
193 B31:  C0121 <= 1
194 B32:  C0122 <= 1
195 B33:  C0123 <= 1
196 B34:  C0124 <= 1
197 B35:  C0125 <= 1
198 B36:  C0126 <= 1
199 B37:  C0127 <= 1
200 B38:  C0128 <= 1
201 B39:  C0129 <= 1
202 B40:  C0130 <= 1
203 B41:  C0131 <= 1
204 B42:  C0132 <= 1
205 B43:  C0133 <= 1
206 B44:  C0134 <= 1
```

```
 B45:  C0135 <= 1
 B46:  C0136 <= 1
 B47:  C0137 <= 1
 B48:  C0138 <= 1
End
```

Stock file

```
STOCH     VACCINE
INDEP     DISCRETE
  RHS R0002 2208    0.33
        RHS R0002 1386    0.2
        RHS R0002 1745    0.47
        RHS R0003 1207    0.2
        RHS R0003 60    0.13
        RHS R0003 626   0.67
        RHS R0004 8076    0.2
        RHS R0004 5777    0.33
        RHS R0004 7077    0.47
        RHS R0005 906   0.47
        RHS R0005 254   0.13
        RHS R0005 168   0.4
        RHS R0006 3808    0.53
        RHS R0006 2206    0.07
        RHS R0006 2621    0.4
        RHS R0007 2907    0.4
        RHS R0007 1148    0.07
        RHS R0007 1762    0.53
        RHS R0008 8878    0.13
        RHS R0008 5890    0.4
        RHS R0008 7670    0.47
        RHS R0009 1778    0.53
        RHS R0009 730   0.2
        RHS R0009 1110    0.27
        RHS R0010 2681    0.07
        RHS R0010 1784    0.27
        RHS R0010 2298    0.67
```

```
        RHS R0011 2221    0.2
        RHS R0011 1039    0.07
        RHS R0011 1594    0.73
        RHS R0012 8785    0.13
        RHS R0012 5290    0.33
        RHS R0012 7515    0.53
        RHS R0013 1751    0.6
        RHS R0013 843   0.2
        RHS R0013 1148    0.2
    RHS R0113 3008    0.33
    RHS R0113 2186    0.2
    RHS R0113 2545    0.47
    RHS R0114 2681    0.07
    RHS R0114 1784    0.27
    RHS R0114 2298    0.67
    RHS R0115 3808    0.53
    RHS R0115 2206    0.07
    RHS R0115 2621    0.4
    RHS R0116 2207    0.2
    RHS R0116 1060    0.13
    RHS R0116 1626    0.67
    RHS R0117 2221    0.2
    RHS R0117 1039    0.07
    RHS R0117 1594    0.73
    RHS R0118 2907    0.4
    RHS R0118 1148    0.07
    RHS R0118 1762    0.53
    RHS R0119 8876    0.2
    RHS R0119 6577    0.33
    RHS R0119 7877    0.47
    RHS R0120 8785    0.13
    RHS R0120 5290    0.33
    RHS R0120 7515    0.53
    RHS R0121 8878    0.13
    RHS R0121 5890    0.4
    RHS R0121 7670    0.47
```

```
    RHS  R0122  1906     0.47
    RHS  R0122  746    0.13
    RHS  R0122  1168     0.4
    RHS  R0123  1751     0.6
    RHS  R0123  843    0.2
    RHS  R0123  1148     0.2
    RHS  R0124  1778     0.53
    RHS  R0124  730    0.2
    RHS  R0124  1110     0.27
ENDATA
```

Time file

```
TIME          VACCINE
PERIODS
    C0001     R0001      TIME1
    C0076     R0014      TIME2
ENDATA
```

Core file

```
* ENCODING=ISO-8859-1
NAME          C:\Users\Michelle\Desktop\ESI6341\Lshaped\
   ↪ Algorithm\Algorithm\vaccine.lp
ROWS
 N  R0125
 G  R0001
 L  R0001a
 L  R0001b
 L  R0001c
 E  R0014
 E  R0015
 E  R0016
 E  R0002
 E  R0003
 E  R0004
 E  R0005
 E  R0006
```

