Vaccine Supply Chain Optimisation

by

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Abstract

The focus on vaccine supply chain management has increased in recent years. Efficient supply chain management enables reductions in costs, fewer delays and improved quality. Competition today implies that timeliness and quality must be improved successively in order to stay profitable. This is accentuated in industries with high product introduction rates and large volumes over short product life cycles. A sense of strategic flexibility must also be incorporated in such business environments.

The work in this thesis was conducted in three phases. The first phase was the development of a scheduling model of the influenza vaccine supply manufacturing process. A model was developed to identify any changes in the current configuration of the process which enable the manufacturing times to be shortened and the responsiveness improved by identifying bottlenecks. Given the available equipment, product delivery dates and equipment requirements for the vaccine products, the problem is to schedule batches in order to meet the delivery dates. The problem was solved using a hybrid model with a heuristic front-end and optimisation at the back-end. It determines the key decisions related to the operation of the system, including the sequence of operations, their durations, the batch sizes and the number of equipment items used. The results show that current supply chain practice is not particularly efficient and that modifying the production schedule results in much earlier delivery dates.

The second phase was to build a mathematical model for problems with capacity planning and design under uncertainty that enables investment analysis of multiple-vaccine supply chains over a long horizon. Given the details of processing time, investment costs and production scale, the problem is to decide which vaccines to invest in and when. Here, it is solved

using a scenario-based stochastic mixed integer linear programming (MILP) planning and design model. Four different scenarios (failure at the clinical-trial stage, success with target demands, success with high demand, success with low demand) for each potential vaccine were considered, as is typical in the industry. These outcomes have different probabilities of occurrence and the fact that the information from different scenarios will become available at different times means that the investment model becomes a stochastic multi-period, multi-stage and multi-scenario MILP. Financial risk analysis was also used to discriminate between options using expected Net Present Value (eNPV) for vaccine production with different scenarios. Numerical results show that this approach enables one to consider and manage the financial risk associated with the different design options, resulting in a set of solutions that can be used for decision-making.

The final phase was to build a vaccination model to provide an understanding of the relationship between the vaccine supply side and the population dynamics of infectious diseases. The failure to supply sufficient vaccines on time to the potential recipients may increase the infection rate (and fatality rate where applicable). The aim of this study was to explore, via mathematical modelling, the impact of immunisation with a partially effective vaccine supply chain on the transmission dynamics of disease infection. The model addresses the questions of whether such a vaccine could ever completely stop the spread of infection and determines the vaccination rate and associated supply chain strategies required to control infection in a population.

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Chapter 1

Introduction

1.1 The Vaccine Supply Chain Problem

Vaccines are now among the most expensive pharmaceutical products and have made a major contribution to public health throughout the world. The vaccine industry provides great technological advances in vaccines and immunology but this is associated with markedly increased research costs. Global Alliance for Vaccines and Immunization (GAVI) mentioned that, for the worldwide development of a new vaccine, costs are quoted ranging from 250 to 500 million US Dollars. The economic objectives of a vaccine company are to recover these costs, plus the margins necessary for paying for failures, for financing research and development, capital investment and other ventures, and for the returns shareholders expect. On the other hand, the customers of a vaccine company or the institutions that look after the customers' interests will want the best quality possible for the lowest price.

The critical decision in the development and production of a vaccine is that of time and scale. A vaccine normally takes between 2 to 10 months for manufacturing, during which much of the time is spent performing quality-testing procedures. A vaccine manufacturing company must invest in production capacity well in advance of knowing the real in-process time and demand and before revenues are available to offset investment costs. In the past, manufacturers knew their domestic and likely export markets. The global market up to now has depended on excess capacity. Manufacturers can choose between two extremes: to

focus only on the core market, implying low availability, high cost, high price, and a risk of competition from manufacturers offering lower prices; or a global market focus, with low cost and high revenues through market segmentation.

In addition, the marketing, distribution, planning, manufacturing, and the purchasing departments along the vaccine supply chain operate independently. In many cases, some of these activities are performed by separate companies. These companies have their own objectives and these are often conflicting. The conflicts between manufacturing and distribution goals are due to high customer service and maximum revenue. Many manufacturing operations are designed to maximise throughput and lower costs with little consideration for the impact on inventory levels and distribution capabilities. Purchasing contracts are often negotiated with very little information beyond historical buying patterns. The result of these factors is that there is not a single, integrated plan for the company - there are as many plans as businesses.

The public sector has begun to provide and update, as frequently as possible, reliable demand information to support manufacturers' capacity investment decisions. The pace of change and the uncertainty about how markets will evolve has made it increasingly important for vaccine companies to be aware of the supply chains they participate in and to understand the roles that they play. Those vaccine companies that learn how to build and participate in strong supply chains will have a substantial competitive advantage in their markets. Clearly, there is a need for a mechanism through which these different functions can be integrated.

The increasing competitive pressures in the global marketplace coupled with the rapid advances in information technology have brought supply chain planning into the forefront of the business practices of most vaccine companies. Supply chain management is a strategy through which such integration can be achieved. Managing the flow of material from supply sources to the ultimate customer involves design, planning and control of supply chains. Efficient supply chain management of these activities offers opportunities in terms of cost, time delay reductions and improved quality, the latter by employing a unanimous view on quality at the source. Competition today implies that time and quality must be improved simultaneously in order to stay profitable. This is accentuated in industries with high product

introduction rates and large volumes over short product life cycles. A sense of strategic flexibility must also be incorporated in such business environments.

1.2 Project Motivation and Objectives

It is often the case that some vaccines are needed at short notice and need to be tailored to particular pathogens. However, the vaccine supply chain tends to be quite slow and unresponsive. The vaccine companies have already realised that efficient supply chain management with an effective supply chain model could allow them to save money and provide good services to the customers. To improve an effective and responsive supply chain, companies must learn to align their supply chains with the demands of the markets they serve. Supply chain performance is now a distinct competitive advantage for companies who operate in this area.

The objectives of the study are threefold. The first is the development of a scheduling model of the key part of an influenza vaccine supply chain, including information on infrastructure, demand management, production and logistics with a view to identifying a means of reducing time-to-market. Also, to understand the main features of influenza vaccine production and the characteristics of its epidemiology in order to obtain representative scheduling models that correctly describe and explain the influenza vaccine supply chain system.

The second is to develop a mathematical model for problems with capacity planning and design under uncertainty that enables analysis of multiple-vaccine supply chains over a long horizon. The model should measure the relative value of the techniques developed by means of performance measurements, more specifically, to create models that aim to guarantee long-term profitability and sustainability for vaccine supply chain systems and to find optimal inventory control policies and parameters so as to minimise costs and maximise fulfilment of customers' orders in the vaccine supply chain.

Finally, we extend a popular mathematical model of disease transmission dynamics, and combine it with different vaccine supply chain strategies to control a sudden outbreak of an infectious disease where the population needs to be immunised quickly. Thus, the aims of this study are (1) to develop a model that combines the supply chain and the disease dynamics, (2) to explore the impact of the supply chain on the infection rate, and (3) to determine the

vaccination rate required to control the infection.

1.3 Thesis Outline

The thesis is organised as follows:

- Chapter 2 reviews some of the technical literature related to the concept of the supply chain, the description of different supply chain strategies and the characteristics of the vaccine production. Subsequent chapters also contain reviews of literature more specific to their topic, such as scheduling, capacity planning, financial risk analysis and disease modelling.

- Chapter 3 considers the findings of the literature review and introduces the overall supply chain scheduling methodology used in the vaccine manufacturing industry.

- Chapter 4 describes a model for capacity planning of a multi-vaccine supply chain over a long horizon.

- Chapter 5 extends the work in Chapter 4 to include the financial risk analysis and the decision-making strategy.

- Chapter 6 investigates a vaccination model to provide an understanding of the relationship between the vaccine supply side and the population dynamics of infectious diseases.

- Chapter 7 presents some concluding remarks and possibilities for future work.

Chapter 2

Literature Review

This chapter reviews different areas of the supply chain literature and considers the main characteristics of the vaccine industry. In Section 2.1, different views of supply chain definitions are introduced. It also considers applications including supply chain management and performance measures. Section 2.2 gives a review of supply chain modelling methods including simulation and analytical models. Section 2.3 presents some examples of applications in the bio/pharmaceutical industry. In Section 2.4, a broad view of the current vaccine industry production profiles and the vaccine characteristics will be included. Finally, Section 2.5 outlines the research objectives and some concluding remarks are given.

2.1 Supply Chain Definitions

"Supply chain" refers to the network of companies involved in designing products, producing the products from raw materials, delivering the end products and providing services to the customers. Supply chains exist in both service and manufacturing organisations, although the complexity of the supply chain may vary greatly from industry to industry and firm to firm. A typical supply chain is presented in Figure 2.1.

The term *supply chain* arose in the late 1980s and came into widespread use in 2000s. Some definitions of a supply chain are given below:

> "A supply chain is a network of facilities and distribution options that performs

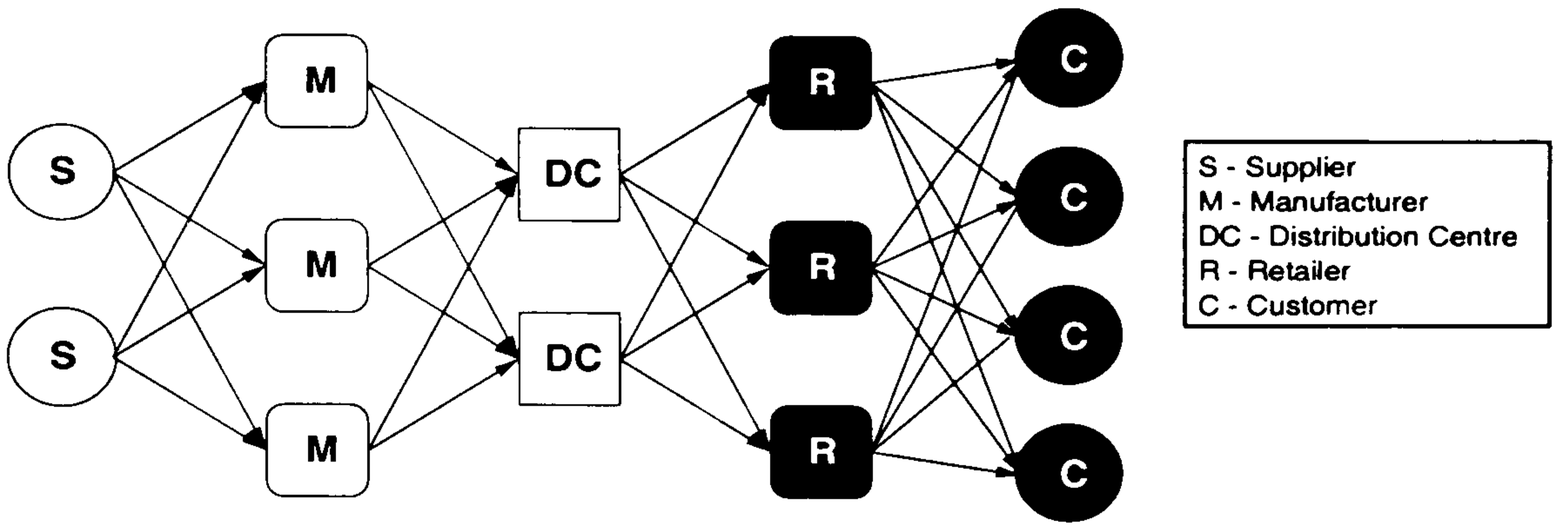


Figure 2.1: Typical Supply Chain

the functions of procurement of materials transformation of these materials into intermediate and finished products, and the distribution of these finished products to customers." (Ganeshan and Harrison, 1995)

"A supply chain is the alignment of firms that bring products or services to market." (Lambert *et al.*, 1997)

> "A supply chain consists of all stages involved, directly or indirectly, in fulfilling a customer request. The supply chain not only includes the manufacturer and suppliers, but also transporters, warehouses, retailers, and customers themselves." (Chopra and Meindl, 2001)

Recently, Anon (2003), quoted from Supply Chain Council, defines the supply chain as:

> "The supply chain - a term increasingly used by logistics professionals - encompasses every effort involved in producing and delivering a final product, from the supplier's supplier to the customer's customer. Four basic processes - plan, source, make, deliver - broadly define these efforts, which include managing supply and demand, sourcing raw materials and parts, manufacturing and assembly, warehousing and inventory tracking, order entry and order management, distribution through all channels, and delivery to the customer."

The pace of change and the uncertainty about how markets will evolve has made it increasingly important for companies to be aware of the supply chains they participate in and to

understand the roles that they play. Having a flexible and responsive supply chain will result in a substantial competitive advantage.

2.1.1 Supply Chain Management and Decision-Making

Supply Chain Management (SCM) has been broadly used in the literature with various meanings by different authors. Due to the development of the philosophy, different authors have different views on the meaning of SCM. Recently, Mentzer *et al.* (2001) define SCM as:

> "The systemic, strategic coordination of the traditional business functions and the tactics across these business functions within a particular company and across businesses within the supply chain, for the purposes of improving the long- term performance of the individual companies and the supply chain as a whole."

There is a difference between the concept of SCM and the traditional concept of logistics. Logistics typically refers to activities that occur within the boundaries of a single organisation and supply chains refer to networks of companies that work together and coordinate their actions to deliver a product to market. In addition, traditional logistics focuses its attention on activities such as procurement, distribution, maintenance, and inventory management. SCM acknowledges all of traditional logistics and also includes activities such as marketing, new product development, finance, and customer service.

In the view of supply chain thinking, these additional activities are now seen as part of the work needed to fulfil customer requests. SCM views the supply chain and the organisations in it as a single entity. It brings a systems approach to understanding and managing the different activities needed to coordinate the flow of products and services to best serve the ultimate customer. This systems approach provides the framework in which to best respond to business requirements that otherwise would seem to be in conflict with each other.

Taken individually, different supply chain requirements often have conflicting needs. For instance, the requirement of maintaining high levels of customer service may be achieved by maintaining high levels of inventory, but then the requirement to operate efficiently calls for reducing inventory levels. It is only when these requirements are seen together as parts of a larger picture that ways can be found to effectively balance their different demands.

Effective SCM requires simultaneous improvements in both customer service levels and the internal operating efficiencies of the companies in the supply chain. Customer service at its most basic level means consistently high order fill rates, high on-time delivery rates, and a very low rate of products returned by customers for whatever reason. Internal efficiency for organisations in a supply chain means that these organisations achieve an attractive rate of return on their investments in inventory and other assets and that they find ways to lower their operating and sales expenses.

Cooper and Ellram (1993) compare SCM to a well-balanced and well-practiced relay team. Such a team is more competitive when each player knows how to be positioned for the hand-off. The relationships are the strongest between players who directly pass the baton, but the entire team needs to make a coordinated effort to win the race.

Anderson *et al.* (2000) identify seven principles of SCM, which enable manufacturers to enhance revenue, cost control, asset utilisation as well as customer satisfaction:

1. Segment customers based on the service needs of distinct groups and adapt the supply chain to serve these segments profitably.

2. Customise the logistics network to the service requirements and profitably of customer segments.

3. Listen to market signals and align demand planning accordingly across the supply chain, ensuring consistent forecasts and optimal resource allocation.

4. Differentiate product closer to the customer and speed up conversion across the supply chain.

5. Manage sources of supply strategically to reduce the total cost of owning materials and services.

6. Develop a supply chain-wide technology strategy that supports multi-levels of decision-making and gives a clear view of the flow of products, service, and information.

7. Adopt channel-spanning performance measures to gauge collective success in reaching the end-user effectively and efficiently.

Lambert and Cooper (2000) describe SCM as the integration of the key business processes from end user through original suppliers. It provides products, services, and information that add value for customers and other stakeholders. The authors also propose a conceptual framework that consists of three closely interrelated elements:

1. Supply chain network structure, in which the key supply chain members with whom to link processes are decided.

2. Supply chain business processes, and the consideration of what processes to link with each of the key supply chain members.

3. Supply chain management components, and these allow the variation of integration level applied for each process link.

Time Based Decision-Making Approaches

The types of time based decision-making approaches for SCM can be classified in three main categories: strategic, tactical and operational.

Strategic decisions are made typically over a long term. The strategic level considers time horizons of more than one year, and requires approximate and aggregated data. These are closely linked to the corporate strategy, and guide supply chain polices from a design perspective. Factors of strategic decisions include not only site selection but also new resources and new markets. Economic, political, social and environmental factors often are also important issues of strategic decisions making. It is obvious that strategic decision-making operates on a large geographical basis, which usually entails a global consideration.

Operational decisions are short term, and focus on supply chain activities over an hour-to-hour basis or a day-to-day basis and require transactional data. The purpose is to manage effectively and efficiently the product flow in the supply chain. Elements of operational decisions include inventory management, production scheduling and planning, operational systems and tools associated with control and coordination. Operational decision making is typically site based.

Tactical decisions are medium term, and focus on supply chain activities over a week-to-week or a month-to-month basis. The tactical level falls in between these two extremes with respect to the time horizon, and the amount and accuracy of data required. Factors of tactical decisions include the types of relationships within the supply chain, the integrated management of operations within the chain, the management of an integrated transportation and distribution structure, and the development and use of planning and information systems to achieve strategic objectives. It is obvious that tactical decision-making operates on a smaller geographical basis than the strategic level.

Node Based Decision-Making Approaches

Although each supply chain has its own unique set of market demands and operating challenges, the issues remain essentially the same in every case. There are many node based decision-making areas in SCM. Ganeshan and Harrison (1995) and Min and Zhou (2002) suggest the following decision-making areas in which companies make in any supply chain:

1. **Location**. The geographic placement of production facilities, stocking points, and sourcing points is the natural first step in creating a supply chain. The location of facilities involves a commitment of resources to a long-term plan.

2. **Allocation**. Allocation determines which distributors (or warehouses), plants, and consolidation points should serve which customers, market segments, and suppliers.

3. **Production**. Production includes what products to manufacture in what plants, allocation of suppliers to plants, plants to distributors, and distributors to customer markets.

4. **Inventory level**. This refers to the means by which inventories are managed. Inventories exist at every stage of the supply chain as either raw materials, semi-finished or finished goods.

5. **Transportation**. This is closely linked to the inventory level decisions, since the best choice of mode is often found by trading-off the cost of using the particular mode of transport with the indirect cost of inventory associated with that mode.

6. **Network structuring**. This refers to deciding on centralisation or decentralisation of a distribution network and determines which combination of suppliers, plants, warehouses, and consolidation points should be utlised or phased-out. It may also involve the exact timing of expansion or elimination of manufacturing or distribution facilities.

7. **Number of facilities and equipment**. Number of facilities and equipment determines how many plants, warehouses, and consolidation points are needed to meet the needs of customers and market segments. It may also determine how many pieces of equipment item are required for material handling.

8. **Number of stages (echelons)**. Echelons are defined as the number of stages in the supply chain at which items are recorded and/or stored. All the nodes indicated in Figure 2.1 are called echelons. The arrows in the figure indicate product movement.

9. **Service sequence**. Service sequence determines delivery or pickup routes and the schedules of vehicles serving customers or suppliers.

10. **Volume**. Volume includes the optimal purchasing volume, production, and shipping volume at each node (e.g. a supplier, a manufacturer, a distributor) of a supply chain.

11. **Size of workforce**. It determines the optimal amount of every raw material, part, work-in-progress, finished product and Stock Keeping Unit (SKU) to be stored at each supply chain stage.

12. **Extent of outsourcing**. It determines which suppliers, IT service providers, and third-party logistics providers should be used for long-term outsourcing contacts and how many (e.g. single versus multiple sourcing) of those should be utlised.

2.1.2 Supply Chain Performance Measures

An important component in supply chain design and analysis is the establishment of appropriate performance measures. Performance measures are used to determine the efficiency and/or effectiveness of an existing system, or to compare competing alternative systems.

Beamon (1998) divides performance measures into two main categories: (1) qualitative, and (2) quantitative.

Qualitative Performance Measures

Qualitative performance measures are those measures for which there is no single direct numerical measurement, although some aspects of them may be quantified. The objectives are identified as follow:

1. **Customer satisfaction**. It applies to the customers who are satisfied with the product and/or service received. Beamon (1998) classifies the customer satisfaction into three elements:

   - **Pre-transaction satisfaction**. Satisfaction associated with service elements occurring prior to product purchase.
   - **Transaction satisfaction**. Satisfaction associated with service elements directly involved in the physical distribution of products.
   - **Post-transaction satisfaction**. Satisfaction associated with support provided for products while in use.

2. **Flexibility**. How easily/cheaply can the supply chain respond to random fluctuations in the demand pattern, or other disturbances.

3. **Supplier performance**. Supplier performance applies to the consistency of how suppliers deliver raw materials to production facilities on time and in good condition.

4. **Information and material flow integration**. The extent to which all functions within the supply chain communicate information and transport materials.

5. **Effective risk management**. All of the relationships within the supply chain contain inherent risk. Effective risk management describes the degree to which the effect of these risks is minimised.

Quantitative Performance Measures

Quantitative performance measures describe the efficiency and/or the effectiveness of the supply chain numerically. They can be categorised into monetary and customer responsiveness metrics. Generally speaking, management and optimisation would seek to:

$$Minimise = \begin{cases} \text{Cost} \\ \text{Inventory Investment} \\ \text{Product Lateness} \\ \text{Customer Response Time} \\ \text{Lead Time} \\ \text{Function Duplication} \end{cases}$$

$$Maximise = \begin{cases} \text{Sales} \\ \text{Profit} \\ \text{Return on Investment} \\ \text{Fill Rate} \end{cases}$$

It is common in the industry to observe separate nodes of the supply chain operating with conflicting objectives. The distribution function might be trying to minimise customer delays in deliveries. However, this is at odds with the fastest deliveries, which increase cost. The possibility of conflicting objectives leads to two aspects of supply chain management and optimisation: (1) a high degree of coordination is necessarily required, (2) many trade-offs must be captured in supply chain optimisation, necessitating a flexible modelling and optimisation framework.

2.2 Supply Chain Modelling

Supply chain modelling is aimed to help decision-making. A supply chain model is built up in order to analyse and/or simulate the raw material purchasing, products pricing, ordering, production management, and inventory management, etc. Considering the complexity of a supply chain, there is no model that can capture all aspects of supply chain processes. To

compromise between model complexity and accuracy/realism, a model builder should ensure that the model reflects the key aspects of the supply chain that are of interest, without making the model too tedious to solve.

There are many kinds of supply chain modelling approaches to help decision-making. Over the years, different scientists have had their own views on categorising the main types of supply chain model. Beamon (1998) divides the supply chain model into four categories: (1) Deterministic analytical models, (2) Stochastic analytical models, (3) Economic models, and (4) Simulation models.

Considering a broad spectrum of the supply chain concept, there may be various classification schemes to categorise supply chain models. Min and Zhou (2002) classify supply chain models into four major categories: (1) Deterministic (non-probabilistic) models, (2) Stochastic (probabilistic) models, (3) Hybrid models, and (4) IT- driven models.

Supply chain models can be broadly classified into two main types: simulation models and analytical models. The former involves replicating as much of the detail of the supply chain as possible in order to describe the real system faithfully. To achieve this, the model must typically include many details about how each node of the supply chain operates, how they interact with each other and the rules and policies they employ to do so. Many of these rules are in the form of logical conditions or complex calculations (e.g. Material/Distribution Requirements Planning (MRP/DRP) which determine orders by looking at a formal plan of operations based on forecasted demands) and therefore the simulation models become very complex with numerous relations that have no closed mathematical form. These models are therefore difficult to solve and highly time intensive. They are mainly useful for applying what-if scenarios so that the effects of any policy change (or sometimes change in structure) of the supply chain can be estimated with good confidence. However, they are far too complex for optimisation studies. The analytical models are designed for this purpose. They usually include only equations and constraints in closed mathematical form. Therefore they are amenable to optimisation techniques at the expense of losing some detail and accuracy. They may also be used as simulation aids where speed is more important than accuracy.

2.2.1 Simulation Models

Simulation models allow a more realistic capture of the supply chain characteristics and they provide a means to evaluate the impact of policy changes carried out by one or more supply chain nodes.

Towill *et al.* (1992) use simulation techniques to evaluate the effects of various supply chain strategies on demand amplification. The authors suggest a Just-In-Time (JIT) blanket approach to improve supply chain dynamics by attacking all cycle times throughout the supply chain. The simulation models can be supported by process control engineering knowledge, so a direct search for a better design can be made more quickly and more intelligently.

Slats *et al.* (1995) state that, "A major drawback of analytical models is the fact that many assumptions are made to reduce the complexity and to make the computation tractable, and to reduce and/or ignore the many uncertainties involved in the logistic chain." They further state in the paper that simulation provides a good means to analyse the performance of total logistic chains in combination with the complexity and uncertainties mentioned in the analytical supply chain modelling. Some major simulation tools utilised to analyse logistic processes are Simple++, SimFactory, GPSS, SimScript, SimanCinema and Taylor II. They also described two logistic laboratories. The first one is called TASTE and it provides tools and means to build a simulation model of an integrated supply chain. This laboratory has already been in use for several years. The second one is called DPSS and is based on several optimisations, heuristic and simulation sub-models for different, hierarchical, logistic planning stages. The final stage of DPSS is supported by TASTE.

Berry and Naim (1996) develop a simulation model and describe dynamic implications of various supply chain redesign strategies. The strategies adopted in the real world supply chain, and replicated in the simulation models, are the introduction of the JIT philosophy in manufacturing plants, the development of a global materials planning system that attains visibility of total supply chain stock, a strategic supplier sourcing policy and the by-passing of the distribution network so as to interface directly with the customer. The results suggest that dynamic performance improvements were achieved by each consecutive redesign strategy and have an impact on customer service level achievement, stock holding requirements and

production costs.

Bose and Pekny (2000) propose a forecasting-optimisation-simulation framework for a case study comprising a consumer goods supply chain. Model predictive planning and scheduling is proposed in which the controlled variables relate to the production plan and output variables typically are related to inventory levels. The forecasting module calculates the future target inventory so as to ensure required customer service levels at the same time as minimising inventory. The scheduling module tries to achieve these inventory levels in the future periods by scheduling tasks.

Perea *et al.* (2000) propose a dynamic modelling approach using the ideas of process dynamics and control to model supply chains. They capture the dynamic behaviour of the supply chain by using ordinary differential equations based on the flow of information and material within the supply chain. The assumptions used in the solution strategy are:

1. the supply chain consists of several nodes
2. all decisions are made locally at each node
3. material and information flows are the only input and output parameters
4. only the retail level sees the actual orders from the customers
5. each node operates a 'pull system' that processes or satisfies orders only when it has a backlog or orders to be processed. The decision-making process tests several heuristic control laws for the model and analyses their impact on the behaviour of the supply chain.

Perea-Lopez *et al.* (2001) study a supply chain of a polymer manufacturer with a production facility, a distribution network and three different product customers. The production facility is represented by a single-stage, multi-product batch reactor model. It considers recipe, processing time, yield and associated cost of each polymer product. The works treat the supply chain as a decentralised system. Individual components can make their own decisions. The authors then analyse the influence of different heuristics on the supply chain dynamics.

A sensitivity analysis is also carried out to identify the largest pertubation that the supply chain can tolerate.

Object-Oriented Simulation

Nowadays, supply chain researchers tend to use an object-oriented approach to develop simulation models. Alfieri and Brandimarte (1997) present a small case study using object-oriented simulation languages. Their case study includes a multi-echelon inventory management system, which consists of three kinds of nodes: (1) factories, which receive production orders and produce the required quantity to replenish stock, (2) stock points, which can be managed by different control policies, (3) demand points, which are the sources of a randomly distributed demand and it is usual to model the demand by using random inter-arrival times for the incoming customers.

Chu (1997) provides a methodology for building object-oriented simulation models. The methodology is based on the ideas of actors and scripts, and is illustrated with queuing models. The advantages and limitations of the object-oriented simulation models methodology are compared to the traditional general purpose programming languages and simulation software packages in the simulation of enterprise systems. The object-oriented simulation models have the advantages of: (1) naturalness of representation, the approach seeks to represent real-world entities and how they actually interact, (2) ability to handle complexity, it is able to model complex multi-server multi-queue systems with complicated features, and (3) flexibility, it originates from the ease with which an object captures individuality.

Recently, Biswas and Narahari (2004) developed an object-oriented decision support system DESSCOM, which enables strategic, tactical, and operational decision making in supply chains. DESSCOM has two major components: (1) DESSCOM-MODEL, a modelling infrastructure comprising a library of carefully designed generic objects for modelling supply chain elements and dynamic interactions among these elements, and (2) DESSCOM-WORKBENCH, a decision workbench that can potentially include powerful algorithmic and simulation-based solution methods for supply chain decision-making.

Hung *et al.* (2006) present an object-oriented modelling approach for realistic supply

chain simulation. The model built is to provide an experimental environment for informed comparison between different supply chain policies. The model is generic in that supply chains of almost any complexity can be constructed by linking together nodes (one of the basic elements of the model), each of which emulates in detail the behaviour of real supply-chain entities, such as manufacturing, scheduling, inventory and order management using industry-standard control policies. The authors also determine the effect of various uncertainties using Monte Carlo simulation.