```
E  R0007
E  R0008
E  R0009
E  R0010
E  R0011
E  R0012
E  R0013
L  R0017
L  R0018
L  R0019
L  R0020
L  R0021
L  R0022
L  R0023
L  R0024
L  R0025
L  R0026
L  R0027
L  R0028
L  R0029
L  R0030
L  R0031
L  R0032
L  R0033
L  R0034
L  R0035
L  R0036
L  R0037
L  R0038
L  R0039
L  R0040
L  R0041
L  R0042
L  R0043
L  R0044
L  R0045
```

```
L  R0046
L  R0047
L  R0048
L  R0049
L  R0050
L  R0051
L  R0052
L  R0053
L  R0054
L  R0055
L  R0056
L  R0057
L  R0058
L  R0059
L  R0060
L  R0061
L  R0062
L  R0063
L  R0064
G  R0065
G  R0066
G  R0067
G  R0068
G  R0069
G  R0070
G  R0071
G  R0072
G  R0073
G  R0074
G  R0075
G  R0076
G  R0077
G  R0078
G  R0079
G  R0080
G  R0081
```

```
G   R0082
G   R0083
G   R0084
G   R0085
G   R0086
G   R0087
G   R0088
G   R0089
G   R0090
G   R0091
G   R0092
G   R0093
G   R0094
G   R0095
G   R0096
G   R0097
G   R0098
G   R0099
G   R0100
G   R0101
G   R0102
G   R0103
G   R0104
G   R0105
G   R0106
G   R0107
G   R0108
G   R0109
G   R0110
G   R0111
G   R0112
L   R0113
L   R0114
L   R0115
L   R0116
L   R0117
```

```
125 L   R0118
126 L   R0119
127 L   R0120
128 L   R0121
129 L   R0122
130 L   R0123
131 L   R0124
132 L   B1
133 L   B2
134 L   B3
135 L   B4
136 L   B5
137 L   B6
138 L   B7
139 L   B8
140 L   B9
141 L   B10
142 L   B11
143 L   B12
144 L   B13
145 L   B14
146 L   B15
147 L   B16
148 L   B17
149 L   B18
150 L   B19
151 L   B20
152 L   B21
153 L   B22
154 L   B23
155 L   B24
156 L   B25
157 L   B26
158 L   B27
159 L   B28
160 L   B29
```

```
 L   B30
 L   B31
 L   B32
 L   B33
 L   B34
 L   B35
 L   B36
 L   B37
 L   B38
 L   B39
 L   B40
 L   B41
 L   B42
 L   B43
 L   B44
 L   B45
 L   B46
 L   B47
 L   B48
COLUMNS
    C0001     R0125                          1
    C0001     R0001                          1
    C0001     R0001a                         1
    C0001     R0014                         -1
    C0002     R0125                          1
    C0002     R0001                          1
    C0002     R0001b                         1
    C0002     R0015                          1
    C0003     R0125                          1
    C0003     R0001                          1
    C0003     R0001c                         1
    C0003     R0016                          1
    C0076     R0125                     2.4311
    C0076     R0014                          1
    C0076     R0002                          1
    C0077     R0125                     2.4311
```

197	C0077	R0015	-1
198	C0077	R0010	1
199	C0078	R0125	2.4311
200	C0078	R0016	-1
201	C0078	R0006	1
202	C0079	R0125	2.8049
203	C0079	R0014	1
204	C0079	R0003	1
205	C0080	R0125	2.8049
206	C0080	R0015	-1
207	C0080	R0011	1
208	C0081	R0125	2.8049
209	C0081	R0016	-1
210	C0081	R0007	1
211	C0082	R0125	3.0618
212	C0082	R0014	1
213	C0082	R0004	1
214	C0083	R0125	3.0618
215	C0083	R0015	-1
216	C0083	R0012	1
217	C0084	R0125	3.0618
218	C0084	R0016	-1
219	C0084	R0008	1
220	C0085	R0125	3.6113
221	C0085	R0014	1
222	C0085	R0005	1
223	C0086	R0125	3.6113
224	C0086	R0015	-1
225	C0086	R0013	1
226	C0087	R0125	3.6113
227	C0087	R0016	-1
228	C0087	R0009	1
229	C0088	R0125	0.2
230	C0088	R0014	1
231	C0088	R0015	1
232	C0089	R0125	0.2

233	C0089	R0015	-1
234	C0089	R0016	1
235	C0090	R0125	0.2
236	C0090	R0016	-1
237	C0004	R0125	0.9
238	C0004	R0002	1
239	C0004	R0010	-1
240	C0004	R0113	1
241	C0005	R0125	0.9
242	C0005	R0006	-1
243	C0005	R0010	1
244	C0005	R0114	1
245	C0006	R0125	0.9
246	C0006	R0115	1
247	C0007	R0125	0.4
248	C0007	R0003	1
249	C0007	R0011	-1
250	C0007	R0116	1
251	C0008	R0125	0.4
252	C0008	R0007	-1
253	C0008	R0011	1
254	C0008	R0117	1
255	C0009	R0125	0.4
256	C0009	R0118	1
257	C0010	R0125	1.9
258	C0010	R0004	1
259	C0010	R0012	-1
260	C0010	R0119	1
261	C0011	R0125	1.9
262	C0011	R0008	-1
263	C0011	R0012	1
264	C0011	R0120	1
265	C0012	R0125	1.9
266	C0012	R0121	1
267	C0013	R0125	0.2
268	C0013	R0005	1

269	C0013	R0013	-1
270	C0013	R0122	1
271	C0014	R0125	0.2
272	C0014	R0009	-1
273	C0014	R0013	1
274	C0014	R0123	1
275	C0015	R0125	0.2
276	C0015	R0124	1
277	C0016	R0125	0.099
278	C0016	R0002	-1
279	C0016	R0010	1
280	C0017	R0125	0.099
281	C0017	R0006	1
282	C0017	R0010	-1
283	C0018	R0125	0.099
284	C0018	R0006	-1
285	C0019	R0125	0.1
286	C0019	R0003	-1
287	C0019	R0011	1
288	C0020	R0125	0.1
289	C0020	R0007	1
290	C0020	R0011	-1
291	C0021	R0125	0.1
292	C0021	R0007	-1
293	C0022	R0125	0.098
294	C0022	R0004	-1
295	C0022	R0012	1
296	C0023	R0125	0.098
297	C0023	R0008	1
298	C0023	R0012	-1
299	C0024	R0125	0.098
300	C0024	R0008	-1
301	C0025	R0125	0.1
302	C0025	R0005	-1
303	C0025	R0013	1
304	C0026	R0125	0.1

305	C0026	R0009	1
306	C0026	R0013	-1
307	C0027	R0125	0.1
308	C0027	R0009	-1
309	C0028	R0125	1000
310	C0028	R0017	1
311	C0028	R0065	1
312	C0029	R0125	1000
313	C0029	R0018	1
314	C0029	R0066	1
315	C0030	R0125	1000
316	C0030	R0019	1
317	C0030	R0067	1
318	C0031	R0125	0.544
319	C0031	R0002	-1
320	C0031	R0003	1
321	C0031	R0020	1
322	C0031	R0068	1
323	C0032	R0125	0.544
324	C0032	R0010	-1
325	C0032	R0011	1
326	C0032	R0021	1
327	C0032	R0069	1
328	C0033	R0125	0.544
329	C0033	R0006	-1
330	C0033	R0007	1
331	C0033	R0022	1
332	C0033	R0070	1
333	C0034	R0125	0.901
334	C0034	R0002	-1
335	C0034	R0004	1
336	C0034	R0023	1
337	C0034	R0071	1
338	C0035	R0125	0.901
339	C0035	R0010	-1
340	C0035	R0012	1

341	C0035	R0024	1
342	C0035	R0072	1
343	C0036	R0125	0.901
344	C0036	R0006	-1
345	C0036	R0008	1
346	C0036	R0025	1
347	C0036	R0073	1
348	C0037	R0125	1.686
349	C0037	R0002	-1
350	C0037	R0005	1
351	C0037	R0026	1
352	C0037	R0074	1
353	C0038	R0125	1.686