Agent-Based Simulation

A more recent simulation approach is to use *agents*. These are autonimous entities, in the simulation model, that communicate with each other by passing messages and are designed to replicate the behaviour of similar entities in the real supply chain. Most agent-based models are implemented in an object-oriented programming language, as these are best suited to this type of simulation.

Garcia-Flores *et al.* (2000) describe an on-going effort in developing an agent-based integrated framework for supporting supply chain management of process industries. The supply chain consists of a number of agents, including retailers, warehouses, plants and raw material suppliers, each with its own functions and features. The interactions between agents are made through the communication language Knowledge Query Message Language (KQML) and the data is modelled using standard exchange of product model data.

van der Vorst *et al.* (2000) further develop an agent-based technique and present a simulation model with emphasis on timed coloured Petri nets (a graphical language with concurrency) to support decision-making. This discrete event simulation method is based on the concepts of business processes, design variables at strategic and operational levels, performance indicators, and business entities for modelling the dynamic behaviour of food supply chains.

Gjerdrum *et al.* (2001) use a set of multi-agent simulation modelling techniques to simulate a simple demand-driven supply chain network system with the manufacturing component being optimised through mathematical programming. The aim of this work is to reduce

operating cost while maintaining a high level of customer order fulfilment.

Garcia-Flores and Wang (2002) then use a set of multi-agent simulation modelling techniques to simulate the dynamic behaviour on inventory management, production sourcing evaluation and refinery operation.

Julka *et al.* (2002*a*) and Julka *et al.* (2002*b*) propose a unified agent-based framework for object-oriented simulation modelling to integrate the various elements of the supply chain such as enterprises, the production processes, the associated business data and knowledge. The framework helps to analyse the business policies with respect to different situations arising in the supply chain. The simulation model can be run based on time periods or on the occurrence of an event (i.e. time driven or event driven).

Janssen (2005) proposes a multi-agent simulation system to improve supply chain management. The author presents a semi-cooperative architecture and demonstrates some advantages of using agent-based simulation. Using the multi-agent system can increase the level of flexibility in the supply chain and enables supply chain members to become more responsive.

2.2.2 Analytical Models

Analytical models can be said to be quantitative as they involve mathematical equations or formulations to optimise the design or operation of supply chains. Measures of efficiency and/or the effectiveness of the supply chain are solved numerically, such as minimising cost or maximising profit. However, many assumptions are made in the analytical models to reduce complexity in order to make the computation faster and easier. One of the key simplifications, or restrictions, is that analytical models usually cannot accommodate the logical conditions that frequently occur in supply chains, such as many replenishment control policies, etc.

There are two major types of analytical supply chain model: (1) Deterministic (non-probabilistic) analytical models, and (2) Stochastic (probabilistic) analytical models. Deterministic analytical models for process planning and scheduling take into account only the certain and exact elements and assume that product demands are known. In an increasingly competitive environment, there are many random or uncertain elements in the supply chain such as customer demands, lead times, and production fluctuation. The stochastic model

takes into account all of these uncertain and random elements.

Vidal and Goetschalckx (1997) review the strategic analytical production-distribution models with emphasis on mixed integer programming (MIP) models. They focus on the identification of the relevant factors included in the formulations, and the characteristics of solution methods and computational experiences. Both deterministic and stochastic models are included in their review.

Deterministic Models

Elson (1972) demonstrates that Mixed Integer Programming (MIP) can be applied to the solution of certain practical site location problems of realistic size. His model involves two types of transportation variables including the supply chain from plant to distribution centre (DC) and from DC to end customers. The model minimises total costs, over a specific time period, including warehouse capital costs for construction and expansion, warehouse fixed and variable operating costs, transport costs and also savings from warehouse closures. The model assumptions are that: (1) certain locations are specified for new warehouses, (2) customer demands are aggregated by region and transport distances are measured to the centroid of demand in the region or possibly to the largest customer in the region, (3) requirements can be specified by level of service using a different mode of transport to be used from the warehouse, (4) transport cost is proportional to the quantity shipped, (5) expansion for the warehouses takes place in the supply chain if there is considerable economic reason, (6) for new warehouses a certain initial capacity is required and then expansion can take place at a specified unit cost up to some maximum capacity, (7) capital investment is justified by the rate of return.

Geoffrion and Graves (1974) build up a supply chain model based on a Benders Decomposition approach as a computational strategy for a static multi-commodity intermediate location problem. The problem is formulated and developed using Mixed Integer Linear Programming (MILP). The model determines the optimal location, size of intermediate distribution facilities between plants and customers, the type of customer services for each DCs, and the pattern of transportation flows for all commodities. The advantage of using the

Benders Decomposition approach is that it provides sequences of related runs, which requires less computing time than doing each run individually. Further to their research, Geoffrion and Graves (1980) apply their theory on modelling a Department of Defence distribution system to reduce excess capacity. They improve the system-wide productivity and customer service by 10% and 15% respectively.

Cohen and Lee (1988) present a deterministic analytical comprehensive model framework for linking decisions and performance throughout the material-production-distribution supply chain. The structure of the model is of four sub-models: (1) a material control sub-model, (2) a production sub-model, (3) a stockpile inventory sub-model, and (4) a distribution sub-model. The model formulations are based on analytical methods to analyse supply chain inventories. Each sub-model uses tractable stochastic models, and many assumptions are made in performing the model analysis.

One year later, Cohen and Lee (1989) extended their research to a global manufacturing and distribution network. The objective of this global manufacturing strategy is to maximise the global after-tax profit through the design of the facility network and control of material flows within the network. The constraints involved in the model are facility capacity, regional demand requirements, material balance and government requirements. In addition, the cost structure contains variable and fixed material procurement costs, production costs, distribution costs and transportation costs.

Cohen and Moon (1990) consider a single period, deterministic model called PILOT to model the relationship between a firm's manufacturing and distribution cost structure and the characteristics of its supply chain strategy. The PILOT model consists of six independent variables to perform the analysis: (1) inbound transportation cost, (2) intermediate product transhipment cost, (3) outbound transportation cost, (4) plant fixed cost, (5) economies of scale intensity factor, and (6) diseconomies of scope intensity factor.

Altiok and Ranjan (1995) develop an approximate decomposition method to model a production/inventory system consisting of multiple stages in series with arbitrary processing times and with intermediate buffer inventories. The approximation decomposition method produces acceptable results for all the measures of the production/inventory system only when

the probability of backorder is less than 0.30, in which cases the system fails to accommodate demand volumes effectively.

Arntzen *et al.* (1995) introduce a large MILP model called "global supply chain model". The objective function is to minimise cost, production time and distribution time, subject to constraints such as meeting the estimated demand and local restrictions. The model requires bills of materials, demand volumes, costs and taxes, and activity day requirements as inputs to provide outputs. The outputs are (1) the number and location of distribution centres, (2) the customer-distribution centre assignment, (3) the number of echelons, and (4) the product-plant assignment. This model was applied to restructure the supply chain of Digital Equipment Corporation and it saved over US$100 million for the company.

Lee and Sasser (1995) develop an analytical model used to evaluate the benefits of product differentiation over supplying a universal product, in terms of manufacturing and logistics costs, among others. The analytical model assumes that the demands per period in these markets are stationary as well as independent across time periods.

Revelle and Laporte (1996) give three new definitions for the plant location problem: (1) with new and different objectives, (2) with multiple products and multiple machines, (3) with spatial interactions. The objective of their research work is to encourage researchers to create and analyse more realistic decisions in plant location problems.

Kim and Lee (1998) explore fixed and variable capacity problems of jointly determining a unit's price and lot size for profit-maximisation under constant, price-dependent demand. They apply constrained Geometric Programming (GP) to obtain global optimality. They also use Kuhn-Tucker condition, margin and sensitivity analyses to investigate model interactions and to provide managerial implications on the optimal capacity decisions.

D'Amours *et al.* (1999) propose a supply chain network approach in which companies are selected and scheduled to produce an order based on a price-time evaluation of bids using an optimal planning model for networked manufacturing. The objective of the model is to fulfil demand of one product on time at minimum cost for a supply chain including manufacture, storage, distribution and customer brokers, and to represent the trade-off in networking decisions in terms of numbers of networked firms and their level of integration.

The results of an illustrated example show a reduction of 28.2% on the accumulated costs associated with the processing of a linearly sequenced order when a high level of information is transferred from the contractors to the networking firm.

Applequist *et al.* (2000) develop a deterministic mathematical programming model, which takes into account demand and inventory uncertainties in order to provide a supply chain model that can balance risk in the chemical manufacturing industries. The authors suggest that the chemical industry supply-chain complexity arises from a number of dimensions, namely, physical scale, temporal scale and degree of uncertainty. The supply chain model contains statistical elements to account for the uncertain parameter distributions, design and operation elements to determine investments as well as production plans and stochastic elements to determine cash flows. They define risk premium to obtain a trade-off of increasing return for increasing risk in terms of the net present value.

Korpela *et al.* (2001) present a framework based on integrating the Analytical Hierarchy Process (AHP) and MIP. The objective is to optimise a supply chain based on customer service requirements within the supply chain. The approach consists of five basic steps: (1) defining the decision problem by stating the objectives and determining the scope of the problem in terms of alternative transportation modes and routes, (2) determining the strategic importance of the customers by using the AHP method, (3) using the AHP method for analysing the customer's preferences for customer service, (4) using the AHP method to support the evaluation, resulting in a preference priority for each alternative link and node, (5) performing MIP-based optimisation to optimise the logistics network based on the priorities.

Dasci and Verter (2001) propose a continuous analytical production-distribution network design model. It represents spatial distributions of cost and customer demand. They argue that while discrete models are capable of identifying an optimal configuration, data and computational requirements increase tremendously for complex cases while model stability and applicability decrease. Discrete models can deal with uncertainties only through a detailed scenario analysis, which typically requires extensive computation and scenario generation efforts.

Yao *et al.* (2005) develops an analytical model to investigate the effect of supply chain parameters on the cost savings to be realised from vendor-managed inventory. The authors show that the inventory cost reductions can be generated from integration depending upon the ratio of the order costs of the supplier to the buyer and the ratio of the carriage charges of the supplier to the buyer.

Stochastic Models

Pyke and Cohen (1993) present a stochastic analytical model of a simple integrated production-distribution system (also called a Markov chain model) to minimise the additional set-up costs and work force change costs subject to a service level constraints. The set-up times, processing times, and replenishment lead times are constant while demands are uncertain. The model illustrated using a single-product, three-echelon problem. The three echelons are a factory, a finished goods stockpile and a single retailer.

Pyke and Cohen (1994) later review the single-product model and present a similar model for a multi-product supply chain with multiple retailer situations. The authors approximate the distributions of key random variables to compute costs and service levels for all products across the supply chain.

Sabri and Beamon (2000) develop an integrated stochastic multi-objective supply chain model under demand uncertainty for use in simultaneous strategic and operational supply chain planning. Their work is performed under two sub-models: (1) a strategic level sub-model (MILP), which determines material flow, production quantity and binary variables of process plant, DCs, customer zone, given fixed costs, capacity constraints, average customer demand, initial unit variable costs, raw material costs at each vendor and strategic subjective parameters; and (2) an operational level sub-model (Mixed Integer Non-Linear Programming (MINLP)), which analyses service levels, inventory ordering policies, production batch size, unit variable costs, production lead time, replenishment lead times based on inputs of cost data, bill of materials, supplier lead time data, transportation time data, demand probability distribution, minimum required service levels and operational subjective parameters. The results they obtained confirm the significance of cost, customer service, and flexibility and

also demonstrated the need to integrate operational and strategic decisions in supply chain design.

2.2.3 Other Models

Christy and Grout (1994) develop an economic, game-theoretic framework for modelling the buyer-supplier relationship in a supply chain. The basis of their work is a 2 x 2 supply chain "relationship matrix", which may be used to identify conditions under which each type of relationship is desired. The conditions range from high to low process specificity, and from high to low product specificity. Thus, the relative risks assumed by the buyer and the supplier are captured within the matrix. For example, if the process specificity is low, then the buyer assumes the risk; if the product specificity is low, then the supplier assumes the risk. For each of the four risk quadrants, the authors go on to assign appropriate techniques for modelling the buyer-supplier relationship.

Grout (1996) uses a mathematical model to structure on-time delivery incentives in a contract between a buyer and a single supplier of raw materials when early shipments are forbidden. In order to find an optimal solution for both the buyers and suppliers, the method uses classical optimisation to solve the optimisation problems in reverse chronological order. The sequence is to optimise the supplier's response function first, then the buyer's. The response function of the supplier provides a given probability of on-time delivery, and the response function of the buyer identifies what the probability of on-time delivery will be in order to minimise cost. The result shows that 100% on-time delivery is non-optimal and a feasible result can only be achieved under specific conditions.

Cohen and Whang (1997) propose a product life-cycle model that studies a set of strategic choices facing manufacturers as the authors design the joint product and service bundle for a product, which may require maintenance and repair support after its sale. The product price, the quality of service and the price to be charged are the parameters for the after-sale service. The authors build up a game-theoretic framework, where there is competition for the provision of after-sales service between the manufacturer and an independent service operator. The results support the valuation of alternative product designs in explicit consideration of

the trade-off between profit from product sale and from the provision of after-sale service. The product life-cycle model can be used to evaluate the asset value of a firm's customer base.

Homburg (1998) proposes a hierarchical procedure for solving MILP and decision problems with multiple objectives. The procedure consists of two different levels including a top-level and a base-level. The main objective at the top-level is to provide general preference information and the objective at the base-level is to determine a compromise solution. For a multi-objective linear program it will be shown that a hierarchical procedure can be structured by deriving weight restrictions from the general preference information of the top-level and by using the interactive multi-objective decision making (MODM) procedure of the Zoints-Wallenius algorithm on the base-level.

Androulakis and Reklaitis (1999) propose the use of the ideas and principles of asynchronous computing as a modelling tool and not just a solution methodology. The authors also investigate optimal decision-making problems that exhibit decentralised characteristics. Such problems consist of a collection of interacting sub-systems, where each sub-system is described by local properties and dynamics, joined together by the need to accomplish a common task that achieves overall optimal performance. The sub-systems have their own special properties to make them fit the framework of asynchronous computing ideally. The properties are: (1) the lack of a single overall objective describing the collective performance, and (2) the asynchronism in implementing topologically optimal decisions based on information which is local in space and time. A methodology for decentralised decision-making is developed with emphasis on the solution of a series of sub-problems in which each minimises a local objective while maximising a common Lagrangian function, and by generating independent approximations for an ascent direction in the space of the dual variables.

Petrovic *et al.* (1999) present a supply chain model as a fuzzy set in an uncertain environment. The uncertain variables include the customer demand, supply deliveries along the supply chain, and external or market supply. The fuzzy model is to determine the order quantities for each inventory and to give an acceptable service level of the supply chain at reasonable total cost.

Gjerdrum *et al.* (2002) develop a MINLP model for finding optimal and "fair" multi-partner profit levels. The authors also present a spatial and binary variable branch-and-bound algorithm to utilise the game theoretical bargaining concepts based on a Nash theorem. The assumption made in the model is that all supply chain players can share all relevant data thus allowing the supply chain network to have a single optimisation model. The results are then compared with those using a simple single level optimisation approach, which focuses on the total profit generation of the entire supply chain.

2.3 Modelling Applications in Bio/Pharmaceutical Industry

A wide range of literature exists in designing and planning of the bio/pharmaceutical supply chain. Current works involving different types of techniques have been applied to the industrial side and the commercial side successfully to improve the bio/pharmaceutical production and sales environment respectively.

Backhouse (1998) presents an investment appraisal framework to support decision-making in pharmaceutical companies. The author illustrates a multi-period linear model for optimal clinical trial design. The model is based on different designs to maximise return on a given development or trial budget, where each design represents different sample size and endpoint measurements. A simple deterministic problem is solved for a series of bounded cases by varying the proposed sample size.

Rotstein *et al.* (1999) present a stochastic analytical model to maximise NPV in terms of avoiding unnecessary investments in pharmaceutical industry. The two-stage stochastic model uses a scenario tree approach to represent a portfolio of three products; the uncertainties are associated with the possible outcomes of each clinical trial for each pharmaceutical product.

Subramanian *et al.* (2000) propose a computing architecture for linked mathematical programming and stochastic optimisation to assess risk in a pharmaceutical pipeline. The authors also introduce the concept of timelines to study multiple unique realisations of the controlled evolution of the discrete event pipeline system.

Gatica *et al.* (2003) propose a stochastic analytical model to describe capacity planning and investment strategy in the pharmaceutical industry. The model is formulated as a

multi-stage, multi-period and multi-scenario MILP. The model takes into account risk measurements and potential return in the project.

In recent years, modelling techniques have been adopted in biopharmaceutical manufacturing. Farid *et al.* (2000) develop a prototype simulation tool, based on a graphical object-oriented programming environment, to assist decision-making in biopharmaceutical manufacturing. The tool considers technical and business parameters in determining the performance of alternatives in terms of cost, time, yield, resource utilisation and risk. Farid *et al.* (2005*a*) then apply different manufacturing strategies under uncertainty for the production of biopharmaceuticals using this decision-making tool. The authors compare the cost of using stainless steel versus disposable equipment for production of early phase clinical trial material. Simulation technique is also applied to the case study in order to handle uncertainties such as times, demands and market success.

2.4 Vaccine Characteristics and Markets

A vaccine is pharmaceutical product that is a biological medicine, made in, composed of, and/or tested through living systems, and thus difficult to standardise. It functions by eliciting an immune response and is generally for preventive use, although therapeutic vaccines (for example, for treatment of some forms of cancer) are now being developed.

Disease prevention is the key to public health. Vaccines particularly benefit the people who receive them, and in turn, those people cannot spread disease to others who have not been vaccinated. Infection cannot spread if it never gains a foothold. Infectious diseases cause enormous suffering, strain the capabilities of our health care system, and deplete financial resources. For the individual, the health care provider, and in the interest of conserving human and financial resources, it is always better to prevent a disease than to treat it.

When a new disease emerges or a familiar one becomes a more significant health threat than it has been in the past, scientists, physicians and public health workers recognise the need for a new way to prevent the disease. Once scientists have identified the organism or toxin that causes the illness, they pursue a number of approaches to develop a vaccine.

The purpose of a vaccine is to bring about active immunity by provoking a response from a

person's immune system and creating a memory within the immune system so that exposure to the active disease agent will stimulate an already primed immune system to fight the disease. Some vaccines are combinations that protect against several diseases, e.g. influenza vaccines. Scientists extensively test these combination vaccines to make sure that none of the antigens detracts from the immune priming effect of the others. Thus the vaccines can provide triple protection, the recipients are spared extra injections, and the public health costs are reduced.

2.4.1 Market Features and Demand Forecasting

The vaccine market is different from other pharmaceutical products. Vaccine sales are primarily to the public sector, while many other pharmaceutical products sales are mainly to the private sector. The size and characteristics of the vaccine market are mainly the primary consideration in the decision of a manufacturer to introduce a new product. Vaccine manufacturers will look at the historical sales and supply-chain behaviour in order to predict the uptake rate of the products to determine the robustness of the market.

The major difficulty in forecasting the vaccine demand is predicting the actual number of doses that should be used in all populations to control the disease effectively. It also depends on the number of doses that are actually purchased, depending on access, willingness and ability to pay, and perception of need. The demand for vaccine can be categorised into three areas: routine, sudden outbreak, and new product introduction.

Forecasting routine vaccine demand is relatively easy compared to sudden outbreaks and new product introduction. Milstien *et al.* (2005) claim that the global demand depends on the number of doses in a series (usually one to three, typically given over a six month period), the target population, a factor for wastage (based on a multi-dose vial presentation) and the factors reflecting the likelihood of reaching the target population (usually based on coverage figures for previous years).

Forecasting for the sudden outbreaks and new product introductions are generally more difficult. Sudden outbreak cannot be predicted, stockpiling may be the only useful method in smoothing out demand for supplementary vaccine requirements. However, stockpiling is

unreliable when the infectious agent is unknown. Milstien and Lambert (2002) provide an outline on stockpiling requirements for emergency response vaccines which might be considered essential on a global scale as shown below:

- Sufficient size with vaccine of sufficient efficacy to protect at-risk populations;
- No other viable treatment options available;
- Vaccines can be mobilised within the required time;
- Real/potential demand and market size can be estimated;
- Inventory of current/potential manufacturers meeting standards exists;
- Identification completed of production and regulatory bottlenecks, total capacity, lead times, and where and how stockpile will be stored;
- Sustainable financing is available;
- Fair distribution mechanisms are agreed;
- Consequences of stockpiling on supply of other vaccines are addressed.

Forecasting the uptake of new vaccine products will depend on the infrastructure, available financing and available supply. This type of forecasting is not easy due to the accuracy of predicting the vaccine needs. An illustrative case presented by the Centers for Disease Control and Prevention in the U.S. is the experience with a Lyme disease vaccine, which was developed and introduced in the United States in January 1999 by GlaxoSmithKline. It was a relatively expensive vaccine, targeted at a specific market segment, both regionally and economically. It was recommended for use by persons aged 15-70 who resided, worked, or recreated in areas of high or moderate risk, and not for the general population. In February 2002, citing diminishing sales, GlaxoSmithKline pulled the vaccine off the market. Some factors involved in the lower than expected sales included the small eligible market, some unforeseen adverse events, and perception of low efficacy.

2.4.2 Typical Vaccine Products and Sources of Supply

The global vaccine market is driven by research-based multi-national companies that develop new, expensive vaccines for which profit margins are usually high. The vaccine market is increasingly split by the divergence between traditional and new vaccines across markets.

Table 2.1 shows a list typical vaccine products tailored for different markets.

Table 2.1: Vaccine Development for Different Countries

Disease	Year	Developing Countries	Developed Countries
Pertussis	1926	DTwP	DTaP or DTP-HepB-Hib
Tetanus	1927	DPwT	DTaP or DTP-HepB-Hib
Yellow Fever	1953	YF	YF
Poliomyelitis	1955	OPV	IPV
Measles	1963	Measles	MMR
Hepatitis B	1981	HepB	DTP-HepB-Hib
Hemophilius influenzae type B	1985	DTwP	DTP-HepB-Hib

Many companies in different countries produce vaccines. In fact, many governments try to reduce prices and optimise supply to conserve foreign exchange by seeking self-sufficiency in vaccine production. Large-scale pharmaceutical production has economics of scale that can lower production costs and thus raise profit margins. The World Health Organisation (WHO) estimated that there are approximately 4,000 vaccine manufacturers producing more than 200 vaccine products in about 45 countries. Generally, the vaccine industry is dominated by a small number of multi-national manufacturers including Aventis Pasteur, GlaxoSmithKline, Merck and Wyeth-Lederle. These multi-national manufacturers serve approximately 70% of today's vaccine market. Small to medium-sized manufacturers, notably Chiron and emerging manufacturers in Korea, India, and Indonesia, share about an additional 10%, while the remaining is attributable to local manufacturers in developed and developing countries. A list of vaccine manufacturers obtained from the WHO is presented in Table 2.2.

Table 2.2: Vaccine Tailoring by Manufacturers

Manufacturers	Measles	DTwP	OPV	MMR	DTaP	IPV	DTP-HepB-Hib	Pneumo	Rotavirus
Aventis Pasteur	✓	✓	✓	✓	✓	✓	✓	✓	✓
Bharat	✓	✓	✓	✓	-	-	✓	-	✓
Bio Farma	✓	✓	✓	-	-	-	✓	-	✓
Butantan	✓	✓	✓	✓	-	-	✓	-	-
Chiron	✓	✓	✓	✓	✓	-	✓	-	✓
CIGB	-	✓	-	-	-	-	✓	-	-
CSL	-	✓	-	-	✓	-	-	-	-
GlaxoSmithKline	-	-	✓	✓	✓	✓	✓	✓	✓
Merck	-	-	-	✓	-	-	-	✓	✓
Panacea	✓	✓	✓	✓	-	-	✓	-	✓
Razi/Pasteur	✓	✓	✓	✓	-	-	-	-	-
Shantha Biotechnics	✓	✓	✓	✓	-	-	✓	-	✓
Vacsera	-	✓	✓	-	-	-	-	-	-
Wockhardt	✓	✓	✓	✓	-	-	✓	-	✓
Wyeth-Lederle	-	-	-	-	-	-	-	✓	✓

2.4.3 Production Processes

The vaccine industry is an entire network, which consists of many different players and process activities. Within a typical vaccine supply chain, the major and the most time consuming stage is manufacturing. There are two key areas that define the activities and resources to produce the final vaccine product, i.e. packed vaccine: (1) primary manufacturing — production of the Active Ingredient (AI), and (2) secondary manufacturing — production of packed vaccines. Vaccines are difficult to produce and the processes are characterised by tasks with long processing times. Careful controls in production and very strict quality control processes are observed to guarantee the safety and effectiveness of the vaccines to be supplied.

The objective of the primary manufacturing site is the production of AI. Since viruses (parasites) can only grow in living cells, vaccines are produced in live cell cultures. The process for many vaccines begins with almost laboratory scale culture and is progressively scaled up to larger and larger culture vessels. Each one of these steps takes a certain time and cannot be accelerated. The viruses for some vaccines are grown in hen's eggs. Vaccines are made in several different ways depending on the microorganism used and the way in which it needs to be grown. The processes also change according to the type of vaccine, which is being produced: inactivated or live.

Following the growth phase, the host organisms need to be further treated to produce the vaccine. This could involve inactivation or splitting into smaller units after which the active component of the vaccine is highly purified. Once again the process varies according to the vaccine being produced, but the final step is always quality control. The individual bulks need to be tested for (1) the identity for the correct organism grown, (2) the changes during the growth period, (3) sufficient vaccine potency, (4) freedom of contamination in the bulk, and (5) the correct ingredients in the correct amounts.

The objective of the secondary manufacturing process is the manufacture of final vaccine products from the AI. If the vaccine which is being produced has more than one constituent, the next stage is to blend the bulks. The vaccine is blended with the other constituents to produce what is referred to as a bulk. Once again many of the tests described above have to

be performed on the blended vaccine. Only after the manufacturer is satisfied that the bulk vaccine meets the stringent criteria set by the product licence would samples of the bulk be released to the authorities so that they can perform their tests.

Following satisfactory quality control tests the bulks are then used to fill the appropriate containers which could be ampoules, vials or syringes. Once again the finished product has to be tested to make sure that it conforms to the product licence, such as, potency, sterility, volume, pH etc.

When the finished product is satisfied and qualified, the manufacturers then send samples of the bulks and the finished product to regulatory bodies such as one of several European Official Medicines Control Agencies so that they can repeat the tests and satisfy themselves that the vaccine is suitable for use in the marketplace. Only after the vaccine is released for use in the marketplace will the manufacturers package it appropriately and ship it to the distribution points.

2.4.4 Vaccine and Pharmaceutical Supply Chains

The previous section gave a brief overview of vaccine manufacturing activities. Considering *all* activities such as distribution, retail and customers in a systematic way, a vaccine supply chain can be constructed. Figure 2.2 gives the structure of the players involved in the vaccine supply chain; they can be separated into four stages.

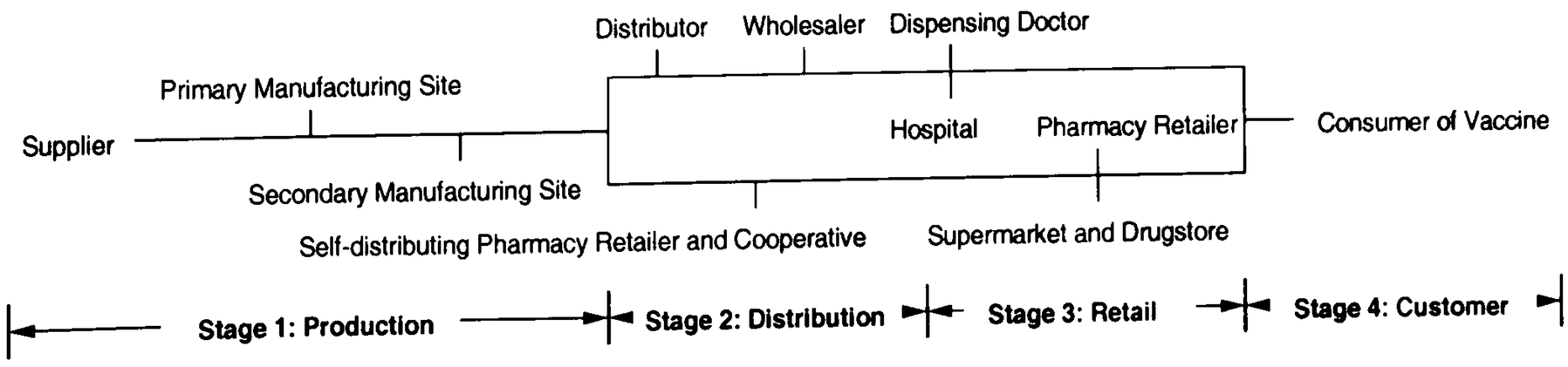


Figure 2.2: The Vaccine Supply Chain

Distribution

Distributors, wholesalers, self-distributing pharmacy retailers and cooperatives are the main distribution centres.