354	C0038	R0010	-1
355	C0038	R0013	1
356	C0038	R0027	1
357	C0038	R0075	1
358	C0039	R0125	1.686
359	C0039	R0006	-1
360	C0039	R0009	1
361	C0039	R0028	1
362	C0039	R0076	1
363	C0040	R0125	0.544
364	C0040	R0002	1
365	C0040	R0003	-1
366	C0040	R0029	1
367	C0040	R0077	1
368	C0041	R0125	0.544
369	C0041	R0010	1
370	C0041	R0011	-1
371	C0041	R0030	1
372	C0041	R0078	1
373	C0042	R0125	0.544
374	C0042	R0006	1
375	C0042	R0007	-1
376	C0042	R0031	1

377	C0042	R0079	1
378	C0043	R0125	1000
379	C0043	R0032	1
380	C0043	R0080	1
381	C0044	R0125	1000
382	C0044	R0033	1
383	C0044	R0081	1
384	C0045	R0125	1000
385	C0045	R0034	1
386	C0045	R0082	1
387	C0046	R0125	1.445
388	C0046	R0003	-1
389	C0046	R0004	1
390	C0046	R0035	1
391	C0046	R0083	1
392	C0047	R0125	1.445
393	C0047	R0011	-1
394	C0047	R0012	1
395	C0047	R0036	1
396	C0047	R0084	1
397	C0048	R0125	1.445
398	C0048	R0007	-1
399	C0048	R0008	1
400	C0048	R0037	1
401	C0048	R0085	1
402	C0049	R0125	2.23
403	C0049	R0003	-1
404	C0049	R0005	1
405	C0049	R0038	1
406	C0049	R0086	1
407	C0050	R0125	2.23
408	C0050	R0011	-1
409	C0050	R0013	1
410	C0050	R0039	1
411	C0050	R0087	1
412	C0051	R0125	2.23

413	C0051	R0007	-1
414	C0051	R0009	1
415	C0051	R0040	1
416	C0051	R0088	1
417	C0052	R0125	0.901
418	C0052	R0002	1
419	C0052	R0004	-1
420	C0052	R0041	1
421	C0052	R0089	1
422	C0053	R0125	0.901
423	C0053	R0010	1
424	C0053	R0012	-1
425	C0053	R0042	1
426	C0053	R0090	1
427	C0054	R0125	0.901
428	C0054	R0006	1
429	C0054	R0008	-1
430	C0054	R0043	1
431	C0054	R0091	1
432	C0055	R0125	1.445
433	C0055	R0003	1
434	C0055	R0004	-1
435	C0055	R0044	1
436	C0055	R0092	1
437	C0056	R0125	1.445
438	C0056	R0011	1
439	C0056	R0012	-1
440	C0056	R0045	1
441	C0056	R0093	1
442	C0057	R0125	1.445
443	C0057	R0007	1
444	C0057	R0008	-1
445	C0057	R0046	1
446	C0057	R0094	1
447	C0058	R0125	1000
448	C0058	R0047	1

449	C0058	R0095	1
450	C0059	R0125	1000
451	C0059	R0048	1
452	C0059	R0096	1
453	C0060	R0125	1000
454	C0060	R0049	1
455	C0060	R0097	1
456	C0061	R0125	0.785
457	C0061	R0004	-1
458	C0061	R0005	1
459	C0061	R0050	1
460	C0061	R0098	1
461	C0062	R0125	0.785
462	C0062	R0012	-1
463	C0062	R0013	1
464	C0062	R0051	1
465	C0062	R0099	1
466	C0063	R0125	0.785
467	C0063	R0008	-1
468	C0063	R0009	1
469	C0063	R0052	1
470	C0063	R0100	1
471	C0064	R0125	1.686
472	C0064	R0002	1
473	C0064	R0005	-1
474	C0064	R0053	1
475	C0064	R0101	1
476	C0065	R0125	1.686
477	C0065	R0010	1
478	C0065	R0013	-1
479	C0065	R0054	1
480	C0065	R0102	1
481	C0066	R0125	1.686
482	C0066	R0006	1
483	C0066	R0009	-1
484	C0066	R0055	1

485	C0066	R0103	1
486	C0067	R0125	2.23
487	C0067	R0003	1
488	C0067	R0005	-1
489	C0067	R0056	1
490	C0067	R0104	1
491	C0068	R0125	2.23
492	C0068	R0011	1
493	C0068	R0013	-1
494	C0068	R0057	1
495	C0068	R0105	1
496	C0069	R0125	2.23
497	C0069	R0007	1
498	C0069	R0009	-1
499	C0069	R0058	1
500	C0069	R0106	1
501	C0070	R0125	0.785
502	C0070	R0004	1
503	C0070	R0005	-1
504	C0070	R0059	1
505	C0070	R0107	1
506	C0071	R0125	0.785
507	C0071	R0012	1
508	C0071	R0013	-1
509	C0071	R0060	1
510	C0071	R0108	1
511	C0072	R0125	0.785
512	C0072	R0008	1
513	C0072	R0009	-1
514	C0072	R0061	1
515	C0072	R0109	1
516	C0073	R0125	1000
517	C0073	R0062	1
518	C0073	R0110	1
519	C0074	R0125	1000
520	C0074	R0063	1

521	C0074	R0111	1
522	C0075	R0125	1000
523	C0075	R0064	1
524	C0075	R0112	1
525	C0091	R0017	-10000000000
526	C0091	R0065	-1000
527	C0091	B1	1
528	C0092	R0018	-10000000000
529	C0092	R0066	-1000
530	C0092	B2	1
531	C0093	R0019	-10000000000
532	C0093	R0067	-1000
533	C0093	B3	1
534	C0094	R0020	-10000000000
535	C0094	R0068	-1000
536	C0094	B4	1
537	C0095	R0021	-10000000000
538	C0095	R0069	-1000
539	C0095	B5	1
540	C0096	R0022	-10000000000
541	C0096	R0070	-1000
542	C0096	B6	1
543	C0097	R0023	-10000000000
544	C0097	R0071	-1000
545	C0097	B7	1
546	C0098	R0024	-10000000000
547	C0098	R0072	-1000
548	C0098	B8	1
549	C0099	R0025	-10000000000
550	C0099	R0073	-1000
551	C0099	B9	1
552	C0100	R0026	-10000000000
553	C0100	R0074	-1000
554	C0100	B10	1
555	C0101	R0027	-10000000000
556	C0101	R0075	-1000