Distributors are companies that take inventory in bulk from suppliers and deliver a range of related product lines to customers. The distributors consist of market warehouses and DCs, which respectively store end products and transport them to the customers.

The main function of the wholesalers is to reduce the number of transactions between the manufacturers and the pharmacy retailers. Ortenzi (2000) divides the wholesalers into two basic types, Full-line and Short-line wholesalers. Full-line wholesalers supply the full range of pharmaceuticals. They stock a large number of lines according to their trade association. Short-line wholesalers concentrate on a much smaller number of fast moving lines. Because they deliver on a less frequent basis, they can offer lower prices than full-line wholesalers. In terms of area, the wholesalers can be split into National and Regional. National wholesalers have many depots that cover almost all the areas. Regional wholesalers have one depot that covers a single area. Although they are much smaller than national wholesalers, they are able to buy branded ethical drugs from manufacturers at the same price of national wholesalers because of pricing regulations. In addition to this, they do not carry the central overhead costs of the nationals.

Self-distributing or self-supply is the practice of large retail chains (e.g. Boots) supplying their retail outlets from warehouses owned by the same group. Cooperatives are other means of direct supply from manufacturers.

Retail

Pharmacy retailers, hospitals, dispensing doctors, and supermarkets and drugstores are the major vaccine retailers from which the public can receive vaccination.

In the UK, pharmacy retailers are registered with the Royal Pharmaceutical Society of Great Britain. The aim of the pharmacy retailers is to dispense pharmaceuticals to the community but under the control of the National Health Service (NHS). In order to dispense NHS prescriptions, the registered pharmacy retailers need also to be admitted to the list of the

local Health Authority (HA). There are a few pharmacy retailers not holding an NHS contract whose business is focused on privately prescribed medicines. These provide a mechanism for the HA to link the number of pharmacy contractors to the needs of the local population and to ensure the full range of pharmaceutical services is available.

There are four types of pharmacy retailer: (1) Neighbourhood pharmacy retailers, (2) High-street pharmacy retailers, (3) Health-centre pharmacy retailers and (4) Supermarket pharmacy retailers. Neighbourhood pharmacy retailers are reliant on the local consumer base for business. High-street pharmacy retailers are, by contrast, less reliant on the local customer base and are characterised by also stocking a large range of non-pharmaceutical products. Health-centre pharmacy retailers are located in or adjacent to a General Practice's surgery on which they rely for business. Pharmacy retailers are increasingly being located in the supermarkets as an additional service to customers of the stores (Anon, 1996).

Hospitals are one more channel for distribution of prescription medicines to patients. It is estimated that around 15% of the total prescription medicines are dispensed by hospitals (Anon, 1996).

In many areas where the business of a pharmacy is not viable, doctors have the right to dispense the medicines they prescribe. It is estimated that doctors dispense about 4% of total prescription medicines (Anon, 1996).

Customers

In the vaccine supply chain, customers are usually the final end users. Most of the customers receive the vaccination in hospitals and/or from dispensing doctors. Only in a few exceptional cases do they receive a vaccination or buy vaccines from pharmacy retailers and supermarkets, although private clinics are increasingly being used.

2.5 Research Objectives and Concluding Remarks

Supply chain management has been extensively adopted in the pharmaceutical industry throughout the past decade. Various studies on supply chain scheduling, capacity planning and supply chain modelling have been reported in this area. However, there has been

less concern for specific research into vaccine production.

The recent sudden outbreaks of transmissive diseases around the world has highlighted that many different countries lack sufficient vaccine supplies and have inadequate immunisation strategies. Supply chain management is an area that is critical to vaccine manufacture and supply if these shortcomings are to be rectified. Governments are now aware of the importance of a good vaccine supply policy and a suitable immunisation strategy to help the people. Thus, vaccine supply chain management is now an emerging research area, and it is expected to become more and more important. A key issue is the combination of supply chain modelling with vaccine production characteristics and associated epidemiology.

Different aspects of supply chain modelling literature were reviewed in this chapter. Simulation models can be categorised into object-oriented and agent-based, both of which are able to handle complexity and aid in making decisions. The vaccine supply chain problem can also be solved by developing analytical models. However, analytical models often require many assumptions and simplifications, which may limit the realism of the model.

This thesis presents a new approach for vaccine supply chain optimisation. Previous work pertaining to the bio/pharmaceutical industry is based on the benefits of both analytical and simulation modelling techniques. The literature related to the vaccine supply chain, can be divided into several research areas. In the remaining chapters of this thesis, we consider the following problems.

- **Scheduling**. A vaccine supply chain is a large and complex system because it consists of a wide range of activities from raw material supply, transformation from raw materials to intermediates, production from intermediates to final products, and finally delivering to the customers. Both simulation and analytical modelling techniques can be applied to a vaccine manufacturing process.

One of the key characteristics of vaccine manufacture is the long time required to transform the raw materials into the final product. In some cases, the overall processing time can be as much as 9 months or more. It is clear that when considering sudden outbreaks of diseases, the current manufacturing facilities and supply chains would not be able to supply sufficient vaccine in time. The operation of the manufacturing process

and supply chain both need to be examined to determine what, if anything, can be done to improve the responsiveness to sudden demands.

Chapter 3 focusses on the scheduling of a typical flu manufacturing process. An approach is adopted that can handle the enormous complexity of the manufacturing process, by decomposing the process and applying different scheduling techniques to each part.

- **Planning**. Considering the longer term, a vaccine manufacturer will have a number vaccines in development and pharmaceutical trials. A key decision to be made is how much plant should be invested in to accommodate the new vaccines, given that many may not pass clinical trials and those that do may not perform in the market as expected. This is the area of planning, and concerns a period of a number of years (*cf.* hours or days in the case of scheduling).

- **Uncertainty Modelling**. Demand uncertainty modelling has been widely used in bio/pharmaceutical industry. Both simulation and analytical modelling can provide decision-making support. For example, Farid *et al.* (2005*b*) report potential benefits of using stochastic modelling techniques to handle uncertain factors so as to calculate finance measures using cumulative probability curves.

  In Chapter 4, we present an optimisation-based approach to capture the above issues to select simultaneously the final vaccine portfolio, the optimal capacity planning and the investment strategy subject to uncertainty of production for each potential vaccine. The details are formulated as a deterministic multi-period MILP planning and design model. In addition, different financial and risk measures are used to provide decision-making in Chapter 5.

- **Disease Modelling**. Some transmissive disease outbreaks (e.g. bird influenza) can be predicted in advance. These predictions are extremely useful in determining how effective an imunisation strategy will be in the event of a sudden outbreak. As there is currently no literature that has addressed this problem, there is a rather pressing need for some advance in this area. Although both simulation and analytical models

can provide performance measurements, simulation models should give more realistic results. In Chapter 6, we develop a combined supply chain and disease dynamics model specifically for the evaluation of supply chain and immunisation strategies for the sudden outbreak of transmissive diseases.

Chapter 3

Application of Scheduling Techniques to Debottleneck a Complex Vaccine Manufacturing Facility

This work describes medium-term planning and scheduling in an influenza vaccine manufacturing facility. As influenza vaccine manufacturers expand into global markets and exploit global multi-sourced supply arrangements, optimisation of complex influenza vaccine facilities is required to lower costs, increase return on assets, and increase market share. The manufacturing process consists of four main stages: egg processing, whole virus purification, split virus purification and packaging. Each requires many different process operations and resources. Overall, the process comprises a large number of process stages with many intermediates, and this level of complexity presents a significant challenge to model. A model is developed to identify any changes in the current configuration of the process which enables the manufacturing times to be shortened and the responsiveness improved by identifying bottlenecks. Given the available equipment, product delivery dates and equipment requirements for the vaccine products, the problem is to schedule batches in order to meet the delivery

dates. The problem is solved using a hybrid model with a computational heuristic at the front-end and optimisation at the back-end. It determines the key decisions related to the system, including the sequence of activities, batch sizes, and timing of process operations. The objectives are (1) to understand how different parameters and decisions affect performance; (2) to identify the most important factors in the supply chain; and (3) to reduce time-to-market without large capital investment, specifically, investigating the benefits of reduced cleaning times and debottlenecking. The main contribution of this work is to apply the scheduling techniques to vaccine manufacturing, which has not been done before. The results show how the influenza vaccine manufacturing plant can manage to meet existing demands and extra demands. Additionally, a debottlenecking study is undertaken.

3.1 Introduction

After the global outbreak of influenza in 2000-2001, the importance of understanding the weaknesses in the manufacturer-to-patient supply chain was highlighted. In recent years, influenza vaccine forecasts have been used to manufacture, distribute and administer treatment to millions of patients. To serve the public properly, the influenza vaccine system requires each entity in the production and supply chain to operate accurately and in a timely fashion.

According to Rimmelzwaan and Osterhaus (2001), the current situation of the influenza supply chain is as follows:

- Influenza viruses frequently undergo rapid and unpredictable changes in their antigenic properties;
- The influenza vaccine has to be updated annually and must include the required representatives of circulating different viruses;
- Influenza vaccine manufacturing is a long activity;
- Demand patterns for influenza vaccines have become increasingly irregular with more marked seasonal fluctuations and a tendency for the lifetime of the vaccine products and markets to diminish.

Influenza vaccine manufacturing processes involve a number of stages, which are performed in sequence, to convert the raw materials into the intermediates and the final products intermittently. As a result, batch processing has been introduced to suit the manufacture of influenza and other vaccines in recent years, particularly those for which demand patterns are likely to change. The advantage of batch operations is to allow the same type of equipment to be used for manufacturing many different products. It is important that sufficient manufacturing flexibility should be available to respond to changes in demand and hence avoid loss of potential sales due to the failure to supply the customers' requirements at the correct time.

Scheduling is an important aspect of batch process operations. The purpose of the scheduling activity is to break down the production plan into feasible operations throughout time. The scheduling horizon spans from a few days to weeks, depending on information availability and uncertainty, and decisions are usually considered on an hourly basis. Scheduling involves allocating resources at specified times so that demands are met. For a schedule to be optimal, limited resources must be utilised in the most efficient way within the scheduling time period in order to fulfil production objectives. Although there are some optimisation variables at the scheduling level, in this application the focus is feasibility, where economics are generally ignored.

Scheduling requires much closer attention to detail than long-term capacity planning. Detailed demand requirements for the various products may be specified on a day-to-day basis. A production schedule must specify the sequence and manner in which the products are to be produced and the times at which the process operations are to be carried out. The demand requirements must be met, respecting constraints such as resource availability, usually while minimising some criterion such as production cost.

Scheduling requires large amounts of data regarding the process recipe, the plant equipment and the demands imposed on the plant. Kondili *et al.* (1993) introduced the State Task Network (STN) representation, which comprises two types of node: state nodes and task nodes to represent material and processing activities respectively. Based on this method, the authors present a discrete-time mixed integer linear programming (MILP) optimisation model

to solve short-term scheduling problems for multipurpose batch plants. Shah *et al.* (1993) developed a new formulation to reduce the computational times for discrete-time scheduling models. Pantelides (1994) proposed an MILP formulation that allows detailed consideration of the design problem taking into account the selection of the required processing and storage equipment items as well as the required levels of provision of other production resources such as utilities, labour, cleaning and transportation. The MILP was based on a detailed discrete-time Resource Task Network (RTN). The RTN framework is a very general representation which allows a wide range of different process problems to be tackled. Barbosa Povoa and Macchietto (1994) proposed a design of a multipurpose batch pilot plant to accommodate the addition of a new product. The model represents in detail structural and operational characteristics as required for production scheduling, while also accounting for cleaning integration. Wilkinson *et al.* (1996) proposed an aggregated formulation derived directly from the detailed formulation via the mathematical manipulation of the RTN formulation.

Based on the above authors' concepts, most supply chain scheduling problems rely on mathematical programming and generic process representations including STN and RTN. Timpe and Kallrath (2000) described a MILP model based on a time-indexed formulation for supply chain planning of a multi-site production network. The main objectives of their work are to maximise the contribution margin so as to maximise total production with regard to costs or yield, and to minimise changeovers, tank stock and transportation in the chemical process industry, food or consumer goods industry. Bok *et al.* (2000) presented a similar MILP model for maximising profit in continuous flexible process networks. The authors also proposed a bilevel decomposition algorithm to reduce the solving time of the large scale problems. Gupta *et al.* (2000) utilised a mid-term supply chain planning with a two-stage stochastic programming methodology to investigate the trade-off between customer demand satisfaction and production costs. Castro *et al.* (2002) used a discrete-time RTN based representation leading to a MILP formulation to model an industrial batch digester cooking system constrained by an insufficient availability of the steam, shared amongst four digesters. Giannelos and Georgiadis (2003) developed a scheduling model to optimise fast goods manufacturing processes using MILP techniques combined with a continuous rep-

resentation of time. Compared with discrete time-indexed formulations, the authors provided a potential method to reduce the number of decision variables.

Nowadays, more biological products, including influenza vaccines, are moving out of the lab and into production, and the manufacturers are scrambling to expand their process operations while maintaining the quality of the products. If the manufacturers can optimise the use of their production site facilities, they can increase throughput and increase revenues, also possibly decrease the manufacturing costs and manufacturing lead times. In order to optimise productivity, a proper scheduling system could be one of the most important tools in design and optimisation of production facilities in biotechnology. For example, Gosling (2003) presented a scheduling formulation and applied it to a case study in biologics manufacturing of purified water. The purified water was used in significant quantities and was often a limiting resource especially when cleaning operations are required. Simultaneous cleaning demands result in scheduling conflicts and possible purified water shortages. The author proposed a range of scheduling tools to analyse individual process stages and their relationships within the overall process to improve the responsiveness of the process operations.

The problem of scheduling operations is not new, especially in industries where capital is at a premium and optimal use of available facilities is critical to survival. Schmidt and Grossman (1996) presented some optimal scheduling models of testing tasks in the new pharmaceutical product development process. Verdenius and Broeze (1999) introduced the concepts of generalised and instance-specific models for biological, ecological and environmental systems. The concepts are modelled by online scheduling for resource allocation. Petrides *et al.* (2002) suggested a debottlenecking analysis to biomanufacturing facilities and they used computer-aided tools for process design and simulation to identify and eliminate bottlenecks in a biomanufacturing plant.

The objectives of this chapter are to develop models of the manufacturing process, with a view to (1) understanding the process in more detail and determining the degree to which increasing demands can be met; (2) identifying bottlenecks; and (3) to reduce time-to-market without large capital investment, specifically, investigating the benefits of reduced cleaning times and debottlenecking in the specific process under investigation. The model also deter-

mines the key decisions related to the system sequence, size, number of resources and the timing of the operations.

The organisation of this chapter is as follows. Section 2 describes the influenza manufacturing process and presents the data required to perform scheduling. Then in Section 3, we present the definition of the scheduling problem. In Section 4, two different scheduling methodologies used in this work are illustrated. Section 5 presents the computational results obtained and different case studies to improve responsiveness of the current situation. Finally, Section 6 concludes the chapter by discussing these approaches, and generalising the scheduling concepts to influenza vaccine manufacturing systems.

3.2 Process Description

The system considered here consists of the influenza vaccine production facilities between the raw material supply and the delivery of influenza vaccine to the customers. The details of the production process and its associated data were provided by a vaccine manufacturer. The data were then modified to maintain confidentiality and verified by the manufacturer. The distinct feature of this scheduling system lies in the variety of realistic constraints which can be incorporated. Egli and Rippin (1986) suggested that the data required for scheduling are mainly divided into two categories: *plant and process specification* and *planning and market data*. They are described in more detail in the subsequent subsections, where they are illustrated using the data associated with our particular example.

3.2.1 Plant and Process Specification

Available Equipment

The available equipment items and their capacities are listed in Table 3.1. The equipment items are usually used to full capacity.

Table 3.1: Process Details

No. (-)	Task (-)	Unit (-)	No. of Units (-)	Capacity (dm^3)	Time (h)	Task Type (-)
1	Inoculation	Inoculator	1	2500	6.5	Upstream
2-6	Incubation	Incubator1-5	5	1250	75	Upstream
7-8	Inspection	Inspector1-2	2	2500	8	Upstream
9	Harvesting	Harvestor	1	600	8	Upstream
10	Purification	Purifier	1	1250	7	Downstream
11-12	Adsorption	Adsorber1-2	2	1250	10	Downstream
13	Filtration I	Filter1	1	300	4	Downstream
14	Centrifugation I	Centrifuge(a-f)	1	300	14	Downstream
15	H.Centrifugation	H.Centrifuge	1	30	4	Downstream
16	Dilution	Dilutor	1	60	2	Downstream
17	Centrifugation II	Centrifuge(g-j)	1	30	8	Downstream
18-19	Filtration II	Filter2-3	2	45	4	Downstream
20-23	Inactivation I	Inactivator1-4	4	60	84	Downstream
24-27	Inactivation II	Inactivator1a-4a	4	60	30	Downstream
28	Ultrafiltration	Filter4	1	180	6	Downstream
29	Filtration III	Filter5	1	180	7	Downstream
a	Blending	Blend V(a)-(b)	2	225	8	Final
b	Filling	Fill Line(a)-(b)	2	225	16	Final
c	Inspection	Inspect Line(a)-(b)	2	225	24	Final
d	Labelling	Label M(a)-(b)	2	225	16	Final
e	Packaging	Pack M(a)-(b)	2	225	16	Final

Production Processes

The full process details are described using the STN representation and shown in Figures 3.1 and 3.2. An STN is a directed graph, introduced by Kondili *et al.* (1993), which consists of three elements: (1) state nodes (denoted by circles), representing the feeds, intermediates and final products, (2) task nodes (denoted by rectangles), representing the process operations which transform material from one or more input states into one or more output states, and (3) arrows, indicating the flow of material. A set of feeds and output products, the batch processing time, and a set of feasible equipment items is associated with each task. From a logistics point of view, a state of the chemical process corresponds to a particular product, which is either fed into or received from a task. Figure 3.1 is the overview of the whole process where Figure 3.2 represents only the "downstream" process shown in Figure 3.1. For each process, equipment modules have been assigned to each task to form a production line. The occupation of the equipment modules of each production line is illustrated as a Gantt chart on which the raw material requirements are also indicated.

The trivalent influenza vaccine is produced by mixing three intermediates called monovalent vaccine bulks named V1, V2 and V3. V3 is a new monovalent vaccine bulk and is regulated to start processing in mid April in the year in question, while V1 and V2 can start processing in mid February (the World Health Organisation require manufacture to start no earlier than this). The reason for introducing the new strain V3 is that the vaccine effectiveness varies from year to year, depending upon the degree of similarity between the influenza virus strains included in the vaccine and the strain or strains that circulate during the influenza season. Vaccine strains must be chosen 9 to 10 months before the influenza season, and sometimes mutations occur in the circulating strains of viruses between the time vaccine strains are chosen and the next influenza season. These mutations sometimes reduce the ability of the vaccine-induced-antibody to inhibit the newly mutated virus, thereby reducing vaccine effectiveness. The new strains require additional regulation and therefore manufacture tends to be somewhat delayed. Figure 3.2 shows that after the purification stage, the raw material is treated differently in three production lines to form three intermediates within the downstream process. The three intermediates undergo Quality Control

(QC) before being sent to the blending stage of the final process for mixing to produce the final influenza vaccine. At the end, the final influenza vaccines are packed and sent to the customers.

Changeover Times

The items of equipment must usually be cleaned between batches and prepared for the next batch, but equipment cleaning means loss of production time. If a vaccine product change also takes place, additional operations may be necessary which may depend on both the preceding and the succeeding product. Thus, the total time for cleaning depends on the sequence chosen for the production variants. In this case, cleaning of each item of equipment takes place every night between 12 midnight and 8 am; no production takes place during this shift. Changeovers between V1 and V2 are always scheduled to coincide with the daily cleaning.

3.2.2 Planning and Market Data

Available Production Data

The starting and finishing dates of the production period must be specified together with the given working pattern. The UK Vaccine Industry Group (UVIG) states that the total production period for a vaccine is about 9 months in an influenza vaccine manufacturing plant. The National Partnership for Immunisation (NPI) mentioned that the influenza activity peaks during late December/early January with widespread activity occurring simultaneously in more countries than at anytime during the last ten years. From the facts above, UVIG suggests that the production period is normally from February to November in order that there are sufficient stocks available for the peak demands. The working pattern is scheduled as 3 shifts of 8 hours; normally 8 am to 4 pm and 4 pm to 12 midnight are for production while 12 midnight to 8 am is scheduled for cleaning. Partially completed batches at the end of a task can remain in the corresponding piece of equipment since all intermediate materials are assumed to be stable in the short term.

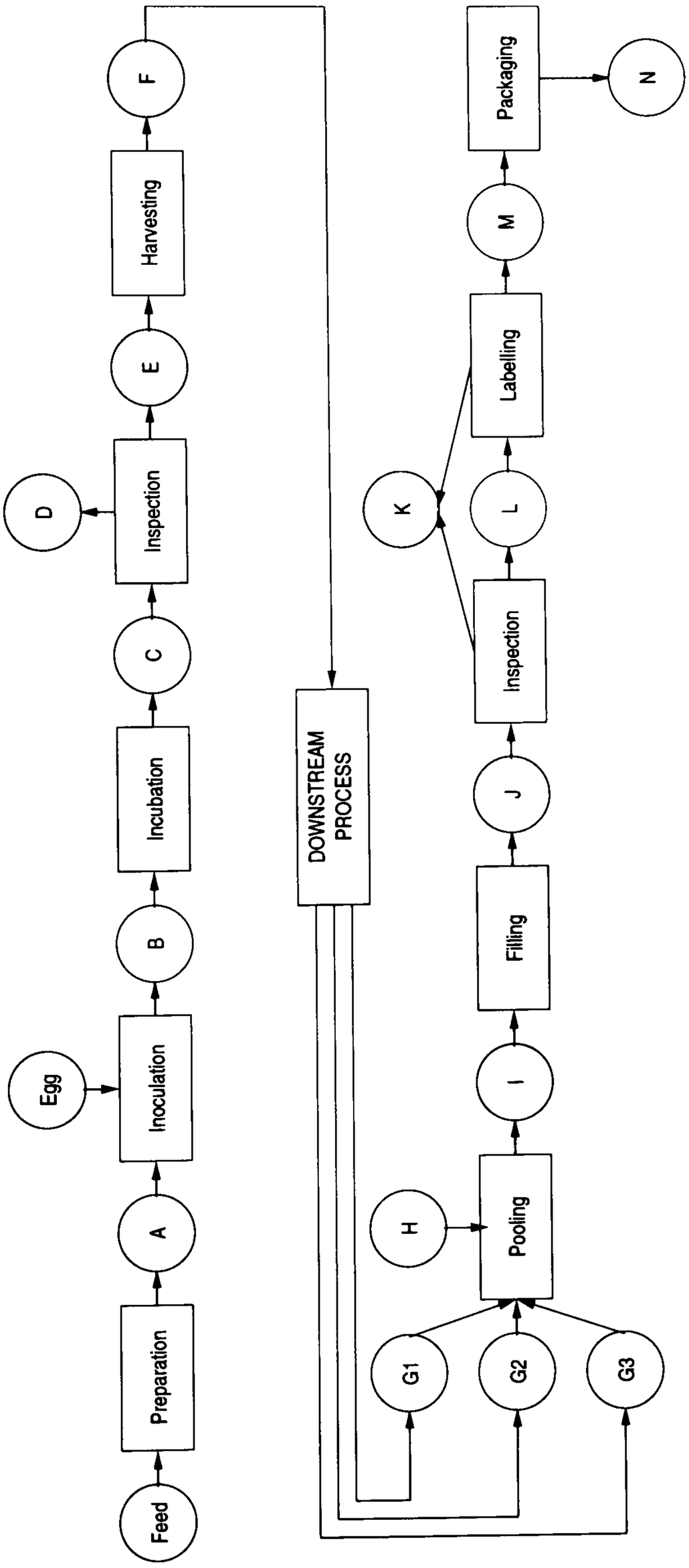


Figure 3.1: STN of the Whole Influenza Vaccine Manufacturing Process

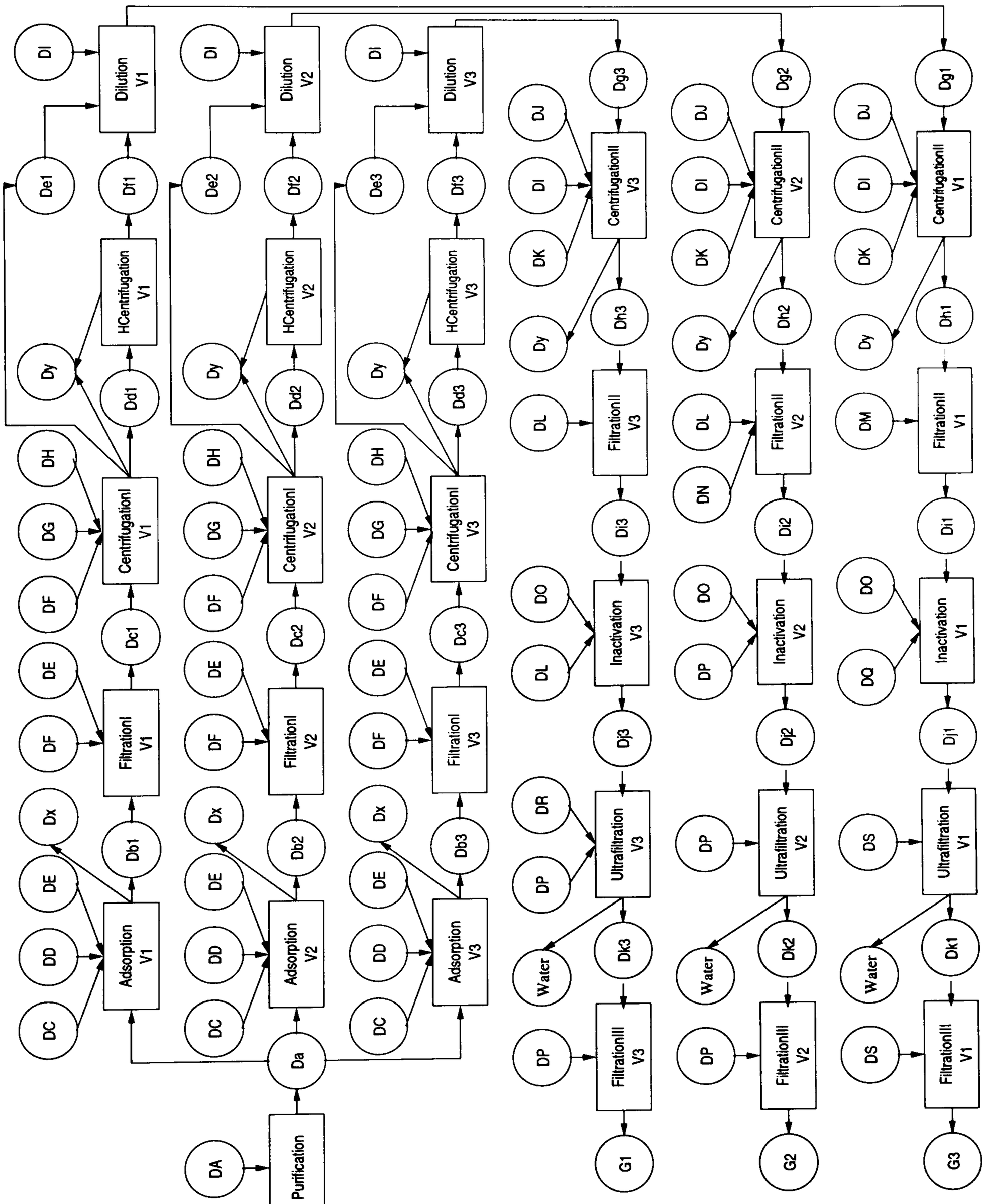


Figure 3.2: STN of the Downstream Influenza Vaccine Manufacturing Process

Demand Data

The vaccine demand requirement plan comprises the customer orders together with delivery dates which must be satisfied during the planning period. The demand is for most European countries and many countries in Africa, the Middle East, Asia and South and Central America, with the first delivery due in late June and the last delivery due in mid November.

Raw Material Deliveries

In the model, raw materials are assumed to be plentiful, so they do not exercise any constraint on the production scheduling.

3.3 Problem Definition

Due to the large size and complexity of the whole production scheduling problem, the multi-stage influenza vaccine production processes in the plants were divided into two sub-processes: (1) upstream-downstream and (2) final processes. This decomposition approach is often used to solve complex scheduling problems that would otherwise be too difficult to solve. Here the process is easy to decompose because sufficient storage is available for the monovalent bulk vaccines. The upstream-downstream process includes all of the stages before the blending stage; the scheduling activity of the upstream-downstream process is to create an effective process schedule, aiming to produce as much of the trivalent bulks as possible as early as possible for the final process. The final process consists of the blending stage to the packaging stage inclusively. Since the final process includes deliveries to customers, in order to produce a profitable process schedule, optimisation is involved. The influenza vaccine scheduling problem can be summarised as follows:

Given:

- Demand forecasts for finished products
- A time horizon of interest
- Available process units and storage tanks

- Available resources
- Production recipes
- Maximum batch sizes and processing time data

Determine:

- The sequence and the timing of tasks and the allocation of equipment item
- The batch sizes of individual tasks
- The amounts of final products sold

Objectives:

The proposed model can accommodate various objectives, such as maximisation of income or profit, maximisation of customer satisfaction, or the minimisation of the costs and resources for specified demand.

3.4 Scheduling Methodology

Even with the reduced complexity attained by decomposing the original problem, the Upstream-Downstream process is still too complex to solve using standard MILP optimisation techniques. For this reason it is necessary to resort to a more heuristic approach with the aim at least of providing good solutions to the scheduling problem.

3.4.1 Heuristic-Based Scheduling for the Upstream-Downstream Process

The upstream-downstream process was scheduled using a fast schedule generation tool, called SimpleSched, developed within the Centre for Process Systems Engineering at Imperial College London. Although there may be commercial available tools that are suitable for this problem, SimpleSched was chosen because it was readily available could easily be modified to suit the needs of the problem.

The algorithm used by SimpleSched starts with a list of production batches ("orders") that are processed in sequence, starting as close as possible to (but not before) a specified start time. In this case, the batches for V3 are added first, all to start from 15 April, so that production of V3 will definitely start on time and take priority over V1 and V2. Then the batches for V1 and V2 are added alternately, to start on 15 February, so that V1 and V2 are alternately produced until production of a second campaign of V3 begins; any orders not processed by this time will be completed after V3 has been produced in full. It then allocates the many individual steps involved in the recipes for the different products referred to in the orders to manufacturing resources, aiming to produce the orders as soon as possible. It uses some basic heuristic allocation rules (e.g. allocate steps to the earliest available resource) to generate good schedules quickly.

The input data are as follows:

- The recipes for each product, in terms of task durations and suitable equipment
- A list of equipment items and their connectivity
- A list of orders for products, each batch of which is processed in order
- A list of unit unavailability, for any units known to be unavailable (e.g. for cleaning)

The algorithm proceeds by considering each order in turn. For each task in sequence, the procedure:

1. Determines earliest start time of the task, i.e. it may not start before the previous task has finished
2. Selects, from the list of suitable equipment items, an item using the following criteria:
   - assign a unit that has not been allocated any tasks
   - otherwise, assign the first unit that is able to start the task on time (i.e. it has completed all of its earlier tasks on time)

- otherwise, find a unit that has a suitable gap in its allocations (i.e. it has been allocated tasks starting before and after the start of the task being considered, but there is still time in between to perform this task.)
- otherwise, select the unit that is available earliest (i.e. the task will not start on time but as early as possible)

By using this scheduling method, the output has a generic campaign layout shown in Figure 3.3. Each monovalent vaccine bulk is produced in a stage-by-stage basis from top to the bottom. Each parallelogram on the diagram consists of many stages and represents a specific monovalent vaccine bulk supply. The first batch is produced at time S, then the next batch follows at time $S + B$, where B is the cycle time. In the base case, the start-up time is 182 hours, and the cycle time is 36 hours.

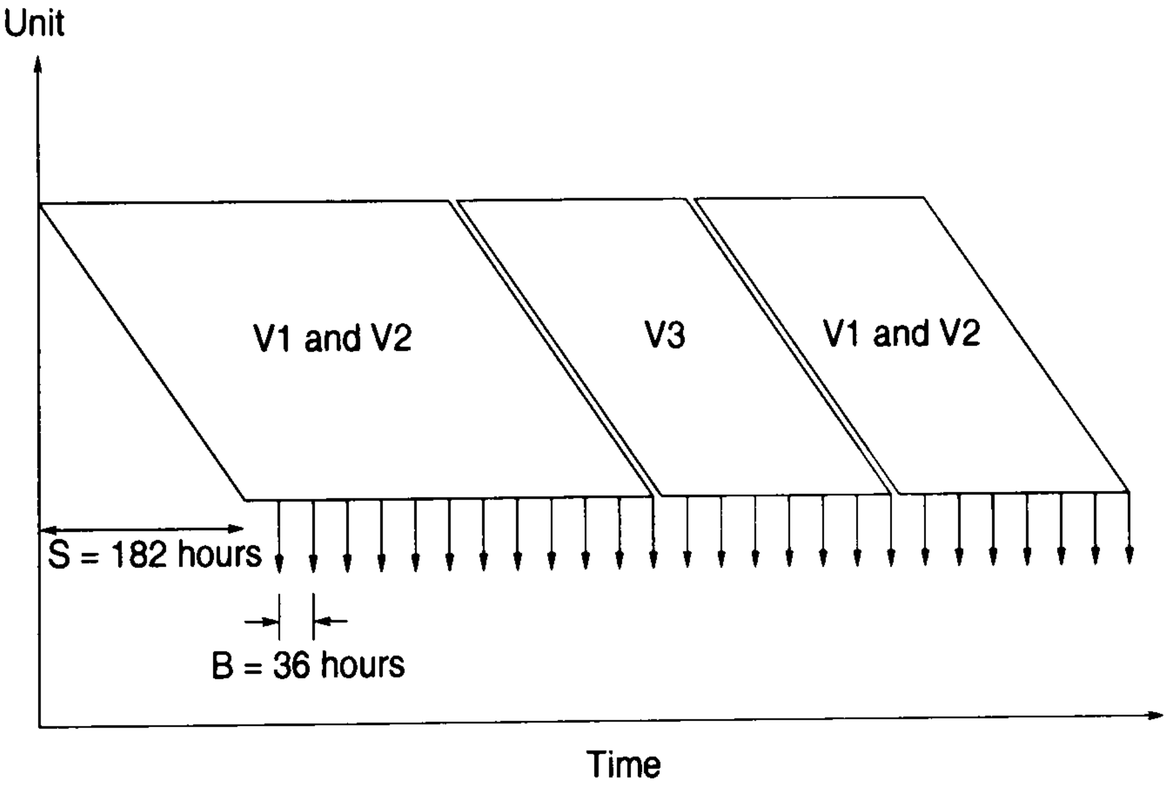


Figure 3.3: Influenza Vaccine Manufacturing Process Campaign Structure

3.4.2 Optimisation-Based Scheduling for the Final Process

Once all the necessary results of the upstream-downstream process schedule were collected from the heuristic-based procedure together with the demand patterns, the blending, filling and packaging processes were then optimised using a general purpose scheduling software tool based on the formulation of Shah *et al.* (1993). This tool was selected as it was available in the department and is commonly used by other academic and industrial organisations.

The model variables represent all tasks, materials, and utilities in each time interval. The formulation is based on a discrete representation of time and the horizon is divided into equal intervals and all transitions (the starting or completion of tasks, or changes in a task's resource requirements, etc) must occur on a time interval boundary.

The objective function of this optimisation-based scheduling model is to maximise the profit subject to the following constraints:

- an equipment item cannot perform more than one task at any time;
- the batch sizes can never exceed the maximum capacity of the corresponding equipment items;
- the amounts of material held in storage can never exceed the storage capacity or be negative;
- a material balance is satisfied for all states.

3.5 Computational Results

The computational results are divided into two parts: upstream-downstream and final processes. In the determination of the best production schedule, the sequences of production variants are generated by the methodologies described in the previous section. Infeasible and non-optimal sequences are progressively eliminated so that only favourable candidates are subject to full evaluation. The production schedule can be altered by external market changes and internal changes in operational policies. Some examples of external market changes may arise when sudden additional orders are received. Internal changes in operational policies may include: (1) cleaning times, (2) installation of new equipment items and (3) debottlenecking. In this section, these scenarios will be investigated to compare with the base case.

3.5.1 Heuristic-Based Upstream-Downstream Schedule

The production schedule generated is shown in Figure 3.4. In Figure 3.4, V1, V2 and V3 are represented by orange, pale orange, and yellow boxes respectively, while the cleaning tasks are represented by black boxes (note that the first row of tasks in Figure 3.4 appear to be cleaning tasks but are actually inoculation tasks that are too short for the shading to be seen in the figure: the black borders of the boxes are all that can be seen). The campaign structure is clearly visible, with alternate batches of V1 and V2 followed by a long campaign of V3. Due to a regulation, the third monovalent vaccine bulk (shown as V3 in Figure 3.4) must only start in mid-April. Therefore, the heuristic-based upstream-downstream schedule provides a schedule with the first and second monovalent bulk vaccine, V1 and V2 respectively, being produced in separated batches from the beginning in one campaign and the third monovalent bulk vaccine, V3, produced afterwards.

The results indicate that the bottleneck is the incubation stage. The key issue in meeting time to market is the tension between getting early batches of trivalent vaccine and sustaining production throughout the season. This is related to the campaign lengths for the monovalent vaccines.

3.5.2 Optimisation-Based Final Schedule

After the heuristic-based scheduling of the upstream-downstream process, the availability in storage of the three finished monovalent vaccine bulks was used to obtain an optimisation-based final schedule. The final process is mainly a mixing process; the three monovalent vaccine bulks are mixed together in the same proportion to generate the final trivalent vaccine bulk. The optimisation-based final schedule is shown on Figure 3.5.

From Figure 3.5, the first stage of the final process is the blending stage which follows the upstream-downstream process schedule and as before, started in early June. The final batch of the trivalent vaccine bulk was produced in October to meet the order date. No bottlenecks are found due to the number of equipment items being sufficient and the activity durations short. The lower part of Figure 3.5 also shows the inventory profiles of the intermediates. 100% of the market demands are satisfied (see also: Figure 3.6(a)).

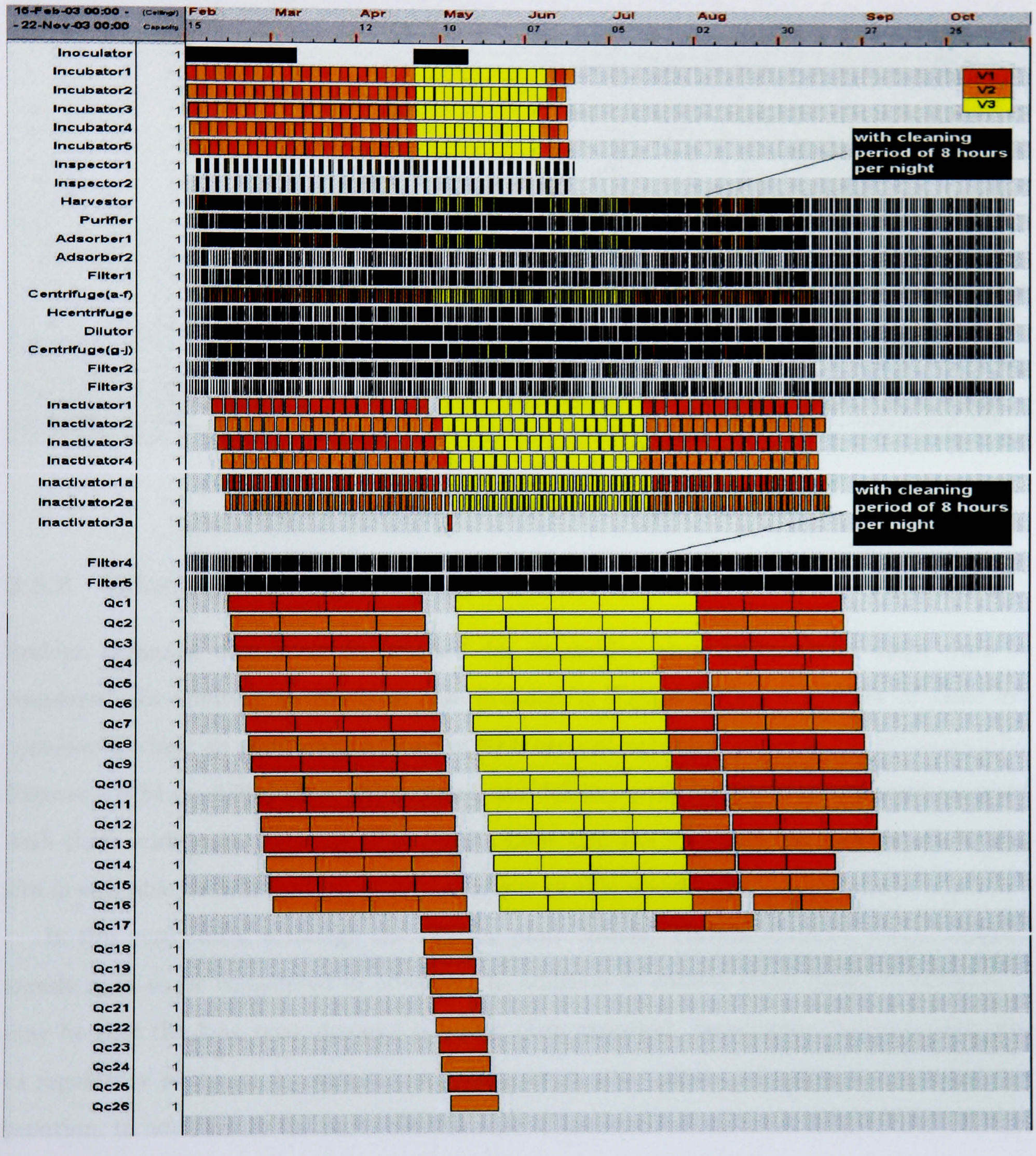


Figure 3.4: Heuristic-Based Upstream-Downstream Schedule (note that Inactivator 4a are not shown here as there are no tasks allocated to it (including cleaning tasks))

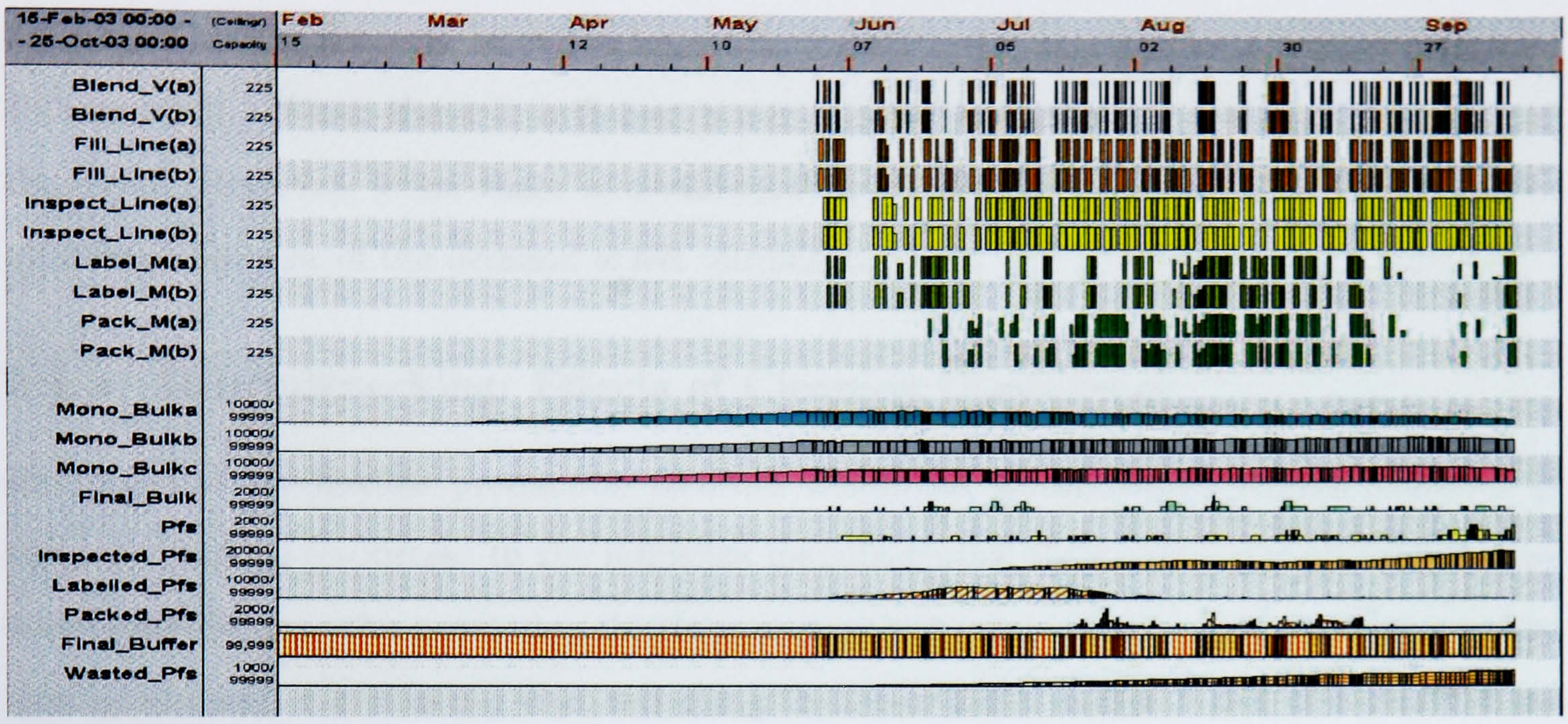


Figure 3.5: Optimisation-Based Final Schedule

3.5.3 Effects of Adding Extra Demands

Sudden demands may occur in practice due to sudden virus outbreaks in large cities or countries. In addition to the base case demand in Figure 3.6(a), a number of cases are considered where an additional demand of 8000 litres of vaccine is added in one of the months. Figures 3.6(b) to 3.6(e) show the demand and delivery patterns when the problem is solved with these additional demands. The results show that the influenza vaccines manufacturing site is still able to fulfil sudden customer orders of this magnitude.

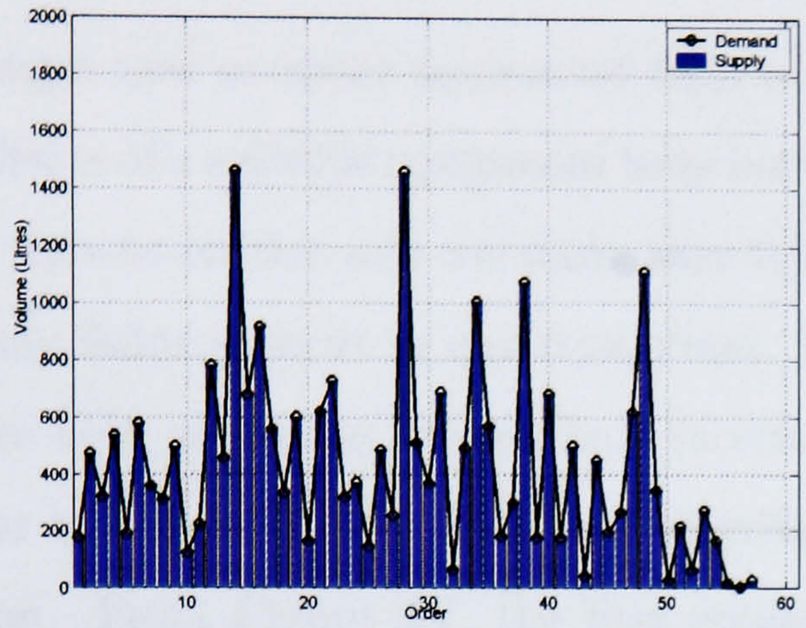
In this case study, although the existing plant satisfies current demand, future demand trends need to be considered in advance. In addition to sudden short peaks in demand, it may be that the long term demand is higher than expected. Sometimes, this can occur due to regulatory problems in competitors' plants or in other plants belonging to the same corporation, in addition to the more obvious case of increased vaccination programmes. Hence, we consider an extreme case where the current demand is doubled. In this case, the existing plant cannot produce sufficient influenza vaccine in the future as shown in Figure 3.6(f). The maximum bulk production throughput is found to be 67 batches per monovalent vaccine bulk. The Customer Service Level (CSL) is reduced from 100% to 93% when the current demand is doubled. Note that the CSL is a supply chain performance measure which is defined as the

fill rate, which is the sum of deliveries made ("sales") over the sum of deliveries requested ("demands"). When there is sufficient inventory, the sum of sales is equal to the sum of demands. However, when there is insufficient inventory, the available inventory would be sold while the rest of the demand is left unfulfilled.

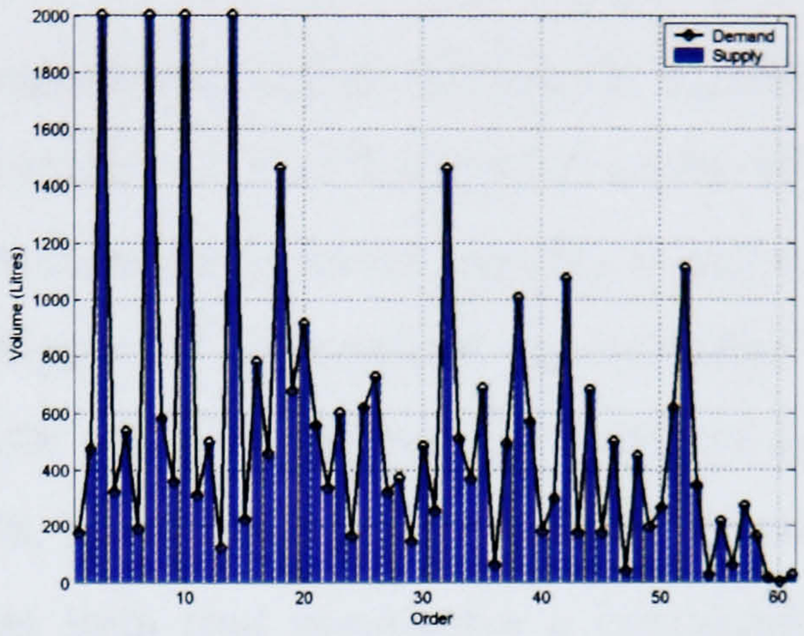
3.5.4 Debottlenecking: Effects of Cleaning Operations

Batch plants are flexible production facilities which can accommodate several products by sharing common resources. In the influenza manufacturing plant, some equipment units are shared several times for processing the three monovalent vaccine bulks. Due to safety, product quality and hygienic reasons, when switching the monovalent vaccine bulks, or even after one or more batches of the same product, the equipment must usually be cleaned. The cleaning task can be done by flushing detergents through various vessels and pipes.

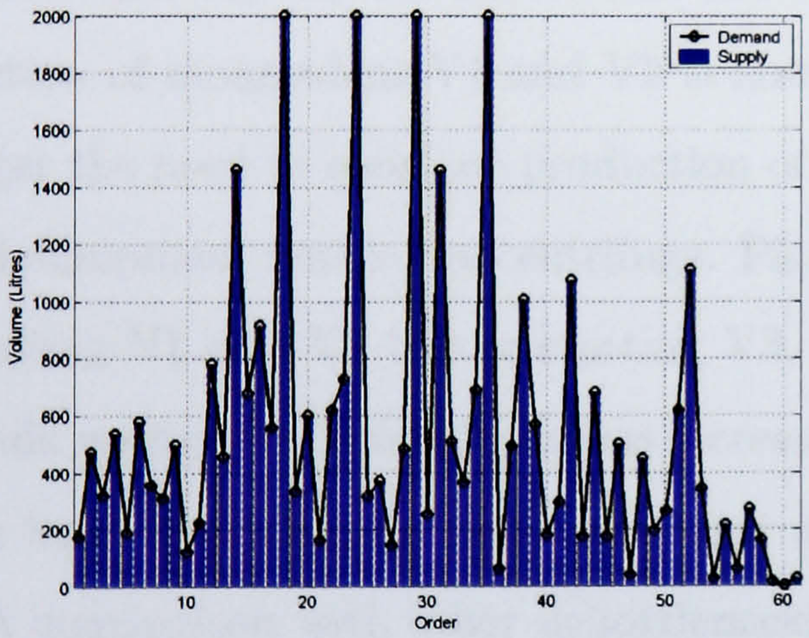
The process operated two manufacturing shifts and one cleaning shift. The move to three shifts, each of which has production and cleaning as necessary is being investigated. Cleaning every night from 12 midnight until 8 am (as was standard practice) was assumed in the base case. In order to make the influenza manufacturing plant operate more efficiently, the cleaning time is shortened to 3 hours immediately after each task for any monovalent vaccine bulk, and production tasks should be squeezed into all the available time as far as possible. The cleaning tasks only occur in the downstream process, so the heuristic-based schedule performance is affected. Figure 3.7 presents a new heuristic-based schedule with the new operating strategy. The figure shows only the first part of process schedule because the second and third parts are mostly the Quality Control (QC) stages, which have no effect on the form of the process schedule. The total bulk production throughput was increased from 67 batches to 93 batches per monovalent vaccine bulk over a single production year. A comparison with other debottlenecking methods is shown on Table 3.2. 100% of CSL is achieved in the double demand case.



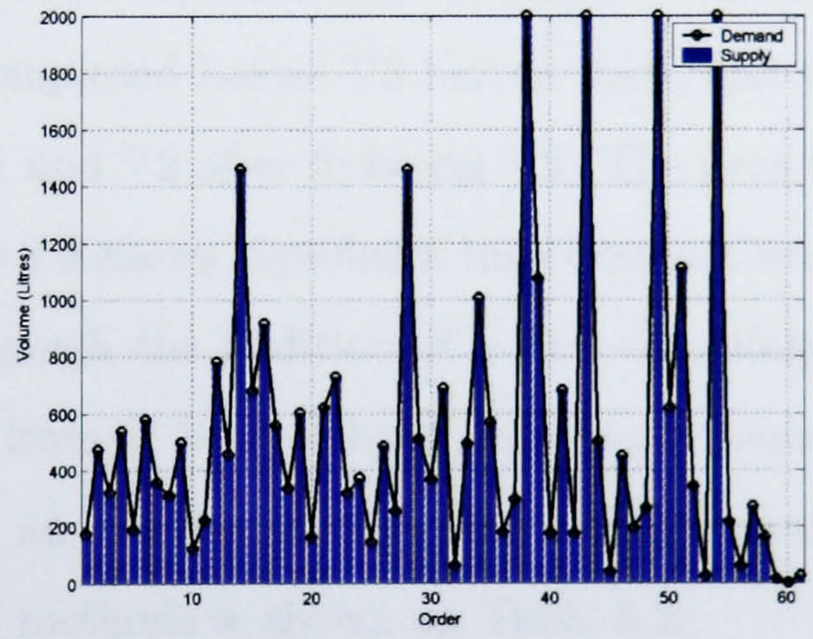
(a) Base demand



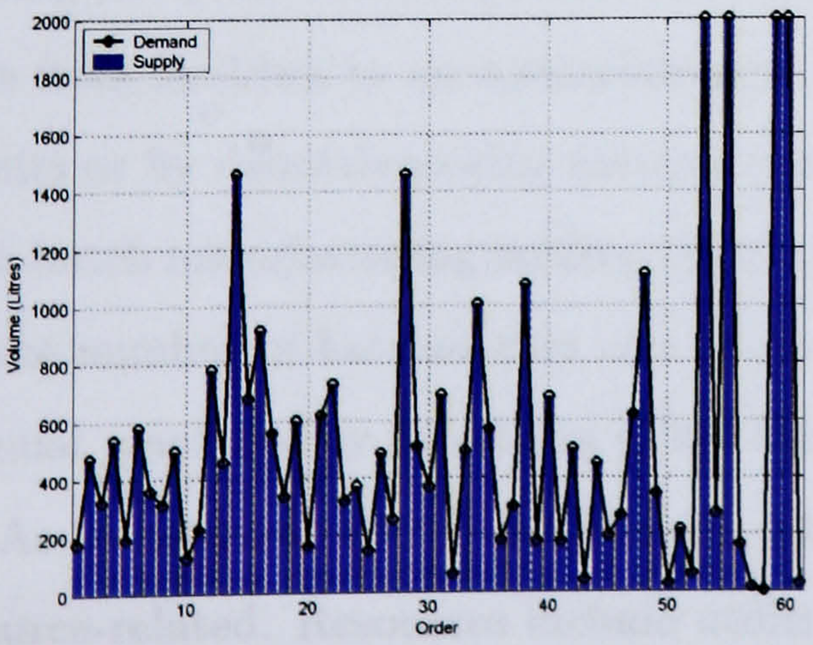
(b) Sudden demand in July



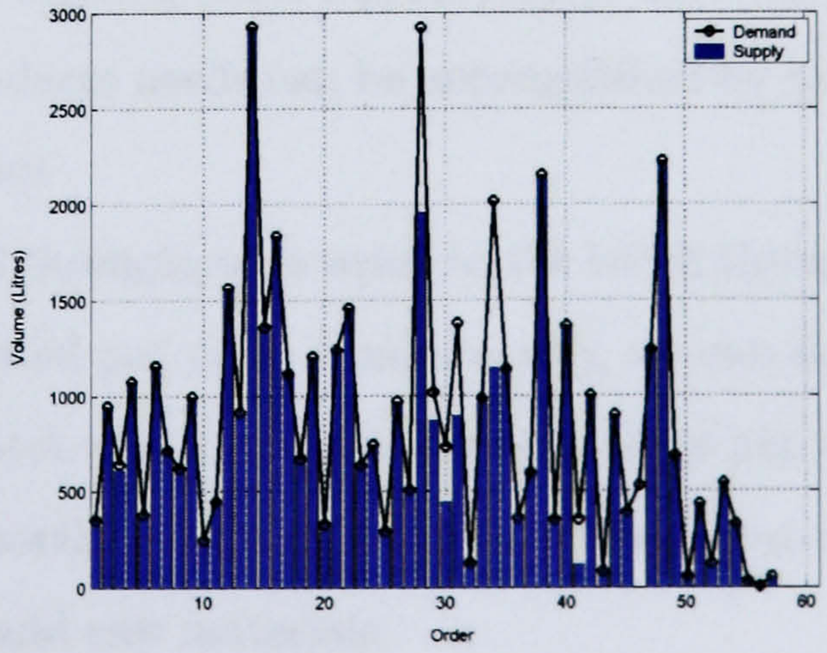
(c) Sudden demand in August



(d) Sudden demand in September



(e) Sudden demand in October



(f) Double demand

Figure 3.6: Sudden demand

3.5.5 Debottlenecking: Effects of Installation of New Equipment Items

Installing a new or spare equipment item may significantly affect the process schedule. The main effects of a suitable equipment item being installed are that it may increase the efficiency, reduce time-to-market and can make sure there is enough equipment capacity to run the plant when any failures occur in any equipment. In Figure 3.7, monovalent vaccine bulks V1 and V2 were held up by the monovalent vaccine bulk V3, since V3 has to be started in April. In order to finish V1 and V2 before starting V3, suitable equipment is added to avoid this situation. From Figure 3.7, the first equipment item that constitutes a bottleneck is the incubator, so in order to solve the problem, a new incubator was first added to the plant and the new heuristic-based schedule for installation of incubator is shown in Figure 3.8. The production pattern on the incubation has improved significantly. It can be seen that the production of monovalent V1 and V2 is now completed before V3 has to start, and there is no longer the need to continue production of V1 and V2 after finishing V3. The next highest utilised equipment unit is the centrifuge. Figure 3.9 shows significant improvement was made by finishing V1 and V2 before starting V3, through the addition of a new centrifuge. The total bulk production throughput was increased from 67 batches to 98 batches per monovalent vaccine bulk by adding an extra incubator and an extra centrifuge over a single production year. A comparison with other debottlenecking methods is shown on Table 3.2.