```
C0101     B11                    1
C0102     R0028          -10000000000
C0102     R0076                -1000
C0102     B12                    1
C0103     R0029          -10000000000
C0103     R0077                -1000
C0103     B13                    1
C0104     R0030          -10000000000
C0104     R0078                -1000
C0104     B14                    1
C0105     R0031          -10000000000
C0105     R0079                -1000
C0105     B15                    1
C0106     R0032          -10000000000
C0106     R0080                -1000
C0106     B16                    1
C0107     R0033          -10000000000
C0107     R0081                -1000
C0107     B17                    1
C0108     R0034          -10000000000
C0108     R0082                -1000
C0108     B18                    1
C0109     R0035          -10000000000
C0109     R0083                -1000
C0109     B19                    1
C0110     R0036          -10000000000
C0110     R0084                -1000
C0110     B20                    1
C0111     R0037          -10000000000
C0111     R0085                -1000
C0111     B21                    1
C0112     R0038          -10000000000
C0112     R0086                -1000
C0112     B22                    1
C0113     R0039          -10000000000
C0113     R0087                -1000
```

593	C0113	B23	1
594	C0114	R0040	-10000000000
595	C0114	R0088	-1000
596	C0114	B24	1
597	C0115	R0041	-10000000000
598	C0115	R0089	-1000
599	C0115	B25	1
600	C0116	R0042	-10000000000
601	C0116	R0090	-1000
602	C0116	B26	1
603	C0117	R0043	-10000000000
604	C0117	R0091	-1000
605	C0117	B27	1
606	C0118	R0044	-10000000000
607	C0118	R0092	-1000
608	C0118	B28	1
609	C0119	R0045	-10000000000
610	C0119	R0093	-1000
611	C0119	B29	1
612	C0120	R0046	-10000000000
613	C0120	R0094	-1000
614	C0120	B30	1
615	C0121	R0047	-10000000000
616	C0121	R0095	-1000
617	C0121	B31	1
618	C0122	R0048	-10000000000
619	C0122	R0096	-1000
620	C0122	B32	1
621	C0123	R0049	-10000000000
622	C0123	R0097	-1000
623	C0123	B33	1
624	C0124	R0050	-10000000000
625	C0124	R0098	-1000
626	C0124	B34	1
627	C0125	R0051	-10000000000
628	C0125	R0099	-1000