3.5.6 Discussion

Increasing the plant flexibility can maximise an existing plant's profitability. Increasing production from facilities to accommodate new products needs can be accomplished by building new units or by debottlenecking existing capacity.

In a batch manufacturing facility, the annual throughput is equal to the batch throughput times the number of batches that can be processed per year. Consequently, we can increase the annual plant size by increasing either the batch size or the number of batches per year or both. As we attempt to do that, we run into bottlenecks that are either equipment-related or resource-related. Resources include utilities and raw materials.

The bottlenecks that limit the number of batches per year are known as *time or scheduling*

bottlenecks. Those that limit the batch size are known as *size* bottlenecks. Finally, those that limit the overall plant throughput are known as *throughput* bottlenecks. Typically, the time or size bottleneck is also the plant throughput bottleneck.

Voudouris (1996) presented a large scale Mixed Integer Linear Programming (MILP) approach to identify the bottlenecks and to streamline the operations, therefore, to suggest design modifications that will improve efficiency and responsiveness of the supply chain of a fine chemical manufacturer. The mathematical model was based on a discrete time representation to capture the dynamics of the system, and it can be utilised to simulate an existing scheduling policy and evaluate its efficiency.

To identify throughput bottlenecks, in addition to size utilisation we must also consider the time utilisation of each piece of equipment. The method to release the bottleneck is to install an additional corresponding bottleneck unit to reduce the unit utilisation. This will continue until a satisficatory throughput is achieved.

In the influenza vaccine manufacturing plant, the main bottleneck is the incubation of 75 hours (see Figure 3.10(a)) and restricted hours of operation: 16 hours operation with 8 hours cleaning time every night. The possible solutions to the debottlenecking problem are compared with the base case (Case A). Case B is to change the cleaning time policy from 8 hours every evening to only 3 hours after each stage as in the previous section (see Figure 3.10(b)). Case C is to change the cleaning time policy as in Case B together with adding an incubator. From Figure 3.10(c), the new added incubator reduces the utilisation rate of the original incubators successfully, however leaving the centrifuge as the only bottleneck amongst all equipment items. Case D is as Case C but a new centrifuge is added. From Figure 3.10(d), the new added centrifuge reduces the utilisation rate of the singular centrifuge. The comparisons were performed using the same doubled demand profile (shown in Figure 3.6(f)) in each scenario. The strategy is to balance capacity until all pieces of equipment are utilised at close to 100%. The results are summarised in Table 3.2. Suggested solutions are to add more incubators and implement a more flexible operating strategy such as 24 hours operation with cleaning time of 3 hours after each stage.

Table 3.2: Comparisons of Different Methods Debottlenecking Strategies

Case	Batches Obtained (% change)	Bottleneck	Customer Service Level
A	67 (-)	Incubation	93%
B	93 (39%)	Incubation	100%
C	98 (46%)	Inactivation	100%
D	98 (46%)	Incubation	100%

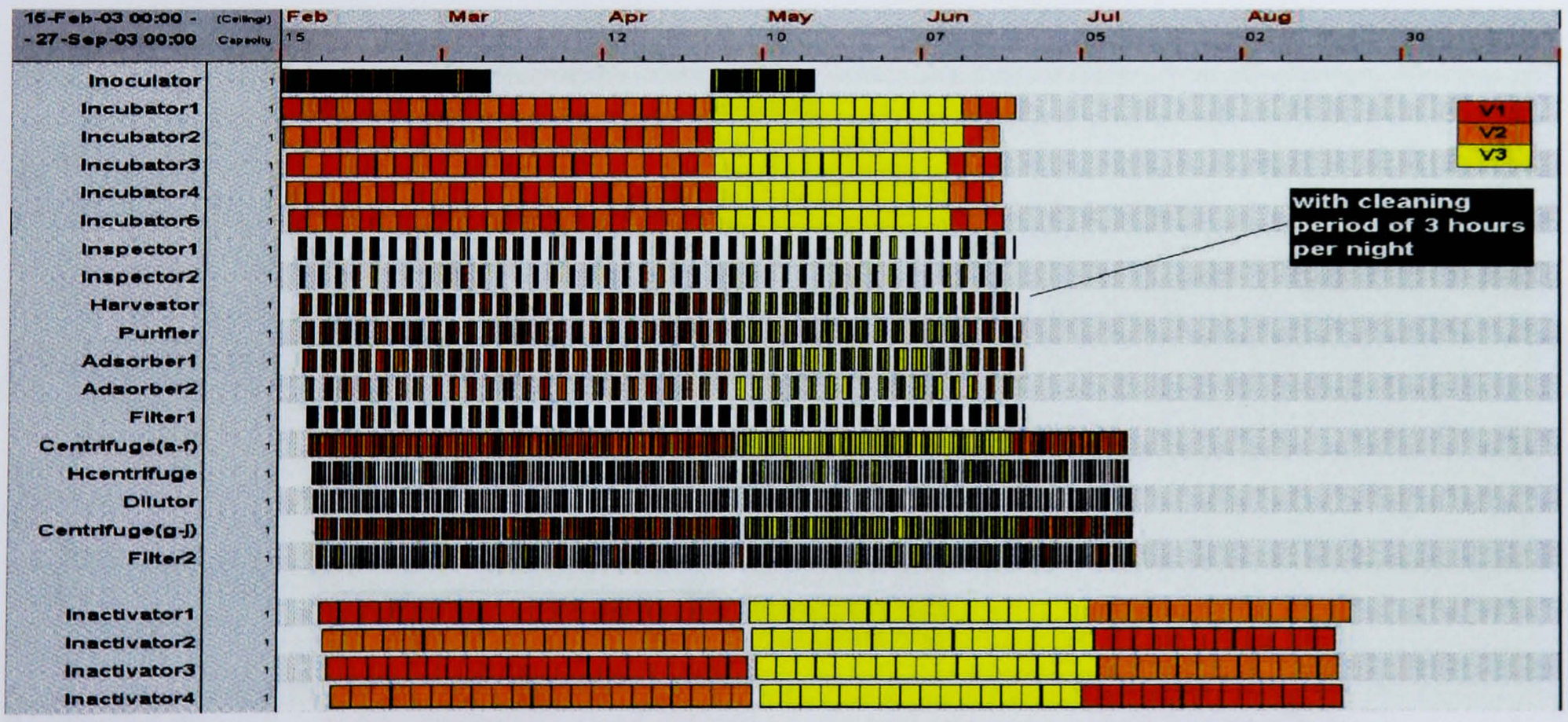


Figure 3.7: Heuristic-Based Upstream-Downstream Schedule: Effects of Cleaning Times

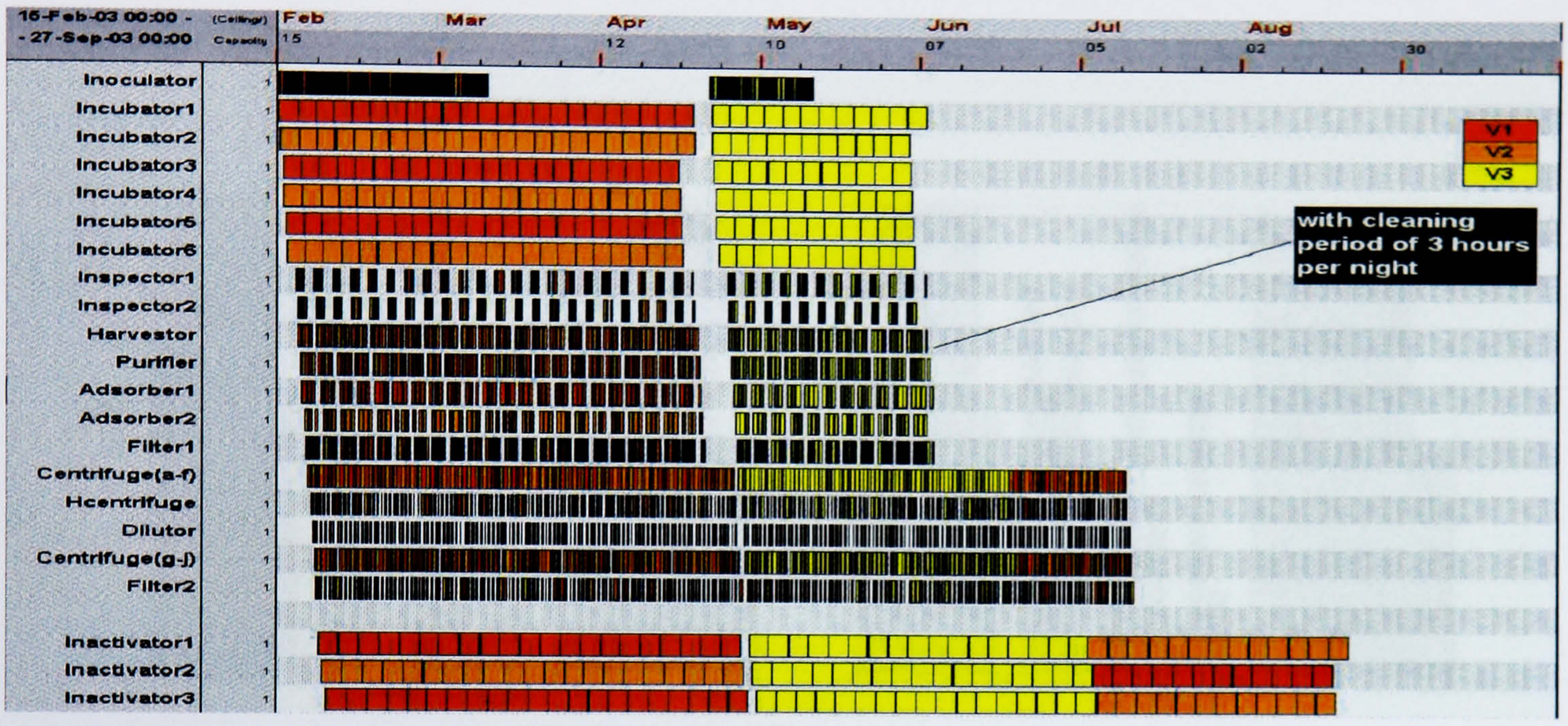
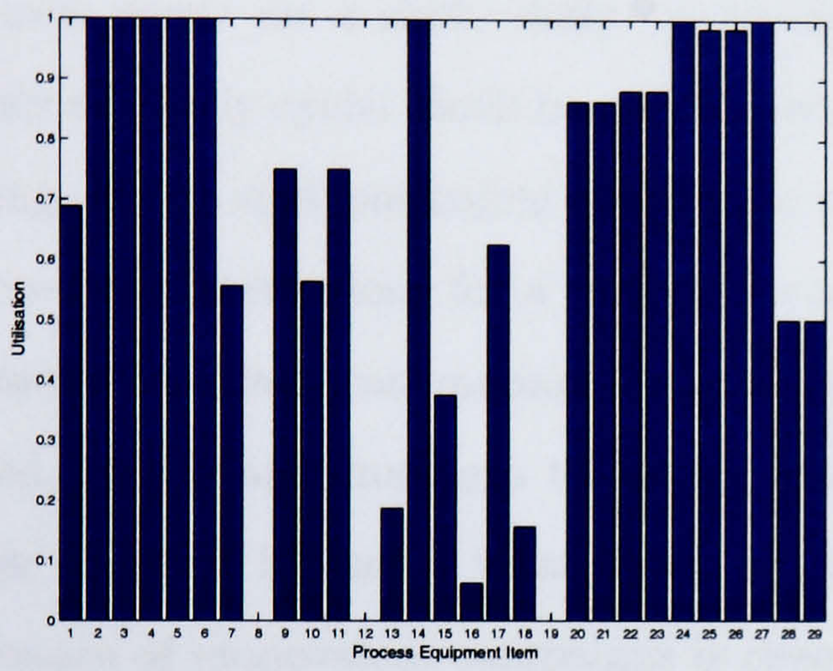
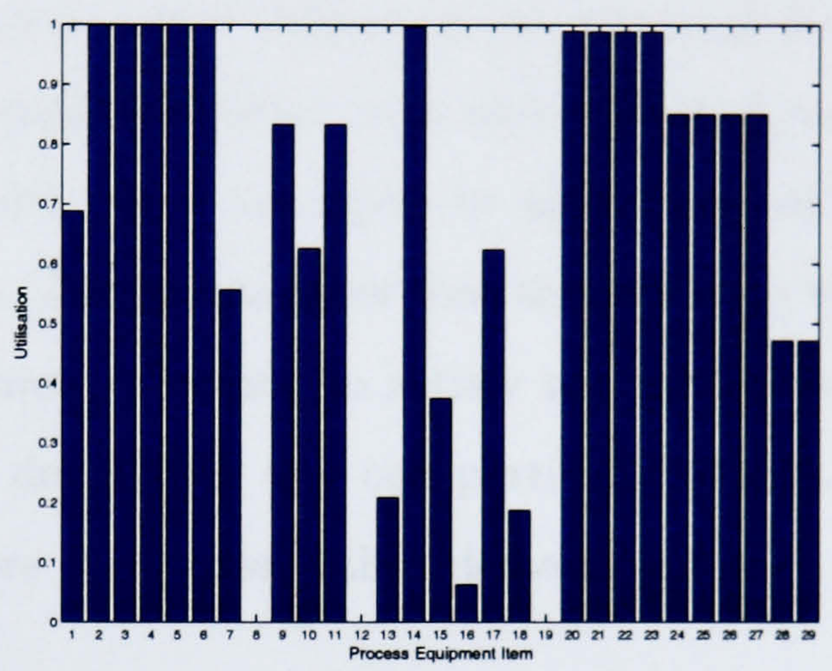


Figure 3.8: Heuristic-Based Upstream-Downstream Schedule: 1 Additional Incubator

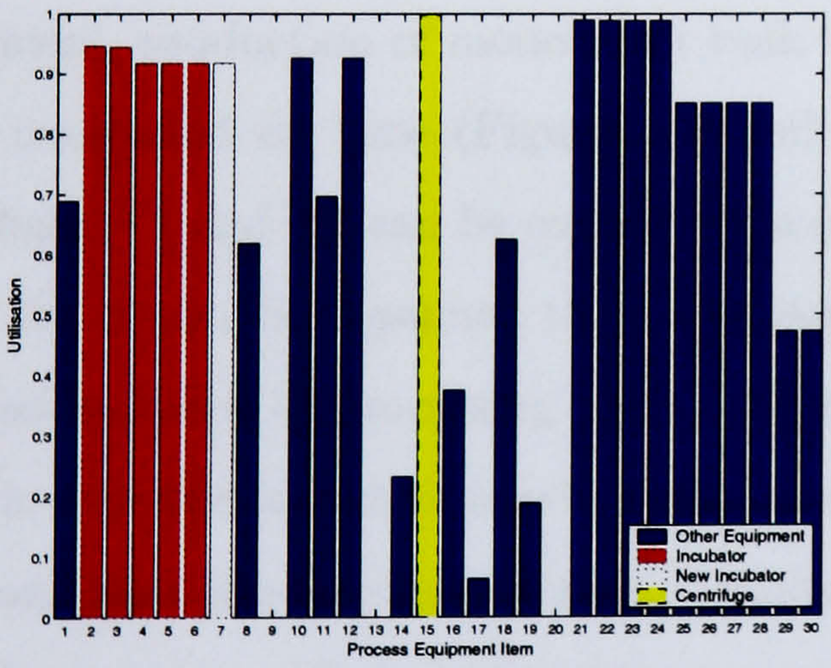
Figure 3.9: Heuristic-Based Upstream-Downstream Schedule: 1 Additional Incubator and 1 Additional Centrifuge



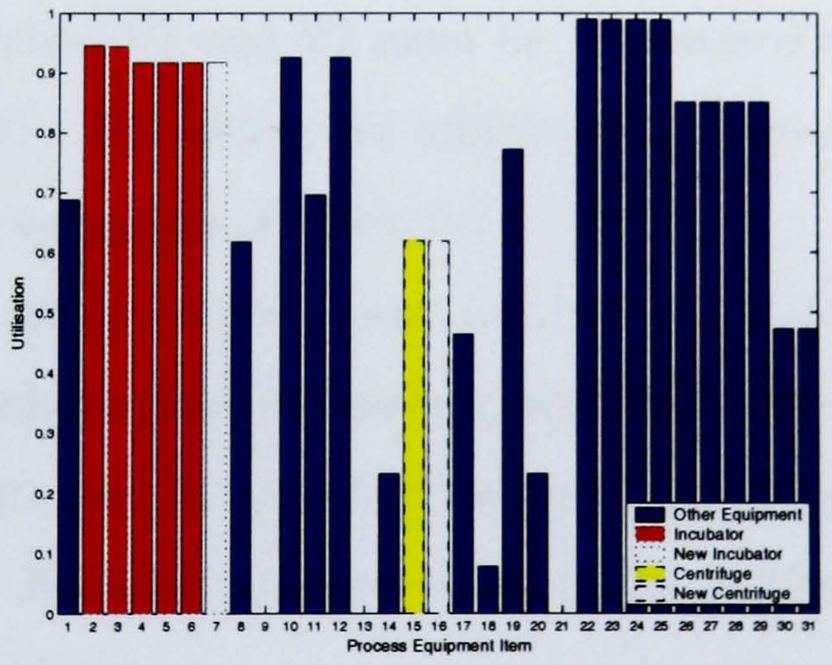
(a) Case A: Base Case



(b) Case B: Cleaning time is reduced from 8 hours to 3 hours per day



(c) Case C: 1 incubator is added



(d) Case D: 1 incubator and 1 centrifuge are added

Figure 3.10: Debottlenecking

3.6 Concluding Remarks

Due to the complexity of the tasks and the regulations, bioprocess scheduling is a potentially difficult activity, complicated by bottlenecks that depend on the schedule. Planning of the work may occur on a shift, daily, or weekly cycle, with infrastructure planning on a six monthly or yearly cycle. Both heuristic-based upstream-downstream and optimisation-based blending, filling and packaging scheduling models were developed to understand all task-resource-time interactions for a vaccine process. The results show that the influenza vaccine manufacturing plant can manage to produce enough vaccine to satisfy the current level of demand, and it also manages to satisfy extra demand in any one particular month. The process schedule indicates what flexibility there is to meet other demand patterns. The importance of monovalent campaigns is clear.

The scheduling model is also used to explore a different shift pattern and new equipment investments as alternative possibilities to increase throughput. This can be seen in the Gantt charts of Figures 3.4 and 3.7 to 3.9, where it can be seen that without capacity investment, production of monovalent bulk vaccines V1 and V2 must be interrupted for V3 to be completed on time (Figures 3.4 and 3.7). By adding an additional incubator and centrifuge, V1 and V2 can be completed in one campaign (Figures 3.8 to 3.9).

In the model, we assumed that: the tasks are run without any delay, transfer times of material included in processing times, unlimited intermediate storage and feed. The more realistic situation is that various material transfers need to take place before and after cleaning tasks and that intermediate storage is limited. However, this would make the problem too difficult to solve. These assumptions were necessary in order to use the heuristic-based scheduling algorithm, as it does not account for material balancing and storage at all. The main difference between the optimisation and heuristic approaches is, of course, that the heuristic approach is not guaranteed to find an optimal schedule. The benefit of the heuristic approach is that the schedules are generated very quickly, and in most cases they are quite satisfactory.

In this chapter, we focussed on the internal details of the vaccine manufacturing plant. Having found some opportunities for improvement in the scheduling of the manufacturing

process, we now turn our attention to the longer term considerations of capacity planning and investment strategies in next two chapters.

Chapter 4

Capacity Investment Planning for Multiple Vaccines under Uncertainty-1:Capacity Planning

In the coming years, competition in the vaccine market is likely to increase and vaccines will begin to resemble the model for conventional pharmaceutical products, requiring rapid market entry in order to minimise lost revenue and avoid the threat of competition. Therefore, companies will need to enhance their manufacturing capabilities, in terms of capacity investment and efficiency, in order to compete effectively within this market. The focus of this work is to describe a scenario-based approach to support capacity-related decision-making and the investment strategy subject to uncertainty of demands for multiple vaccines given the details of processing time, investment costs and production scale. Our model is appropriate for products in different stages of R&D and development, they may have different expected clinical trial outcomes. These outcomes may have different probabilities of occurrence and because the information from different trials will become available at different times, this means that the investment planning model becomes a stochastic multi-period, multi-stage and multi-scenario mixed integer optimisation model. A probabilistic analysis is also used to find an approximate expression for the expected Net Present Value (eNPV) for vaccine production with different scenarios. To complement the use of financial risk management,

definitions of some classical risk measures are developed and applied in Chapter 5.

4.1 Introduction

Manufacturing vaccines is time consuming, resource intensive, heavily regulated and occurs in a highly risky industry sector, where the typical market demands and changes are difficult to predict. Although it is hard to operate in the vaccine industry, profits and rewards are substantial. To ensure that the best vaccine development decisions are taken, efficient long-term economic planning is an important consideration for any vaccine manufacturer. The trend today is to try to predict future market demands and future market changes so as to maximise profits and minimise costs.

Many decisions have to be made to achieve good returns under given constraints and limited resources. In the vaccine industry, one has to determine production, distribution, sales and inventory plans based on the customers' orders and market information while observing all relevant constraints. Since vaccine development is a long-term process, strategic planning is closely linked to the vaccine industry's business plans and direction as well as the R&D pipeline. The capacity planning decisions for new and existing vaccines depend on different factors. Capacity has historically been limited to the commercially attractive markets when a new vaccine is introduced. The production costs of newly-launched vaccines are sensitive to experience effects, therefore newly-launched vaccines are always characterised by high prices and high costs. As manufacturers gain experience in making a particular vaccine, certain process measures will improve, in particular bulk batch yields, and as a result, even without additional plants or capital expediture, capacity tends to increase over time. The installed production capacity for established vaccines mainly depends on the future demand. For example, GlaxoSmithKline (GSK) announced in July 2005 that they will invest 94.3 million euro to double production capacity for their Influsplit/Fluarix influenza vaccine at their Sachsisches SerumWerk (SSW) plant in Dresden, Germany (see GlaxoSmithKline (2005)). GSK will build a second plant at the site and increase its annual production capacity from 30 million influenza vaccine doses per year currently, to 60 million doses annually before the end of this decade.

GAVI and Mercer Management Consulting Group suggested that the capacity investment alternatives can be divided into 3 phases: new product launch, market penetration and product maturity (see Godal (2002)). Vaccine capacity investment development both within and across markets has been heavily influenced by the product lifecycle. The details are summarised in Table 4.1.

Table 4.1: Economics for Vaccine Lifecycle Stages in Industrial/Developing Countries

Factor	Newly-Launched Product	Market Penetration	Product Maturity
Number of Producers	Low	High (Industrial)	High (Global)
Pricing	High	High (Industrial)	Low (Global)
Cost	High	Medium	Low
Profitability	High	High	Moderate
Available Capacity	Low	High	Potential Surplus
Availability	Poor	Good (Industrial)	Good (Global)
Market Demand	Low	High (Industrial)	High (Global)
Examples	Rotavirus, DTaP	Hib, HepB	DTP, BCG

In the vaccine industry, capacity planning is used to create investment, production, distribution, sales and inventory plans based on customer and market information while observing all relevant constraints. Capacity planning problems are always considered as long-term and strategic; the time scale is typically a number of years. At the strategic level, mixed integer linear programming (MILP) is often used to facilitate enumerating discrete options. Birewar and Grossmann (1989) considered and analysed the demanding task of simultaneous production planning and scheduling. Sahinidis and Grossmann (1989) presented a multi-period MILP optimisation model for long range planning in the chemical industry. The model was used for optimal selection and expansion of processes given the time varying demand forecasts and chemical prices. They investigated several strategies (including branch and bound, and heuristics) to reduce the computational expense of solving large-scale, long-range planning problems. Later, Sahinidis and Grossmann (1991) and Sahinidis and Grossmann (1992)

then reformulated the multi-period MILP model based on a variable disaggregation technique which exploits lot sizing substructures. The reformulation strategy was used for long term planning and batch scheduling. Comprehensive examples for long-term planning problems and the effects of the time discretisation approach can be found in Liu and Sahinidis (1995). More recently, Gupta and Maranas (1999) presented a solution procedure for mid-term planning problems based on Lagrangean relaxations of complicating constraints, creating smaller, easy-to-solve subproblems.

The problems of capacity planning of production capacity and product portfolio are subject to a pool of uncertainties, particularly demand and clinical trials outcome/success. Much of the work in recent years has focussed on the scenario-based approach which deals with capacity planning under uncertainty and account for different possible future outcomes through the use of scenarios. The scenario-based approach was pioneered by Dantzig (1955), who dealt with multi-stage problems under uncertainty, particularly two-stage programming problems with uncertain demands. The character of the problem is that events and decisions are divided into two stages. The decisions made in the first stage are the only ones that have to be determined at the time of making the decision. The decisions in the second stage are based on the first stage decisions and are made when the demand uncertainty is revealed. There have been several instances of this type of model reported in the process engineering literature. Shah and Pantelides (1992) presented a design procedure for batch process plants under uncertainty and used the approach of scenarios which tries to predict all future outcomes. Subbrahmanyam *et al.* (1994) also adopted this approach together with discrete probability distributions, where the probabilities are assumed to be known in advance. Ierapetritou and Pistikopoulos (1994) presented a problem of two stage production planning under uncertainty. They used Gaussian quadrature techniques to estimate the expectation of the objective function. Liu and Sahinidis (1996) further modelled the uncertainty in demands and prices using discrete random parameters, leading to multi-scenario, multi-period problems. Petkov and Maranas (1997) extended the work of Birewar and Grossmann (1989) to treat the multi-period planning model for multi-product plants under demand uncertainty. Gupta and Maranas (2000) extended a mid-term planning model of McDonald and Karimi

(1997) to solve a two-staged stochastic programming approach on a mutli-site mid-term supply-chain planning under uncertainty problem. Iyer and Grossmann (1998) used a bilevel decomposition technique to solve a multi-scenario long-term planning problem in the reduced space of binary variables for different forecasts of demands and prices. Ahmed and Sahinidis (1998) presented a robust two-stage optimisation model to deal with uncertainty, introducing a robustness measure that penalised second stage costs that are above the expected cost. Ahmed and Sahinidis (2000) further proposed heuristics for deterministic capacity planning problems using analytical techniques. More recently, Ahmed and Sahinidis (2003) further extended the capacity expansion problems to the stochastic case using probabilistic analysis to handle capacity expansion costs under forecast uncertainties. Gatica *et al.* (2001) presented an optimisation-based stochastic MILP model that captured the uncertainty of capacity planning for the pharmaceutical industry so as to select the optimal investment strategy for producing new drugs.

Issues of multi-product problems, multi-period problems, detailed planning problems, two-stage problems, and stochastic multi-scenario problems have all been approached separately in the past. In order to combine all these issues in this multiple vaccines capacity planning problem, a new algorithm is required. The main objectives of this chapter are (1) to develop a mathematical model for problems with planning and design under uncertainty that allow the analysis of multiple vaccine manufacturing facilities over a long horizon. The model should account for all of the production rates of the vaccine intermediates and the final vaccine products as well as the fulfilment of the customers' orders; (2) to find optimal investment decisions and product selection with their plans of production and sales, balancing risk and expected Net Present Value (eNPV) by capturing the system logic and data necessary for the optimisation activity.

The first generation of this type of model was built by Samuelsson (1999). The model contained mainly a deterministic part and a simple stochastic part with 2 outcomes (pass and fail). Gatica *et al.* (2001) extended this model to take into account 4 stochastic outcomes and 4 products where the first product is treated purely as deterministic (i.e. the first product does not need to go to clinical trials). The challenge of this chapter is to capture the main

characteristics of the vaccine industry. In order to do so, all products should be subject to clinical trials: so all products are stochastic and the deterministic stage is purely for the initial investment phase.

The chapter is organised as follows. Section 2 defines the problem in terms of an illustrative example together with an outline of the scenario-based model. Section 3 presents the mathematical formulation for the capacity investment planning model and related input data. Section 4 illustrates the computational results obtained from the model with discussion. Finally, some concluding remarks are given in Section 5. Chapter 5 will focus on the financial risk analysis and the decision-making analysis.

4.2 Problem Statement

The system to be considered for capacity investment planning comprises multiple vaccine production facilities between the raw material supply and the delivery of vaccines to the customers. Consider a manufacturing site that has four different vaccine products (product 1, 2, 3, 4) in different stages of development at the current time. All products are in clinical trials and it is not certain whether they will be successful products or even pass clinical trials. Based on market and epidemiology studies, the nominal predicted demands for the four vaccine products are forecasted. The model then considers four possible outcomes for each vaccine: (1) passes clinical trials and the demand is 25% higher than forecast (known as the High, or H, scenario); (2) passes clinical trials and the demand is as forecast (Target, or T, scenario); (3) passes clinical trials and the demand is 25% lower than forecast (Low, or L, scenario); and (4) fails clinical trials (Failure, or F, scenario). The fact that these outcomes have different probabilities of occurrence and that the information from different clinical trials will become available at different times means that the capacity planning problem will become a large scale multi-period, multi-stage and multi-scenario optimisation problem.

The model considers a 17-year horizon. Since there are 4 possible products with 4 outcomes, there are $4^4 = 256$ possible demand scenarios. The layout is illustrated as a scenario tree diagram in Figure 4.1. Note that the scenario tree in Figure 4.1 implies a temporal relationship between the introduction of the four different products. This is not necessarily

so; the diagram is only intended to show the relationship between the scenarios and that none of the outcomes are known in stage T1. Indeed, in the example presented here, all four products complete clinical trials at the same time (as can be seen from the forecasted demands in Table 4.3). Scenario trees are excellent tools to choose between several courses of action. They provide a highly effective structure within which options can be laid out and the possible outcomes of selecting those options can be investigated. They also form a balanced picture of the risks and rewards associated with each possible course of action.

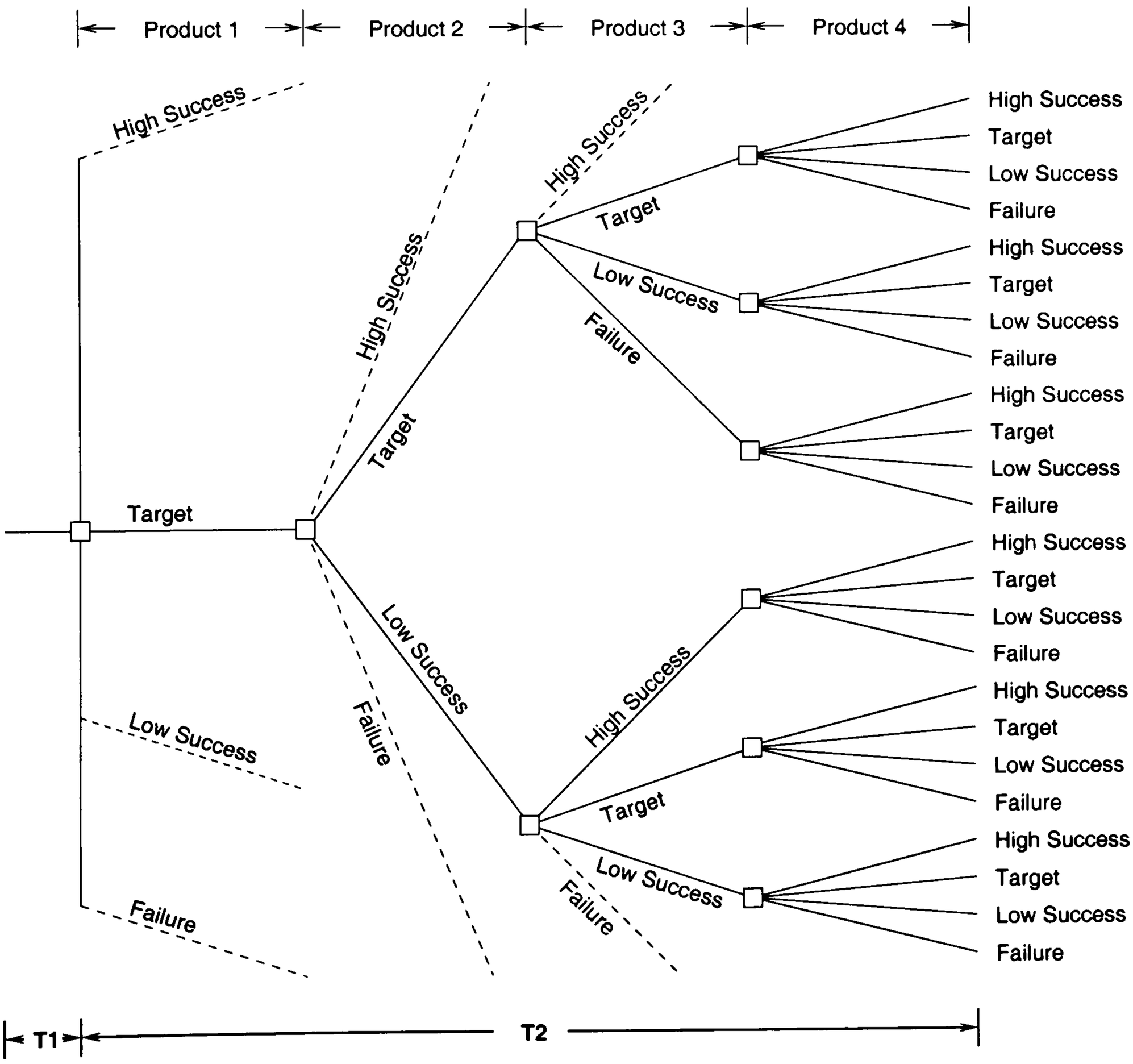


Figure 4.1: Scenario Tree

The structure of the model is divided into two phases as shown in Figure 4.1. The first phase, T1, is treated as deterministic. T1 is assumed to have no production, however manufacturing suite investment and construction, production selection and scaleup decisions must be made at this stage. The second phase, T2, is treated as stochastic. T2 involves production for all the successful vaccines, it considers multiple scenarios, each scenario resulting from the completion of a clinical trial for a particular vaccine. However, only those products that have been selected in stage T1 and pass clinical trials can be manufactured in stage T2; those that have not been selected in stage T1 cannot be manufactured even if they are successful.

The scenario-based model provides important decisions associated with each scenario. The decisions may determine whether or not to make capacity expansion investments and how much of each vaccine to produce in order to fulfil the customers' orders.

The key binary variables (0 or 1) in the scenario-based model are used to capture capacity expansion decisions. The manufacturing site consists of several suites, where each suite provides utilities and facilities for production, scaleup, and qualification of any or all of the vaccines. The number of the suites initially available is fixed and we shall assume that there are no restrictions on how many new suites can be invested in at any time. However, there is a construction lead time for the new suites to be developed. Although there are no limitations on the amount of vaccines that can be stored, as inventory cost is assumed to be negligible, there is a product lifetime for the vaccines. If a decision is taken that a vaccine be produced, it does not necessarily need to meet a certain minimum demand. If a vaccine fails in its clinical trial, the demand is consequently zero over all time periods. On the other hand, a successful product may have one of the T, H or L demand patterns as described above.

Based on the given probabilities of success for each vaccine, the objective of the model is to find optimal investment decisions with their plans of sales and suite allocation which maximise the eNPV over the planning horizon.

4.3 Mathematical Formulation

The capacity investment planning model captures the above issues so as to obtain an optimal capacity planning and investment strategy subject to the uncertainty of the clinical trials

for each potential vaccine. The model is based on the work by Samuelsson (1999). A two-stage stochastic MILP investment and detailed planning model was derived in parallel with a comprehensive deterministic MILP model. The model formulation is given below.

4.3.1 Nomenclature

Indices

p	product
t, θ	time period
k	scenario

Sets

T_1	set of time periods in the first stage
T_2	set of time periods in the remaining stages

Parameters

A_0	number of suites already in place
D_{pt}	nominal forecasted demand of product p at time t
f	inflation rate
g	interest rate
H_t	available production time at time period t
L_p	production losses of product p
L^{sq}	loss factor incurred by scaleup lead times
M	maximum number of suites
r_p	production rate of product p
δ	construction lead time
ϵ_t	discount factor (function of f, g and t)
η	fixed operating cost

ν_{pt}	forecasted sales price of product p at time t
ω	capital investment cost
π_k	probability that scenario k will occur
σ_p	research and development cost of product p
τ	product changeover time
ξ_p	variable operating cost of product p
ζ_p	life time of product p

Integer Variables

A_t	number of suites available for production at time t
	in the first stage
A_{tk}	number of suites available for production at time t in scenario k
	in the remaining stages
E_t	number of suites purchased at time t
	in the first stage
E_{tk}	number of suites purchased at time t in scenario k
	in the remaining stages
P_{tk}	number of products produced at time t in scenario k
	in the remaining stages

Binary Variables

V_p	=1 if product p is selected
	in the first stage, 0 otherwise
V_{pk}	=1 if product p is selected in scenario k
	in the remaining stages, 0 otherwise
Y_{ptk}	=1 if product p is produced at time t in scenario k
	in the remaining stages, 0 otherwise

Z_{pt} =1 if scaleup of product p takes place at time t
in the first stage, 0 otherwise

Z_{ptk} =1 if scaleup of product p takes place at time t in scenario k
in the remaining stages, 0 otherwise

Continuous Variables

B_{ptk} amount of product p produced at time t in scenario k
in the remaining stages

I_{ptk} inventories held of product p at the end of time t in scenario k
in the remaining stages

S_{ptk} amount of product p sold at time t in scenario k
in the remaining stages

T_{ptk} production time of production p at time t in scenario k
in the remaining stages

W_{ptk} wasted amount of product p at time t in scenario k
in the remaining stages

NPV_k net present value in scenario k

SR_k sales revenues in scenario k

CI_k capital investment in scenario k

OC_k operating cost in scenario k

RDC total cost for research and development

4.3.2 Mathematical Formulation

Suite Availability Constraints

The number of suites available can be increased by taking the decision to invest in a new one at any given time, but the new suite will not be available until after the construction lead

time, δ. The initial number of suites available is A_0. For phase T_1, the equation is:

$$A_t = E_{t-\delta} + A_0 \qquad \forall t \in T_1 \tag{4.1}$$

For T_2, the investment decision depends on the scenario, k:

$$A_{tk} = E_{t-\delta,k} + A_{t-1,k} \qquad \forall t \in T_2, k \tag{4.2}$$

Production Constraints

If product p is produced during time period t and in scenario k, then $Y_{ptk} = 1$ and hence the number of products produced during each time period in each scenario is given by the constraints:

$$P_{tk} = \sum_p Y_{ptk} \qquad \forall t \in T_2, k \tag{4.3}$$

However, a product can only be manufactured if it has been selected.

$$Y_{ptk} \leq V_{pk} \qquad \forall p, t, k \tag{4.4}$$

The amount of product manufactured, B_{ptk} is limited by the production rate per suite, the number of available suites, the total production time, and the value of Y_{ptk}. Hence the desired constraint is:

$$B_{ptk} \leq r_p T_{ptk} Y_{ptk} \qquad \forall p, t \in T_2, k$$

However, this constraint is bilinear and it is desirable to maintain a linear model. The following three constraints are equivalent to the above.

$$B_{ptk} \leq r_p M H_t Y_{ptk} \qquad \forall p, t \in T_2, k \tag{4.5}$$

$$B_{ptk} \leq r_p T_{ptk} \qquad \forall p, t \in T_2, k \tag{4.6}$$

where M is a suitably large number.

The total time spent producing vaccines must be less than the total time available for production. The total time available is $H_t A_{tk}$ if the process is 100% efficient. The loss parameter, L^{sq}, accounts for any inefficiencies in manufacturing. The total time available in suite-hours is also adjusted to account for product changeovers. If τ is the product changeover time, then a suitable approximation of the minimum time required for changeovers for capacity planning is $\tau(P_{tk} - A_{tk})$; where $(P_{tk} - A_{tk})$ is the number of changeovers expected and τ is the average changeover time. Therefore the total time spent producing vaccines is constrained by:

$$\sum_p T_{ptk} \leq H_t A_{tk}(1 - L^{sq}) - \tau(P_{tk} - A_{tk}) \qquad \forall t \in T_2, k \tag{4.7}$$

Inventory Constraints

The amount of each vaccine stored at the end of time period t is equal to the amount stored at the end of period $t-1$ and the net production at time t minus the amount sold and the amount wasted at time t.

$$I_{ptk} = I_{p,t-1,k} + (1 - L_p)B_{ptk} - S_{ptk} - W_{ptk} \qquad \forall p, t \in T_2, k \tag{4.8}$$

Production Lifetime Constraints

Each product has a maximum life time of ζ_p. This means any vaccine produced at time t cannot be sold after time period $t + \zeta_p$. To make sure that the inventory held at time t is not stored after time $t + \zeta_p$ and delivered to customers, the term I_{pt} has to be balanced by the amount sold up to time $t + \zeta_p$. This forms the product life time constraints:

$$I_{ptk} \leq \sum_{\theta=t+1}^{t+\zeta p} S_{p\theta k} \qquad \forall p, t \in T_2, k \tag{4.9}$$

Scaleup Constraints

Before a new product is manufactured a certain time has to be dedicated to scaleup. The scaleup time can reflect technology transfer and the time needed to fulfil product requirements. These constraints force one time period to be allocated for scaleup, provided that product p is selected for manufacturing. A product can be produced at a certain time, t, only if scaleup has taken place prior to that time period.

$$\sum_{t \in T_1} Z_{pt} \leq V_p \qquad \forall p \tag{4.10}$$

$$\sum_{t \in T_2} Z_{ptk} \leq V_{pk} \qquad \forall p, k \tag{4.11}$$

$$\sum_{t \in T_1} Z_{pt} + \sum_{t \in T_2} Z_{ptk} \leq V_p \qquad \forall p, k \tag{4.12}$$

Sales Constraints

The sales, S_{ptk}, can be no more than the forecasted demand, D_{ptk}, for each product, p, for each time period, t, and scenario, k.

$$S_{ptk} \leq D_{ptk} \qquad \forall p, t \in T_2, k \tag{4.13}$$

Product Selection Constraints

The products selected in stage T2 (production), V_pk, can only be selected from the subset of products that have been selected in the stage T1 (investment), V_p.

$$V_{pk} \leq V_p \qquad \forall p, k \tag{4.14}$$

Objective Function

For the NPV calculations, the discount factor, ϵ_t, is required. This parameter is a function of the inflation rate, f, the interest rate, g, and time, t.

$$\epsilon_t = \left(\frac{1+f}{1+g}\right)^{t-1} \qquad \forall t \tag{4.15}$$

The optimisation criterion is to maximise the eNPV over the planning horizon. The objective function consists of revenues from sales, SR_k, cost of capital investment, CI_k, operating cost, OC_k, and research & development cost, RDC_k. SR_k is the product of the sale prices, ν_{pt} and the amount sold, S_{ptk} at each time, t, and in each scenario, k.

$$\mathrm{SR}_k = \sum_t \epsilon_t \sum_p \nu_{pt} S_{ptk} \tag{4.16}$$

The capital investment, CI_k, is the product of the investment cost of each suite, ω and the number of suites built at each time, t, E_{tk} and in each scenario, k.

$$\mathrm{CI}_k = \sum_t \epsilon_t \omega E_{tk} \tag{4.17}$$

The operating cost, OC_k, is a summation of a fixed cost, η, which is paid over each time period that a suite is available, A_{tk}, and a variable cost, ξ_p, which is dependent on the amount produced, B_{ptk}, for each product, p, at each time, t, and in each scenario, k.

$$\mathrm{OC}_k = \sum_t \epsilon_t \left(\eta A_{tk} + \sum_p \xi_p B_{ptk}\right) \tag{4.18}$$

The total research & development cost, RDC, is the sum of the cost, σ_p, of each product selected, V_p.

$$\mathrm{RDC} = \sum_p \sigma_p V_p \tag{4.19}$$

The Net Present Value, NPV_k for each scenario, k, is the summation of all the revenues minus all the costs at each k . It is defined as:

$$\text{NPV}_k = \text{SR}_k - \text{CI}_k - \text{OC}_k - \text{RDC} \tag{4.20}$$

The objective function is stated as:

$$\max \text{eNPV} = \sum_k \pi_k \text{NPV}_k \tag{4.21}$$

This gives the eNPV of the investment and production plan under uncertainty in clinical trial success. π_k is the probability of each scenario, k.

4.3.3 Input Data

The data for our capacity planning example are shown in Table 4.2. The forecasted products demand data is listed in Table 4.3. The product demand scenarios are required and are showed in Table 4.4. The scenario probabilities of each product are showed in Table 4.5. Finally, the sale prices are listed in Table 4.6.

Table 4.2: Reference Data

Parameters	Descriptions	Value
A_0	integer number of suites already in place [-]	2
f	inflation rate [-]	0.035
g	interest rate [-]	0.05
H_t	available production time at time period t [month]	11 $\forall$ t
L_p	production losses of product p [-]	0.1 $\forall$ p
L^{sq}	loss factor incurred by scaleup lead times [-]	0.1
M	maximum number of suites [-]	30
r_p	production rate of product p ['000 doses per month]	6 $\forall$ p
δ	construction lead time [month]	1
η	fixed operating cost [rmu]	10
ω	capital investment cost [rmu]	100
σ_p	research and development cost of product p [rmu]	50 $\forall$ p
τ	product changeover time [month]	0.5
ξ_p	variable operating cost of product p [rmu]	10 $\forall$ p
ζ_p	life time of product p [year]	1 $\forall$ p

Table 4.3: Forecasted Product Demand ['000 doses], D_{pt}

Year	Product 1	Product 2	Product 3	Product 4
1994	0.0	0.0	0.0	0.0
1995	69.3	104.0	138.6	173.3
1996	109.9	164.8	219.7	274.7
1997	138.6	207.9	277.3	346.6
1998	160.9	241.4	321.9	402.4
1999	179.2	268.8	358.4	447.9
2000	194.6	219.9	389.2	486.5
2001	207.9	311.9	415.9	519.9
2002	219.7	329.6	439.4	549.3
2003	230.3	345.4	460.5	575.6
2004	239.8	359.7	479.6	599.5
2005	248.5	372.7	497.0	621.2
2006	256.5	384.7	513.0	641.2
2007	263.9	395.9	527.8	659.8
2008	270.8	406.2	541.6	677.0
2009	277.3	415.9	554.5	693.1
2010	283.3	425.0	566.6	708.3

Table 4.4: Product Outcome, D_{pk}

Outcome	Product 1	Product 2	Product 3	Product 4
High	1.25	1.25	1.25	1.25
Target	1.00	1.00	1.00	1.00
Low	0.75	0.75	0.75	0.75
Failure	0.00	0.00	0.00	0.00

Table 4.5: Probability per Outcome

Outcome	Product 1	Product 2	Product 3	Product 4
High	0.10000	0.10000	0.10000	0.10000
Target	0.35534	0.57430	0.47257	0.30863
Low	0.24466	0.02570	0.12743	0.29137
Failure	0.30000	0.30000	0.30000	0.30000

Table 4.6: Forecasted Product Sales Price [rmu], ν_{pt}

Year	Product 1	Product 2	Product 3	Product 4
All	11.00	10.50	10.00	9.00

4.4 Computational Results

The model is built using the modelling system **GAMS** version 2.50 (Brooke *et al.* (1988)) and solved using **CPLEX** 6.0. A margin of optimality (OPTCR) of 0.01 was set. The key computational results of the optimisation are the following:

- NPV distribution
- Production times and suite investment indication
- Capacity utilisation

More specifically, the results of the optimisation give *for each scenario*: the NPV, production times for each year, suite investment over time and the capacity utilisation for each year. These are used to plot the graphs shown in this section.

4.4.1 NPV Distribution

The case study considers a portfolio of four potential vaccines given their demands, sale prices, and associated costs (see Table 4.2 to 4.6). The planning horizon is 17 years, and there is one production suite already in place at the beginning of the horizon. Figure 4.2 shows the NPV distribution for the multi-scenario problem, which was generated by plotting the scenario probability against the scenario NPV for each scenario. It is noted that the NPV forms a non-Gaussian distribution in which the peaks are distributed unevenly. Figure 4.2 also shows a high probability of achieving a positive NPV since the majority of scenarios lie above zero. The eNPV is shown as the bold dashed line at 3432 rmu in the figure. The figure shows the highest NPV value is associated with scenario HHHH which has a probability of approximately 0.3% and NPV of 6763 rmu. The worst scenario is found to be FFFF which has a probability of approximately 2.7% and NPV of -228.2 rmu. There are some scenarios that lie in the negative region but with very low probabilities: scenarios FFFT, FFFH, FFFL and FFFF. The total probability of making a loss is calculated as 2.7%. These scenarios are the worst cases where most of the potential products have at least one failed vaccine in them. The data are summarised in Table 4.7.

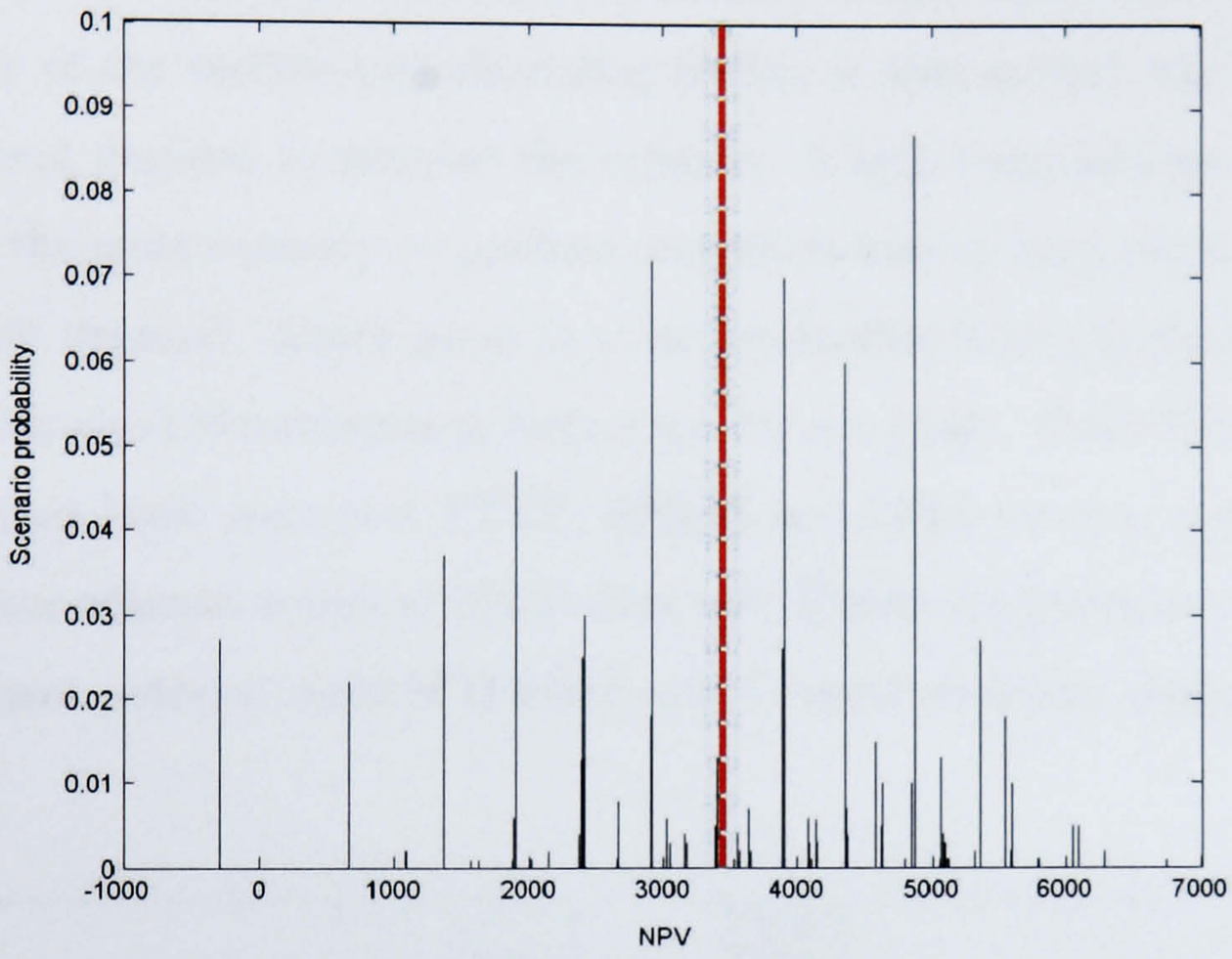


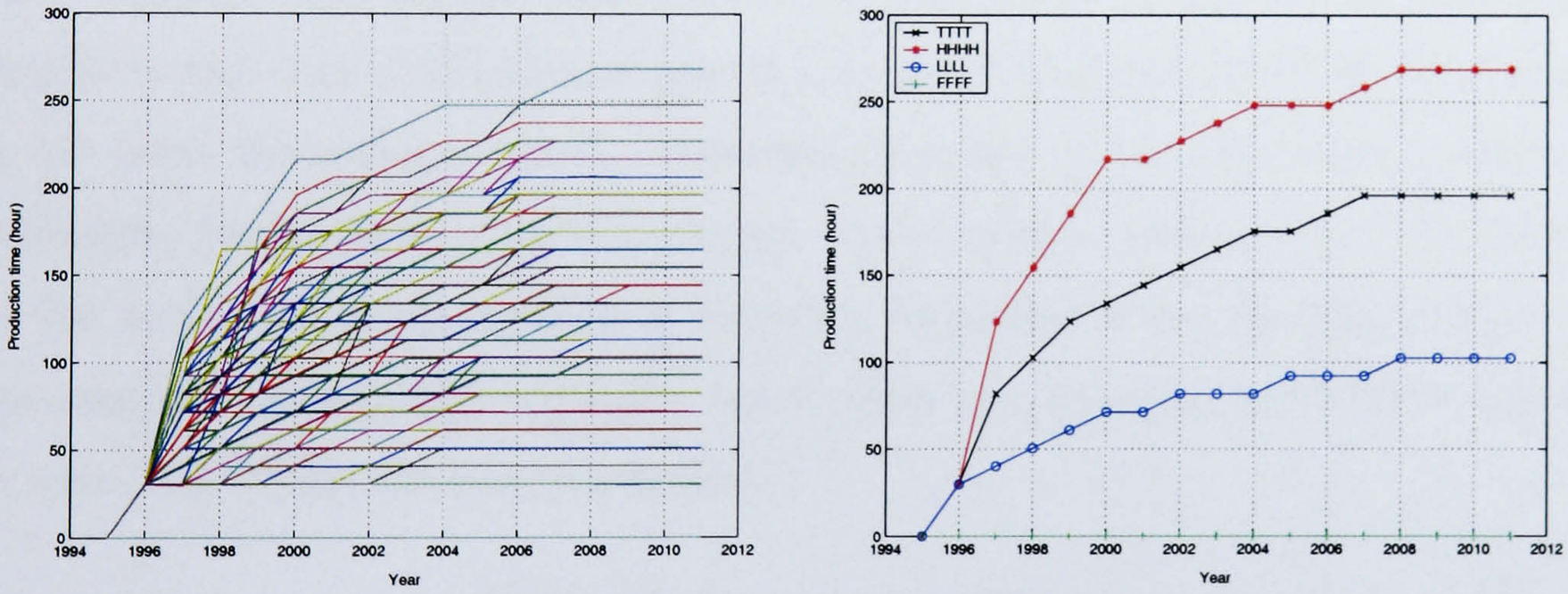
Figure 4.2: NPV Distribution

Table 4.7: NPV Calculation

Best case NPV	6763 rmu
Worst case NPV	-288.2 rmu
Probability of loss	0.0270
eNPV	3432 rmu

4.4.2 Production Times and Suite Investment Indication

The production time is the total time dedicated to production of vaccines. Figure 4.3 represents the total production time for each year of each vaccine for different scenarios. Every time the capacity of the vaccine manufacturing facility is approached, the model decides to make an investment decision to increase the capacity. A high demand case, such as scenario HHHH, requires the most capacity to produce enough vaccine to earn the maximum possible profit and to fulfil demand. Every jump in total production time (as shown in Figure 4.3) indicates that additional investments in suite capacity are made. From Figure 4.3(b), it can be seen clearly that basic scenarios TTTT, HHHH and LLLL require capacity investment in additional suites whereas scenario FFFF does not. Figure 4.4 provides clearer pictures of the suite investment pattern: most of H-based and T-based scenarios require investments to fulfil demand.