```
C0125     B35                    1
C0126     R0052          -10000000000
C0126     R0100              -1000
C0126     B36                    1
C0127     R0053          -10000000000
C0127     R0101              -1000
C0127     B37                    1
C0128     R0054          -10000000000
C0128     R0102              -1000
C0128     B38                    1
C0129     R0055          -10000000000
C0129     R0103              -1000
C0129     B39                    1
C0130     R0056          -10000000000
C0130     R0104              -1000
C0130     B40                    1
C0131     R0057          -10000000000
C0131     R0105              -1000
C0131     B41                    1
C0132     R0058          -10000000000
C0132     R0106              -1000
C0132     B42                    1
C0133     R0059          -10000000000
C0133     R0107              -1000
C0133     B43                    1
C0134     R0060          -10000000000
C0134     R0108              -1000
C0134     B44                    1
C0135     R0061          -10000000000
C0135     R0109              -1000
C0135     B45                    1
C0136     R0062          -10000000000
C0136     R0110              -1000
C0136     B46                    1
C0137     R0063          -10000000000
C0137     R0111              -1000
```

```
    C0137     B47                       1
    C0138     R0064             -10000000000
    C0138     R0112                 -1000
    C0138     B48                       1
RHS
    rhs       R0001a                50000
    rhs       R0001b                50000
    rhs       R0001c                50000
    rhs       R0014                 10000
    rhs       R0002                  1386
    rhs       R0003                    60
    rhs       R0004                  5777
    rhs       R0005                  -254
    rhs       R0006                  2206
    rhs       R0007                  1148
    rhs       R0008                  5890
    rhs       R0009                   730
    rhs       R0010                  1784
    rhs       R0011                  1039
    rhs       R0012                  5290
    rhs       R0013                   843
    rhs       R0113                  2186
    rhs       R0114                  1784
    rhs       R0115                  2206
    rhs       R0116                  1060
    rhs       R0117                  1039
    rhs       R0118                  1148
    rhs       R0119                  6577
    rhs       R0120                  5290
    rhs       R0121                  5890
    rhs       R0122                   746
    rhs       R0123                   843
    rhs       R0124                   730
    rhs       B1                        1
    rhs       B2                        1
    rhs       B3                        1
```

```
    rhs       B4                    1
    rhs       B5                    1
    rhs       B6                    1
    rhs       B7                    1
    rhs       B8                    1
    rhs       B9                    1
    rhs       B10                   1
    rhs       B11                   1
    rhs       B12                   1
    rhs       B13                   1
    rhs       B14                   1
    rhs       B15                   1
    rhs       B16                   1
    rhs       B17                   1
    rhs       B18                   1
    rhs       B19                   1
    rhs       B20                   1
    rhs       B21                   1
    rhs       B22                   1
    rhs       B23                   1
    rhs       B24                   1
    rhs       B25                   1
    rhs       B26                   1
    rhs       B27                   1
    rhs       B28                   1
    rhs       B29                   1
    rhs       B30                   1
    rhs       B31                   1
    rhs       B32                   1
    rhs       B33                   1
    rhs       B34                   1
    rhs       B35                   1
    rhs       B36                   1
    rhs       B37                   1
    rhs       B38                   1
    rhs       B39                   1
```

```
737      rhs         B40                       1
738      rhs         B41                       1
739      rhs         B42                       1
740      rhs         B43                       1
741      rhs         B44                       1
742      rhs         B45                       1
743      rhs         B46                       1
744      rhs         B47                       1
745      rhs         B48                       1
746  ENDATA
```

APPENDIX I – STOCHASTIC OPTIMIZATION MODEL RESULTS

The results generated by the stochastic optimization model first introduced in Chapter 5 is presented below.

```
1
2  Evaluating the Best Solution from M = 30 candidate solutions
     ↪ ...
3   Best average: 140207 found on iteration 1
4   Best average: 137823 found on iteration 2
5   Best average: 136680 found on iteration 5
6   Best average: 136388 found on iteration 21
7   Best average: 136109 found on iteration 23
8   Best average: 135421 found on iteration 29
9  The OPTIMAL stage 1 variables:
10  Stage 1 var 0 = 613.471
11  Stage 1 var 1 = 12356.3
12  Stage 1 var 2 = 17457.3
13  Stage 1 var 3 = 106965
14  ----------------------------------------------------------
15  Computing the UpperBound...
16  ----------------------------------------------------
17  The stage 2 variables:
18  Stage 2 var 0 = 1745
19  Stage 2 var 1 = 1784
20  Stage 2 var 2 = 3808
21  Stage 2 var 3 = 626
```