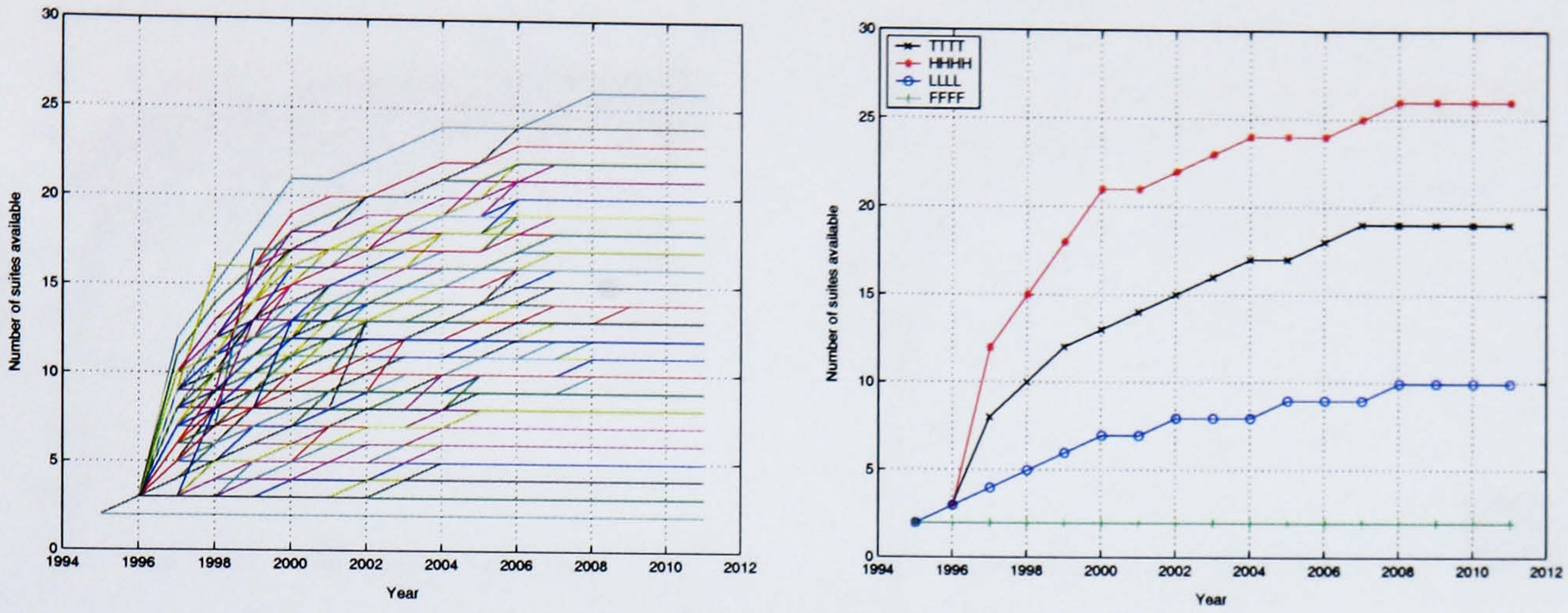
(a) All scenarios

(b) 4 basic scenarios

Figure 4.3: Production Time

4.4.3 Capacity Utilisation

The capacity utilisation rate measures the percentage of capacity used at any time. Figure 4.5(a) shows the capacity utilisation of all suites for all scenarios over time. Figure 4.5(b) shows the 4 basic scenarios. A change in the rate indicates a change in the direction of



(a) All scenarios

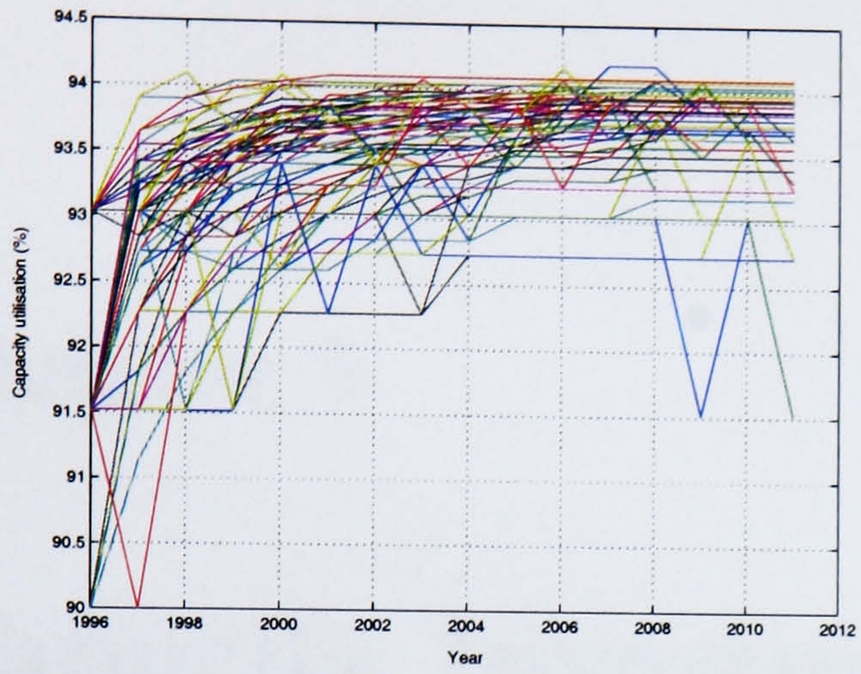
(b) 4 basic scenarios

Figure 4.4: Suite Investment

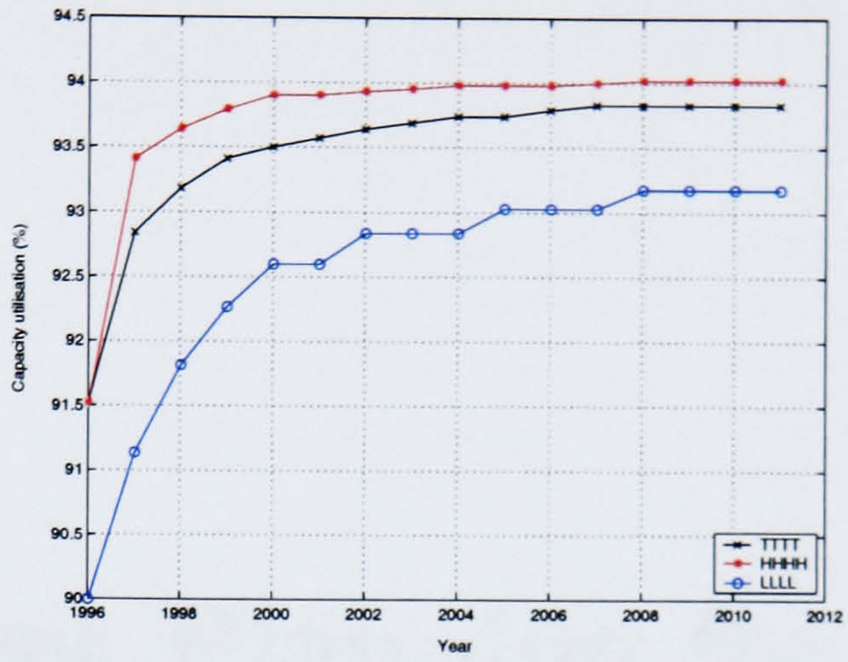
economic activity. The capacity utilisation of scenario FFFF is zero for all time periods, which is to be expected as all products have failed clinical trials and there can be no demand. Table 4.8 shows the average capacity utilisation over time for the four basic scenarios. As the utilisation moves closer to 90% the facility is practically at full capacity. The table also shows the number of suites invested in from the beginning of the planning horizon. The vaccine manufacturing facility originally had 2 suites, and in scenario HHHH 24 additional suites were built within the planning horizon.

Table 4.8: Capacity Utilisation

Scenario	**No. of additional suites**	**Avg. capacity utilisation per suite**
TTTT	17	93.48%
HHHH	24	93.75%
LLLL	8	92.55%
FFFF	0	0%



(a) All scenarios



(b) 4 basic scenarios

Figure 4.5: Capacity Utilisation

4.5 Concluding Remarks

A multi-scenario stochastic MILP model was presented in order to determine the capacity planning and investment strategy for a multiple vaccine production case study. The model is able to give an optimised solution for the decision-making process involving product selection, product manufacturing and capacity expansion strategy based on the maximisation of the eNPV. The model also involves many logistical aspects including resource allocation and operations management.

The problem was initially assumed by setting up with an appropriate infrastructure, pre-allocation of resources and adopted operation policies, however real-time responses to various contingencies was allowed in the model. The model may also be extended to a multi-disciplinary approach to include real marketing risk data and taxation, etc with input from the various experts involved. Therefore, the model can optimise the investment strategy and production decisions in order to maximise eNPV within these risk constraints.

An important issue to be considered for this work is financial risk. Risk management has become an essential part in all decision-making processes. However, dealing with financial risk problems requires augmentation of the model. This will be discussed in Chapter 5.

Chapter 5

Capacity Investment Planning for Multiple Vaccines under Uncertainty-2:Financial Risk Analysis

Capacity investment planning is a major decision for a vaccine company. Traditionally, due to the inherent flexibility used in almost all vaccine processes and risk-averse decisions, companies always started with limited capacities, thereby reducing the initial capital investment. However, in order to fulfil fast-growing vaccine demands, good and balanced financial risk management for capacity expansion is required to satisfy future demand without over committing capital. To complement the use of financial risk management, known probabilistic definitions of some classical risk measures such as Expected Downside Risk (EDR), Opportunity Value (OV), Value-at-Risk (VaR) and Conditional Value-at-Risk (CVaR) are adapted to be used in a scenario-based model for capacity investment planning for manufacture of multiple vaccines. Using these definitions, new models that manage financial risks and aid decisions are developed. Computational results and decision-making analysis methods are also presented and discussed. Numerical results show that this approach enables one to con-

sider and manage the financial risk associated with the different design options, resulting in a set of solutions that can be used for decision-making.

5.1 Introduction

The previous chapter has provided a stochastic modelling approach to determine the capacity planning and investment strategy for a multiple vaccine production case study. The model involves product selection, product manufacturing and a capacity expansion strategy based on the maximisation of the expected Net Present Value (eNPV). However, the stochastic model does not provide any control on the variability over the different possible outcomes associated financial risk; it assumed that the decision-maker is risk-neutral. However, most decision-makers are risk-averse, i.e. they have a major preference for lower variability for a given level of return.

The focus on planning capacity expansion in the vaccine industry has increased in recent years. Capacity expansion may require a significant amount of capital investment over a long period of time. The market demands for vaccines depend strongly on the outcome of clinical trials. An investment decision, often based on Net Present Value (NPV), has to be made in advance: whether or not to invest in capacity expansion or research and development in order to meet the customer demands. Manufacturing capacity has typically been initially limited to the commercially attractive markets when a new vaccine is introduced. Once a vaccine is in process development, the vaccine companies will take the decision whether or not to invest in expanding the production capacity. This investment decision is significant in terms of risk. If the capacity is over-estimated, it will result in wasting a large sum of money; if the capacity is under-estimated, it will result in losing market share to competitors. There are two main aspects of making capacity investment decisions. The first aspect is the cost of constructing and operating a vaccine manufacturing plant. Generally speaking, the capital and operating costs per unit of capacity fall as more facilities are installed. However, in absolute terms:

- a larger plant is more expensive to build and operate than a smaller one;

- the capital expenditure required to serve the global market is a multiple of that required to serve a local market;
- once the facility is in place, it only delivers economic benefit to the company if it is actually utilised, otherwise it requires higher cost than a smaller, better utilised facility.

The second aspect is the relative immutability of capacity decisions (a potential concern to the Global Alliance for Vaccines & Immunization (GAVI)). Once the decision is taken, the requirements of good manufacturing practice are needed as they affect biologicals and mean that capacity expansion is both very expensive and time-consuming. GAVI is an authority which has substantial potential negotiating power with the vaccine companies to gain early access to newly introduced vaccines, if its procurement mechanism is well calculated. GAVI has the responsibility to reduce the risk of capital expenditure for the vaccine companies before any capacity expansion or new facilities are installed. It can increase the operating and capital efficiency of a plant by enabling the construction of a larger plant that would otherwise have been the case, with some proportion of its utilisation underwritten. From the company's point of view, this factor is likely to extend the period when it faces limited or no competition.

Many capacity expansion decision tools are based on linear programming concepts. However, these tools are usually formulated under the assumption that future scenarios are known with certainty. It is assumed that all of the model coefficients, constraint values, and solution values are known precisely and do not vary. Decisions are often made within an environment of risk, uncertainty, or conflict. However, decision theory is concerned with decision-making under conditions of risk and uncertainty. Uncertainty cannot be eliminated; only managed. Not only are there uncertainties present, but also our assessment of their levels of uncertainty are usually quite inaccurate (Mitchell, 1995). Additional facets of uncertainty involve a lack of understanding by the decision-maker about the loss categories that exist, and which losses can occur.

The only certainty in business is the presence of risk. Risk can be defined as a chance of danger, damage, loss, injury or any other undesired consequences. A more scientific definition of risk is the extent to which there is uncertainty about whether potentially significant

and/or disappointing outcomes of decisions will be realised. Inherent in this definition are the dimensions of outcome uncertainty, outcome expectations and outcome potential. The meaning of risk has been studied in many areas. Baird and Thomas (1990) defined risk according to eight different perspectives, consisting of finance, marketing, management, strategy and psychology. The authors also stated that risk is a multi-dimensional construct and differs according to business function. Mitchell (1995) defined risk as the product of the probability of loss and the significance of that loss to the organisation or individual. Thus, if the probability of loss is $P(\text{loss}_n)$ and the significance of the loss is $l(\text{loss}_n)$ for an event n, then the risk is given by:

$$\text{Risk}_n = P(\text{loss}_n) \times l(\text{loss}_n) \tag{5.1}$$

To model financial risk management, Eppen *et al.* (1989) first proposed a traditional financial risk measure named Expected Downside Risk (EDR). They devised a mathematical expression for EDR to measure the cost variability in a two-stage stochastic programming model for manufacturing capacity planning. Similar EDR mathematical models were also developed by Barbaro *et al.* (2003) for design and planning under uncertainty. They suggested that the EDR is the likelihood that a security or other investment will decline in price, or the amount of loss that could result from that potential decline. Barbaro and Bagajewicz (2004*a*) further proved that EDR is not unvarying with risk, such that a lower EDR does not necessarily have lower risk. Later, Barbaro and Bagajewicz (2004*b*) applied the use of EDR to an inventory and options case study. They showed that the usual assumption that the introduction of inventory reduces risk at low profit expectations is not always true, and that financial risk management tools need to be revised with appropriate objectives. Recently, Aseeri and Bagajewicz (2004) complemented the use of Value-at-Risk (VaR) and proposed a new concept, Opportunity Value (OV), to weigh opportunity loss versus risk reduction.

Financial risk management has always been commonly used in banks, insurance companies and major financial institutes to evaluate risks. It also applies to pharmaceutical manufacturing industries to make capacity investment decisions before demand is known to minimise investment risks. Simulation models for pharmaceutical development described in

the literature are mostly financially-based. Blau *et al.* (2000) used a probabilistic simulation model of a pharmaceutical product development pipeline to prioritise candidate drugs based on their reward:risk ratios. Rogers *et al.* (2002) presented a stochastic optimisation model, called OptFolio, of pharmaceutical Research and Development (R&D) portfolio management using a real options approach for making optimal project selection decisions. The above models assumed that all future cash flows are known.

In this work, the objectives are focussed on the financial risk analysis and the decision-making analysis. The **financial risk analysis** step includes tasks: (1) to complement the stochastic model results using financial risk measurements in order to provide a more realistic assessment of the options, (2) to reduce the downside risk using different approaches to show how the downside risk can be managed, and (3) to determine the optimal number of suites for investment. However, different decision-makers may have different strategies to decide their 'optimal' number of suites. Thus, in order to provide a better view of how the investment strategy may be determined, alternative approaches are compared in the **decision-making analysis** step. The decision-making analysis step provides different decision-making criteria to handle the risk analysis in the capacity expansion study. Specifically, the decision-making criteria of capacity expansion are discussed from the standpoint of financial risk management. Each of the decision-making strategies is discussed separately, and is illustrated for the suite investment problem using the NPV metric.

The organisation of this chapter is as follows. Section 2 provides some background on uncertainty and financial risk management. Section 3 discusses the concept of a traditional financial risk measure, named EDR, and its relation with financial risk, and a new model using EDR as a measure of financial risk is presented. Also, it reviews the general theory of some other common financial risk measurements. Section 4 describes some financial risk management techniques to be applied to the scenario-based vaccine manufacturing model. In Section 5, the decision theory and associated methods are illustrated. Section 6 presents some alternative decision-making methodologies to handle the various criteria for analysis of risk in the expansion of capacity. Finally, some concluding remarks are given in Section 7.

5.2 Financial Risk Theory

Expected Downside Risk (EDR) is an integral measure that establishes a relation between the reduction in risk and the loss of profit potential at expectations below the target value. The definition and formulations of EDR are illustrated here. This risk measure was first introduced by Eppen *et al.* (1989) in the framework of capacity planning for the automobile industry. To add EDR formulations to the capacity investment planning model, first Δ_k is defined as the positive deviation from a minimum desired profit z for each scenario k: $\Delta_k = z - \text{NPV}_k$ if NPV_k is less than z and 0 otherwise. This is modelled using the following two constraints.

$$\Delta_k \geq z - \text{NPV}_k \qquad \forall k \tag{5.2}$$

$$\Delta_k \geq 0 \qquad \forall k \tag{5.3}$$

The expected downside risk is then the sum of Δ_k weighted by the scenario probability, π_k:

$$\text{EDR} = \sum \pi_k \Delta_k \tag{5.4}$$

EDR is, in fact, a special case of a general risk measure defined by Stone (1973). For a continuous probability density function f, it is defined as follows.

$$\text{risk} = \int_{-\infty}^{y} |z - x|^n f dx, \tag{5.5}$$

where z is again the target profit. In this general metric, deviations above the target profit may be considered since y need not equal z. n is a non-negative parameter that reflects the decision taker's attitude to risk. Taking $y = z$, as is common, the general risk measure can be defined for the model outline above as:

$$\text{risk} = \sum \pi_k \Delta_k^n \tag{5.6}$$

Values of n that are less than 1 represent a *risk-seeking* attitude; whereas values above 1 represent a *risk-averse* attitude. Some approaches for selecting n are given by Fishburn (1977). For certain values of n, the metric reduces to some well-known risk measures. With $n = 0$, the metric represents the probability of attaining an outcome less than z. The EDR metric is obtained when $n = 1$ and a semi-variance metric can be derived by setting n to 2. Finally, for a sufficiently large n, the metric discriminates based on the worst-case scenario.

Successively "tighter" constraints on EDR may be applied to generate a series of solutions from the model. Tightening the constraint on EDR is an efficient way to bring desirable and good robust solutions. This is usually done as follows:

$$\text{EDR} \leq \text{RF} \times \text{EDR}^* \tag{5.7}$$

where EDR* is an EDR obtained by optimizing the eNPV at the highest risk level, i.e. the model is generated without any risk constraints. RF is a parameter that lies in the range $0 \leq \text{RF} \leq 1$.

Aseeri and Bagajewicz (2004) suggested other financial risk metrics, which are also added to the scenario-based vaccine manufacturing model. The metrics include Value-at-Risk (VaR), Opportunity Value (OV), and Conditional Value-at-Risk (CVaR). These four measures are used to analyse and reduce the the risk of high losses in the NPV distribution of the scenario-based model. All of these concepts are illustrated below using the problem of capacity investment planning for multiple vaccines. They are defined as follows:

(i) *Value-at-Risk* or VaR is a measure to estimate a given portfolio's losses if the outcome of the uncertainties is worse than expected. A general definition of VaR is given by the difference between the mean value of the NPV and the NPV value corresponding to the p-quartile of the cumulative distribution (value at p probability). Equivalently, VaR can also be defined as the maximum allowable loss with a certain confidence level $\alpha \times 100\%$. VaR has been used as a point measure very similar to the variance and it is commonly used in financial analysis when the NPV distributions are not normal. Here, the VaR is formulated, in terms of NPV, as the minimal portfolio NPV for a confidence level $\alpha \times 100\%$. (see Figure 5.1)

(ii) *Conditional Value-at-Risk* or CVaR is a related risk measure to VaR. Rockafellar and Uryasev (2000) define CVaR as the conditional expectation of losses exceeding VaR at a given confidence level. It is impossible to show CVaR on a cumulative probability curve.

(iii) *Opportunity Value* or OV was proposed by Aseeri and Bagajewicz (2004). It is defined in a similar way to VaR but at the other end of the cumulative probability curve. It is the value that a portfolio might gain, over the expected value, if the uncertainties are better than expected. Solutions with high OV perform better for very successful uncertain outcomes and therefore are likely to be chosen by risk-seeking decision-makers. (see Figure 5.1)

5.3 Financial Risk Analysis Results

The results are obtained by using the model from the previous chapter. The model assumes an appropriate infrastructure, pre-allocation of resources and adopted operation policies.

The graphs shown in this section are generated by taking the results of the model from Chapter 4 (i.e. the NPV from the 256 scenarios) and plotting the NPV cumulative probability curve. The cumulative probability curve can be obtained by arranging the scenarios in order of ascending NPV, then, for each scenario, calculating the cumulative probability by summing the probabilities of all of the scenarios with lower or equal NPV. When determining the effects of different parameters (e.g. sales price) on the risk of investment, this procedure is repeated to generate a number of cumulative probability curves, each corresponding to a different value of the parameter.

5.3.1 Hypothetical Cumulative Probability Curves and Comparisons

Typically, VaR measures the deviation of the NPV from the eNPV at 5% risk but 1% and 10% are used in some cases. To compare the performance of VaR and the other risk measures, two hypothetical cumulative probability curves are shown in Figure 5.1 and the resulting measures shown in Table 5.1. From Table 5.1, if VaR is the only risk measure used to make the decision, then L1 would be picked by the risk-averse decision-maker since L1 has a smaller VaR than L2. However if the upside potential is more important to the decision-maker, L2 provides a better OV and thus a better choice. Similarly, eNPV rates L2 higher than L1, whereas EDR

gives the opposite: L2 is again seen as a more profitable but more risky decision.

The solution chosen depends on which measure is used: VaR and EDR usually selecting safe alternatives; eNPV and OV giving bigger potential gains at a higher risk level.

It is also noted that there is a disadvantage in using VaR for decision-making. Despite VaR being a popular risk measure, it is not typically used in mathematical models for optimal portfolio selection. It is difficult to optimise and Artzner *et al.* (1999) stated that VaR lacks a theoretical property for a coherent risk measure.

Another risk measure is called Risk Premium (RP). RP is defined as the subtraction of the Certainty Equivalent (CE) from the eNPV, where CE is the median of the NPV distribution.

$$\text{RP} = \text{eNPV} - \text{CE} \tag{5.8}$$

The CE lines for L1 and L2 are drawn at 50% risk level in Figure 5.1 to illustrate where the RP lies. If RP > 0, the cumulative probability curve is risk-averse, otherwise if RP < 0, the cumulative probability curve is risk-seeking. The RP values for L1 and L2 are compared in Table 5.1. If the decision-maker is risk-averse and would prefer to avoid risk at the expense of a potentially smaller return, he/she would choose L1; whereas, if the decision-maker is risk-seeking, he/she would choose L2 as L2 provides a better eNPV even though the EDR is larger. A *risk-neutral* decision maker would seek a balance between a large eNPV and a low EDR.

Table 5.1: Comparison of VaR and EDR

Cumulative Probability Curve	eNPV	VaR (5%)	OV (95%)	CVaR (5%)	EDR (at z=0)	RP
L1	3432	2347	2107	3277	7.78	27
L2	6140	3257	2345	5726	53.50	-228

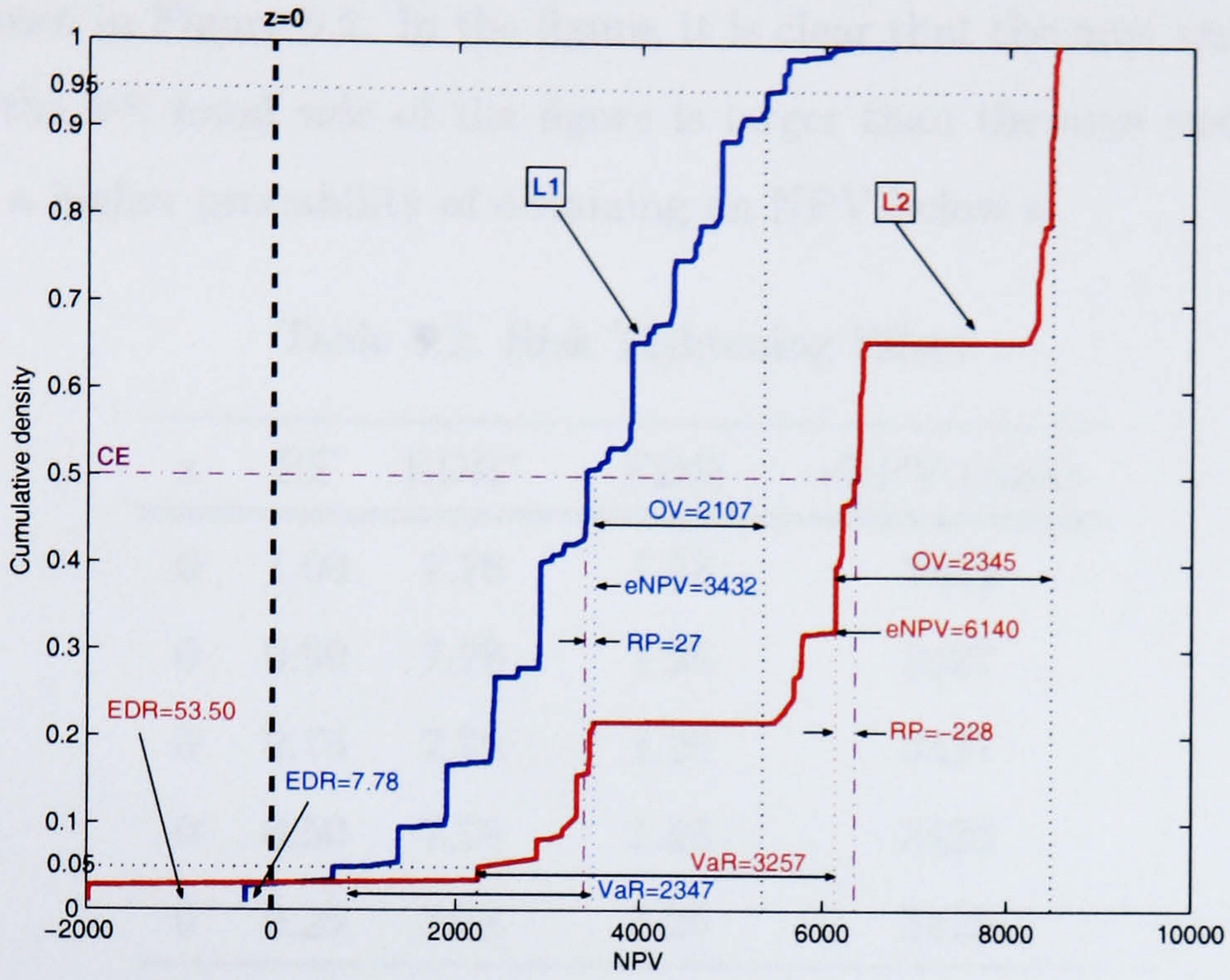


Figure 5.1: Hypothetical Cumulative Probability Curves (cumulative distribution functions) with Risk Measures

5.3.2 Effect of Tightening the Risk Factor (RF)

EDR is an indication to reflect the maximum allowed risk that the decision-maker can allow. Our 256-scenario model as described in Chapter 4 was run with different values of the tightening parameter, RF. The aim here is successively to minimise the downside risk. Decision-makers generally prefer a low value of EDR rather than a high one, since the higher the value of EDR the higher the probability of obtaining an NPV below the target value, z, (not necessarily zero). If the EDR is close to zero, then the risk associated with each investment decision is very low: it makes the investment more attractive from a risk perspective. The results shown in Table 5.2 were obtained by tightening RF. In the figure, two sets of minimum desired profit, z, were considered with different RF values in order to reduce the EDR. The results show that when RF decreases, the eNPV also decreases. It is also possible to obtain an infeasible solution if the downside risk is constrained over the limits imposed by the decision variables. The downside risk cannot be reduced further because all scenarios are based on discrete solutions obtained from the model. The relationship between EDR and

eNPV is also shown in Figure 5.2. In the figure, it is clear that the area underneath the line of RF=1.00 on the left hand side of the figure is larger than the area under each of other lines, indicating a higher probability of obtaining an NPV below z.