```
Stage 2 var 4 = 1039
Stage 2 var 5 = 2907
Stage 2 var 6 = 7281.27
Stage 2 var 7 = 8519.93
Stage 2 var 8 = 6460.8
Stage 2 var 9 = 906
Stage 2 var 10 = 1148
Stage 2 var 11 = 730
Stage 2 var 12 = 0
Stage 2 var 13 = 0
Stage 2 var 14 = 5892
Stage 2 var 15 = 0
Stage 2 var 16 = 0
Stage 2 var 17 = 0
Stage 2 var 18 = 0
Stage 2 var 19 = 0
Stage 2 var 20 = 0
Stage 2 var 21 = 0
Stage 2 var 22 = 0
Stage 2 var 23 = 0
Stage 2 var 24 = 0
Stage 2 var 25 = 0
Stage 2 var 26 = 0
Stage 2 var 27 = 0
Stage 2 var 28 = 0
Stage 2 var 29 = 0
Stage 2 var 30 = 0
Stage 2 var 31 = 0
Stage 2 var 32 = 0
Stage 2 var 33 = 204.266
Stage 2 var 34 = 1209.2
Stage 2 var 35 = 0
Stage 2 var 36 = 0
Stage 2 var 37 = 0
Stage 2 var 38 = 0
Stage 2 var 39 = 0
```

```
Stage 2 var 40 = 0
Stage 2 var 41 = 0
Stage 2 var 42 = 0
Stage 2 var 43 = 0
Stage 2 var 44 = 0
Stage 2 var 45 = 0
Stage 2 var 46 = 0
Stage 2 var 47 = 0
Stage 2 var 48 = 0
Stage 2 var 49 = 0
Stage 2 var 50 = 0
Stage 2 var 51 = 0
Stage 2 var 52 = 0
Stage 2 var 53 = 0
Stage 2 var 54 = 0
Stage 2 var 55 = 0
Stage 2 var 56 = 0
Stage 2 var 57 = 0
Stage 2 var 58 = 0
Stage 2 var 59 = 0
Stage 2 var 60 = 0
Stage 2 var 61 = 0
Stage 2 var 62 = 0
Stage 2 var 63 = 0
Stage 2 var 64 = 0
Stage 2 var 65 = 0
Stage 2 var 66 = 0
Stage 2 var 67 = 0
Stage 2 var 68 = 0
Stage 2 var 69 = 0
Stage 2 var 70 = 0
Stage 2 var 71 = 0
Stage 2 var 72 = 0
Stage 2 var 73 = 0
Stage 2 var 74 = 0
Stage 2 var 75 = 0
```

```
Stage 2 var 76 = 0
Stage 2 var 77 = 0
Stage 2 var 78 = 0
Stage 2 var 79 = 0
Stage 2 var 80 = 0
Stage 2 var 81 = 0
Stage 2 var 82 = 0
Stage 2 var 83 = 0
Stage 2 var 84 = 0
Stage 2 var 85 = 0
Stage 2 var 86 = 0
Stage 2 var 87 = 0
Stage 2 var 88 = 0
Stage 2 var 89 = 0
Stage 2 var 90 = 0
Stage 2 var 91 = 0
Stage 2 var 92 = 0
Stage 2 var 93 = 0
Stage 2 var 94 = 0
Stage 2 var 95 = 0
Stage 2 var 96 = 0
Stage 2 var 97 = 0
Stage 2 var 98 = 0
Stage 2 var 99 = 0
Stage 2 var 100 = 0
Stage 2 var 101 = 0
Stage 2 var 102 = 0
Stage 2 var 103 = 0
Stage 2 var 104 = 0
Stage 2 var 105 = 0
Stage 2 var 106 = 0
Stage 2 var 107 = 0
Stage 2 var 108 = 0
Stage 2 var 109 = 0
Stage 2 var 110 = 0
Stage 2 var 111 = 0
```

```
Stage 2 var 112 = 0
Stage 2 var 113 = 0
Stage 2 var 114 = 0
Stage 2 var 115 = 0
Stage 2 var 116 = 0
Stage 2 var 117 = 0
Stage 2 var 118 = 0
Stage 2 var 119 = 0
Stage 2 var 120 = 0
Stage 2 var 121 = 0
Stage 2 var 122 = 0
Stage 2 var 123 = 0
Stage 2 var 124 = 0
Stage 2 var 125 = 0
Stage 2 var 126 = 0
Stage 2 var 127 = 0
Stage 2 var 128 = 0
Stage 2 var 129 = 0
Stage 2 var 130 = 0
Stage 2 var 131 = 0
Stage 2 var 132 = 0
Stage 2 var 133 = 0
Stage 2 var 134 = 0
The LowerB Avg: 139177 with 0.05 CI: (138787, 139566)
The UpperB Value: 140767 with 0.05 CI: (140745, 140790)
CPU TIME: 101.037 seconds
```