Table 5.2: Risk Tightening Effect

z	RF	EDR*	EDR	eNPV (rmu)
0	1.00	7.78	7.78	3432
0	0.90	7.78	1.25	3427
0	0.75	7.78	1.25	3427
0	0.50	7.78	1.25	3426
0	0.25	7.78	1.25	3425
50	1.00	9.13	9.13	3430
50	0.90	9.13	4.52	3426
50	0.75	9.13	2.60	3420
50	0.50	9.13	2.60	3420
50	0.25	9.13	infeasible	infeasible

5.3.3 Effect of z-Variation

To analyse different alternatives using the downside risk constraints, a range of values of the minimum desired profit, z, from 0 rmu to 100 rmu has been investigated. Various solutions are obtained by minimising downside risk at different z and the results are shown in Table 5.3. When z is incremented, the value of eNPV decreases. This is due to the relationship between downside risk and expected profit established by equations 5.2 to 5.4. A set of solutions showing different downside risk characteristics is shown in Figure 5.3. When risk is minimised at higher z values, the solutions show considerable reduction in downside risk at NPV values lower than the corresponding z value. Moreover, there is a smaller relative reduction in EDR from EDR* at higher z values, thus minimising risk at a high value of z brings about lower downside risks at lower NPV values.

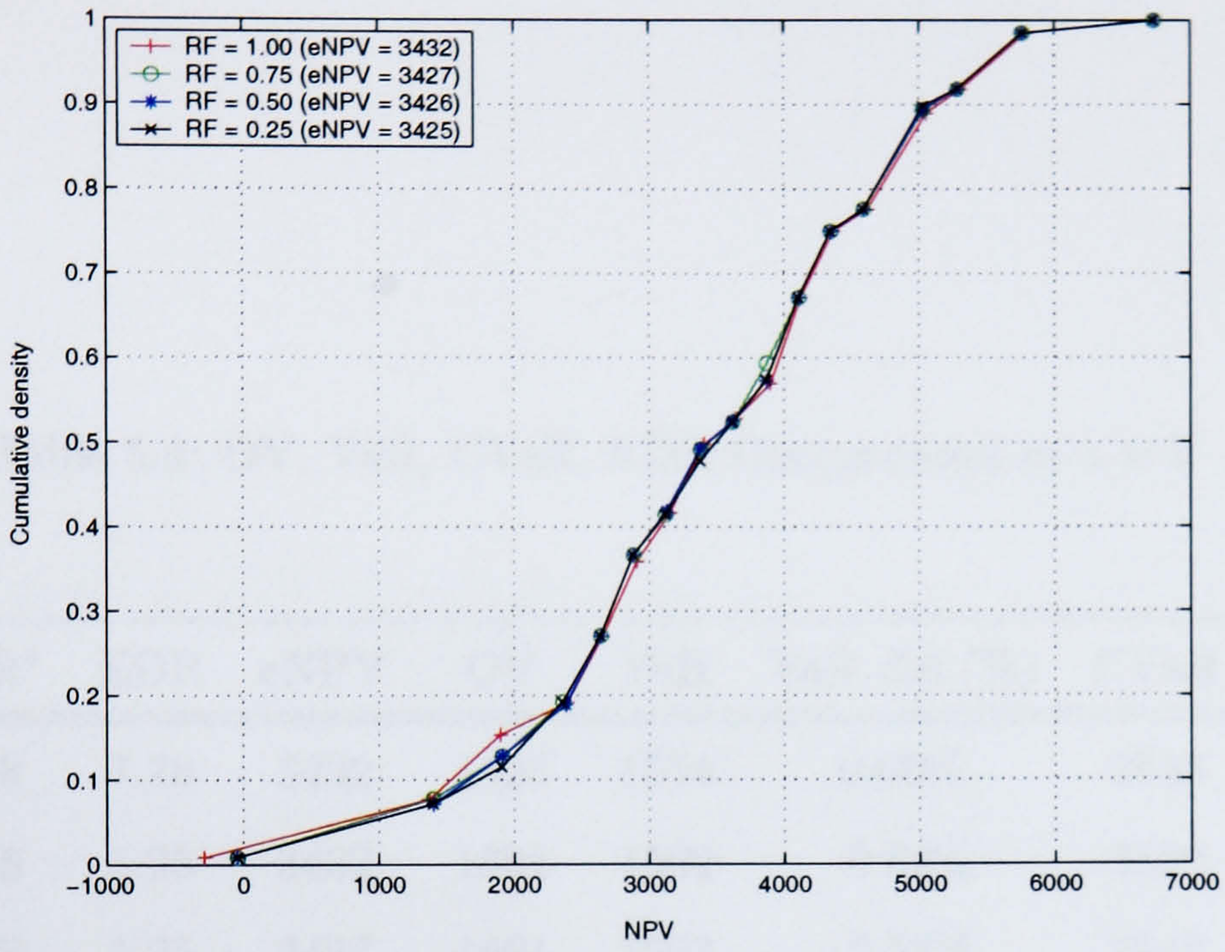


Figure 5.2: Effect of RF on the Cumulative Probability Curve

Using the variation of RF-values, two models with different values of z are compared for OV, VaR, CVaR, EDR and their reductions in value which are shown in Tables 5.4 and 5.5. The comparisons are performed using the deviation of profit at different confidence levels (α=1%, 5% and 10%) from the eNPV.

Table 5.3: Effect of z-Variation at RF=0.75

z	RF	EDR*	EDR	EDR reduction (%)	eNPV
0	0.75	7.78	1.25	83.9	3432
10	0.75	8.05	3.44	57.3	3432
50	0.75	9.13	4.52	50.5	3430
100	0.75	10.48	5.87	44.0	3425

Table 5.4: OV, VaR, CVaR, EDR Comparisons at $z = 0$

α	RF	EDR*	EDR	eNPV	OV	VaR	VaR diff.(%)	CVaR	CVaR diff.(%)
0.90	1.00	7.78	7.78	3432	1623	1554	0.00%	2648	0.00%
0.90	0.90	7.78	1.25	3432	1601	1562	-0.52%	2520	4.84%
0.90	0.75	7.78	1.25	3427	1601	1593	-2.53%	2545	3.89%
0.90	0.50	7.78	1.25	3426	1601	1536	1.16%	2516	4.98%
0.90	0.25	7.78	1.25	3425	1602	1562	-0.49%	2517	4.94%
0.95	1.00	7.78	7.78	3432	2107	2347	0.00%	3277	0.00%
0.95	0.90	7.78	1.25	3432	2074	2297	2.10%	3049	6.96%
0.95	0.75	7.78	1.25	3427	2075	2291	2.37%	3048	6.98%
0.95	0.50	7.78	1.25	3436	2075	2291	2.38%	3048	6.99%
0.95	0.25	7.78	1.25	3435	2076	2290	2.43%	3047	7.02%
0.99	1.00	7.78	7.78	3432	2599	3721	0.00%	3721	0.00%
0.99	0.90	7.78	1.25	3432	2577	3474	6.64%	3474	6.64%
0.99	0.75	7.78	1.25	3427	2578	3473	6.66%	3473	6.66%
0.99	0.50	7.78	1.25	3436	2578	3473	6.67%	3473	6.67%
0.99	0.25	7.78	1.25	3435	25799	3472	6.69%	3472	6.69%

Table 5.5: OV, VaR, CVaR, EDR Comparisons at $z = 50$

α	RF	EDR*	EDR	eNPV	OV	VaR	VaR diff.(%)	CVaR	CVaR diff.(%)
0.90	1.00	9.13	9.13	3430	1626	1554	0.00%	2646	0.00%
0.90	0.90	9.13	4.52	3426	1601	1545	0.65%	2537	4.09%
0.90	0.75	9.13	2.60	3426	1602	1629	-4.75%	2520	4.74%
0.90	0.50	9.13	2.60	3420	1607	1556	-0.10%	2508	5.19%
0.95	1.00	9.13	9.13	3430	2100	2344	0.00%	3275	0.00%
0.95	0.90	9.13	4.52	3426	2075	2296	2.05%	3086	5.75%
0.95	0.75	9.13	2.60	3426	2076	2290	2.32%	3047	6.95%
0.95	0.50	9.13	2.60	3420	2082	2284	2.56%	3041	7.12%
0.99	1.00	9.13	9.13	3430	2603	3718	0.00%	3718	0.00%
0.99	0.90	9.13	4.52	3426	2578	3472	6.61%	3647	1.92%
0.99	0.75	9.13	2.60	3426	2579	3472	6.63%	3472	6.63%
0.99	0.50	9.13	2.60	3420	2584	3466	6.78%	3466	6.78%

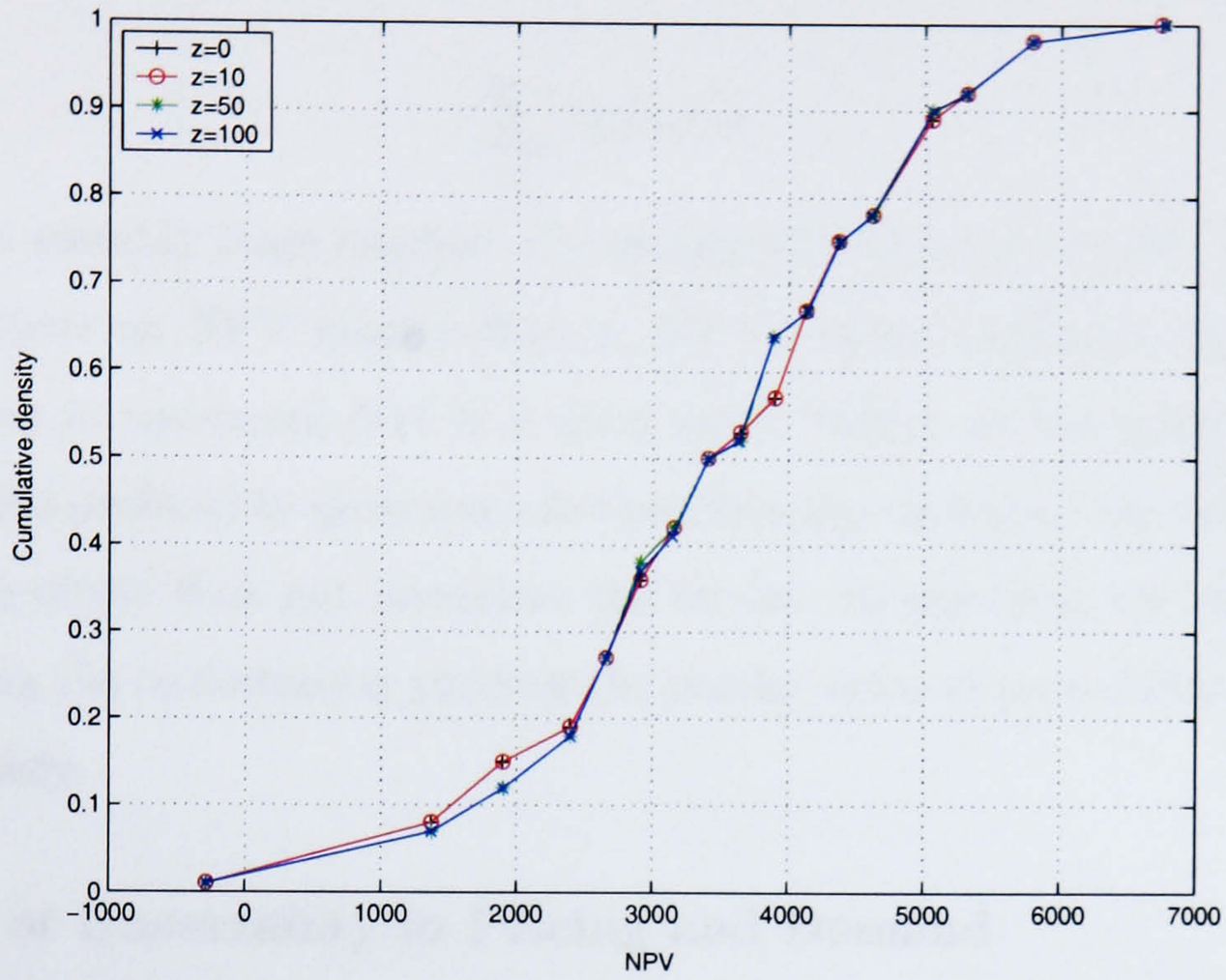


Figure 5.3: Effect of z-Variation on the Cumulative Probability Curve

5.3.4 Effect of Limiting the Probability of a Poor Outcome

In section 5.2, the effect of reducing the Expected Downside Risk (EDR) was discussed. This approach restricts the *risk* associated with a decision alternative (while maximising the eNPV). An alternative approach is to consider the *probability* of a poor outcome: i.e., one might want to ensure that there is no more a certain probability, α, that the NPV will be less than a certain threshold, z. This is expressed mathematically as:

$$Pr(\text{NPV} \leq z) \leq \alpha \tag{5.9}$$

The general risk metric given by equation 5.6 reduces to this form when n is 0, but a more efficient formulation is given here.

The probability is defined using the scenario probabilities, π_k, and newly defined binary variables, $J_k \in \{0, 1\}$, that take a value of 1 if scenario k yields an NPV less than z and 0 otherwise. The probability is then constrained by the following.

$$z - \text{NPV}_k \leq MJ_k \qquad \forall k \tag{5.10}$$

$$\sum_k \pi_k J_k \leq \alpha \tag{5.11}$$

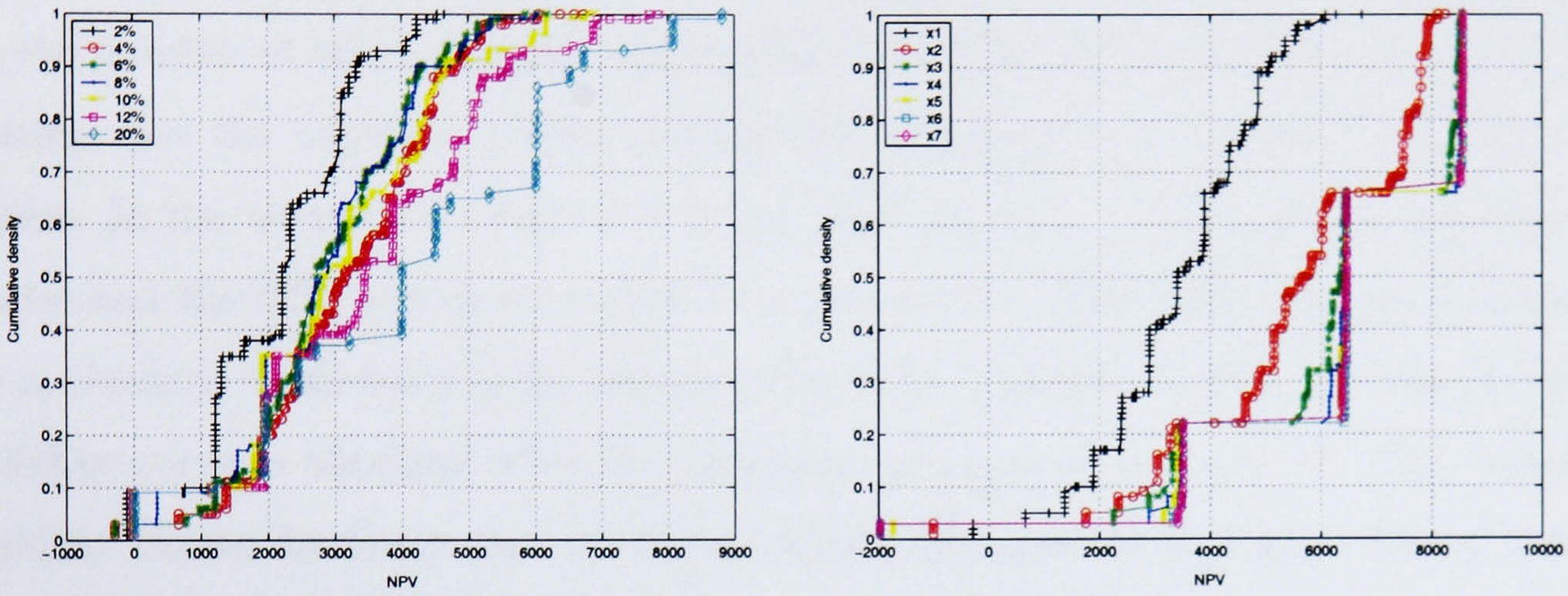
where M is a suitably large number. Constraint 5.10 forces J_k to be 1 for each scenario that fails to achieve an NPV greater than z; for the other scenarios, J_k may be 1 or 0, so the summation in constraint 5.11 is a valid upper bound on the probability. Using an overestimate of the probability gives a smaller problem size and since the probability is being constrained from above does not invalidate the model. In any case, the other J_k variables will be set to 0 by the optimisation yielding the precise value of probability if the constraint is difficult to satisfy.

5.3.5 Effect of Uncertainty in Pricing and Demand

The pricing of current vaccines is characterised by heavy tiering. The major drivers of price tiering in the global vaccine market are manufacturing economics and customers' demands. An important precondition for price tiering is the relative difficulty of parallel imports in biologicals, since manufacturers would be unlikely to supply at very low prices if doing so threatened higher priced markets. Customers' demand is also a critical issue to set the prices of the vaccines due to the economic valuation gap between the developing countries and developed countries. The ability of the vaccine companies to manufacture and supply extra demands to fulfil sudden requirements is also a key factor to consider.

Figure 5.4(a) shows how the cumulative probability curves vary when the prices of multiple vaccines increase in increments from 2% to 20%. The cumulative probability curves shift from risk-averse to risk-seeking. The reason is that when the prices increase at fixed cost and constant sales, the risk of obtaining a low NPV decreases. Figure 5.4(b) shows how the cumulative probability curves vary when the demands of multiple vaccines increase in increments from 2 times to 7 times. Again, the cumulative probability curves also shift from risk-averse to risk-seeking. However, the downside risks of the cumulative probability curves in Figure 5.4(a) remain very small while the downside risks of the cumulative probability curves in Figure 5.4(b) increase when the demand is increased. Although the trends of the cumulative probability curves on both figures are similar, it is important to note that higher

demands require increased capacity, thus there is a higher risk of low profits due to the increase in investment cost and operating cost.



(a) Effect of Uncertainty in Pricing

(b) Effect of Uncertainty in Demand

Figure 5.4: Effect of Uncertainty in Pricing and Demand on the Risk Curve

5.3.6 Effect of Uncertainty in Available Capacity

In practice, capacity expansion planning depends not only on NPV but also on various factors such as limitation of land, pollution policies, etc. These effectively limit the number of suites that can be built. In the original capacity planning model, the number of suites that can be invested in was assumed to be unlimited. The highest number of suites was found to be 26 purchased in the HHHH scenario where the initial number of suites was 2. Assuming x is the maximum number of suites that may be built, where $2 < x < 26$, consider the following models:

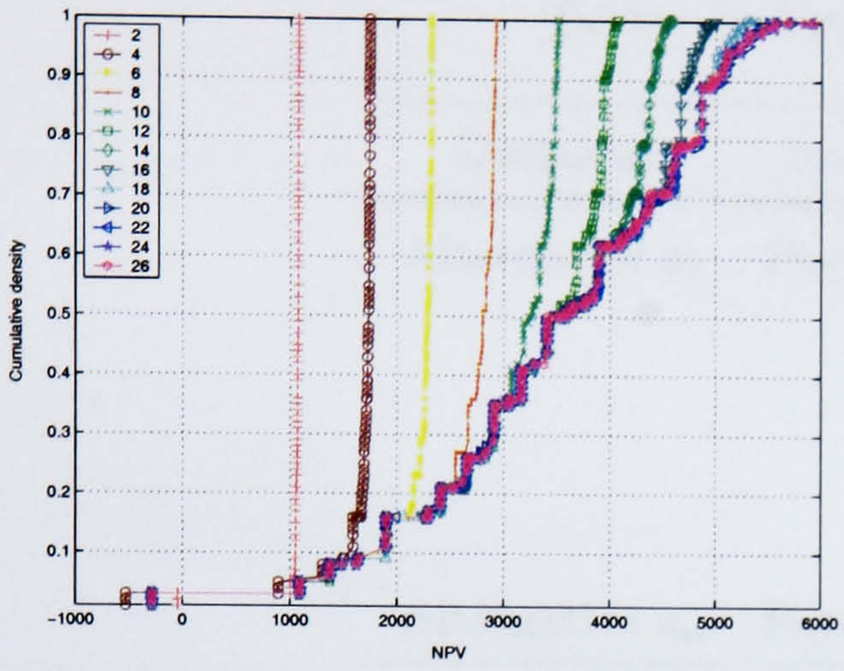
- Strategy A: Limited scenario-dependent suite investment of x with initial number of suites to be 2 ("wait-and-see" strategy)
- Strategy B: All investment must take place at the beginning, with the number of suites installed to be x ("here-and-now" strategy)

The results obtained from the capacity planning model are illustrated in Figure 5.5. The figure shows the NPV and the associated risk for different numbers of suites being installed if and when required (Strategy A) and at the beginning (Strategy B). Figure 5.5(a) shows that when the number of suites is small, the cumulative probability curve has a straight portion indicating that the capacity is fully utilised and unable to meet demand for many of the scenarios. In the worst case, where $x = 2$, the plant is unable to meet the demand for most scenarios and the NPV can never exceed a certain number. The best cumulative probability curve is obtained when the x is 26. On the other hand, in Figure 5.5(b), the best cumulative probability curve is obtained when the maximum number of suites is 12. The cumulative probability curves for fewer than 12 suites remain the same as in Figure 5.5(a), however, when the maximum number of suites becomes greater than 12, the cumulative probability curves shift to the left, meaning a higher risk of obtaining negative NPVs (because too many suites have been purchased at the beginning). In practice, if the vaccine company over-estimates the required capacity, some suites are unused but operating costs to keep the idle suites functional are not incurred. Thus, a good decision has to be made in advance to avoid unnecessary financial loss. Decision analysis can help to make such a decision, hence different methods for decision-making under risk will be discussed in next section.

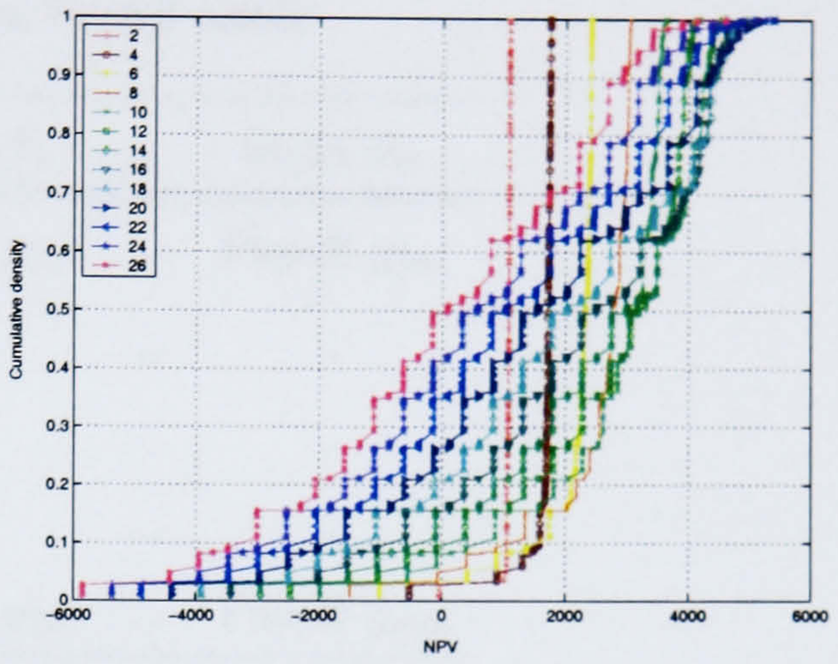
5.4 Decision-Making Theory

Although models help managers gain insight and understanding, they cannot make decisions. Decision-making often remains a difficult task due to the uncertainty regarding future conflicting values or objectives. Decision analysis is a set of well developed techniques and tools for analysing a wide variety of management decisions under various situations. This approach is called decision-making under uncertainty. The main assumption is that the decision-maker can arrive at a probability estimate for the occurrence of each of the possible outcomes.

A large body of literature provides the methodology in performing decision-making (Yang and Qiu, 2005). Most decision-making methods involve two steps. The first step in the decision analysis procedure is to identify the alternatives considered by the decision-maker. These alternatives are called *decision alternatives*. The selection of the best decision alternative de-



(a) Number of Suite to be Installed When Required



(b) Fixed Number of Suite to be Installed at the Beginning

Figure 5.5: Effect of Uncertainty in Available Capacity on the Risk Curve

pends on how much profit the investor will make from each decision. Profit will depend on the future events associated with a decision situation. A decision-maker may have an idea of possible future events, but it is uncertain which particular event will occur. Thus the second step in the decision analysis is to identify the future events that might occur. These events are referred to the *states of nature*. The states of nature are defined so that exactly one of the listed states of nature will occur.

Given the decision alternatives and the states of nature, in order to select the the best decision alternative, information on the profit associated with each combination of a decision alternative and a state of nature is required. The outcome resulting from making a certain decision and the occurrence of a particular state of nature is referred to as payoff. A general payoff table is presented in Table 5.6 to show these types of decision situations. Entries in a payoff table can be stated in terms of profits, costs, or any other measure of output that may be appropriate for the particular situation.

In this case, decision-making approaches are considered with knowledge of the probabilities of the states of nature. Once a payoff table is organised, several criteria are available for decision-making. They will each yield different decisions. The decision-maker must select

Table 5.6: Typical Payoff Table

Decisions	State θ_1	...	State θ_m
Alternative a_1	Payoff y_{11}	...	Payoff y_{1m}
.	.	...	.
.	.	...	.
.	.	...	.
Alternative a_n	Payoff y_{1n}	...	Payoff y_{mn}

the criterion or combination of criteria that best suits his or her needs. The criteria are:

- Expected Value
- Maximax Criterion
- Maximin Criterion
- Minimax Regret Criterion
- Hurwicz Criterion
- Equal Likelihood (Laplace) Criterion

When a compound word like **maximax** is given, the first portion **max** chooses the maximum among the maxima of the second portion **max**. The **maximin** means that we select the maximum among the minima.

To perform the decision analysis described above on capacity sizing, the models from the previous section *Effect of Uncertainty in Available Capacity* are chosen as an illustrative example. A payoff table, for different criteria generated from the capacity planning model, is shown in Table 5.7. The decision space is whether to select strategy A or B (invest in suites as needed or all at once) and how many suites to invest in: in all, 26 alternatives. The Status of Nature correspond to NPV_k in the model: the NPV for each scenario. The table shows, for each decision alternative, the best NPV ($\max_k \text{NPV}_k$), the expected NPV

(eNPV $= \sum_k \pi_k \text{NPV}_k$) and the worst NPV ($\min_k \text{NPV}_k$). These are the main criteria used for decision making: the other states are rarely needed. In the following section, decision analysis is illustrated for the various criteria using the values in the table.

Table 5.7: Expected Value, Min and Max Criteria using NPV

Strategy A ("wait-and-see")				**Strategy B ("here-and-now")**			
No. of Suites	Max	Expected	Min	No. of Suites	Max	Expected	Min
2	1076.98	1036.68	-46.38	2	1076.98	1036.68	-46.38
4	1742.30	1619.23	-530.17	4	1742.30	1612.81	-530.17
6	2319.98	2121.06	-288.28	6	2402.11	2085.16	-1013.95
8	2922.50	2551.05	-288.28	8	3048.59	2408.77	-1497.74
10	3512.47	2902.29	-288.28	10	3635.03	2573.03	-1981.52
12	4072.46	3140.43	-288.28	12	4147.83	2590.20	-2465.31
14	4592.00	3313.45	-288.28	14	4579.36	2464.57	-2949.09
16	4995.84	3417.01	-288.28	16	4862.35	2213.14	-3432.88
18	5391.48	3470.65	-288.28	18	5043.82	1884.80	-3916.66
20	5712.95	3485.66	-288.28	20	5357.19	1489.37	-4400.45
22	5901.67	3489.21	-288.28	22	5380.59	1015.97	-4884.23
24	5925.00	3488.57	-288.28	24	5067.68	537.29	-5368.02
26	5925.39	3482.35	-288.28	26	4583.90	53.45	-5851.80

5.5 Decision-Making Analysis Results

5.5.1 Expected Value

The expected value is calculated by multiplying each decision outcome (payoff value) for each state of nature by the probability of its occurrence. Assuming that the model has n different outcomes and the probability of each outcome is π, the expected value of some variable x

that takes values x_i can be calculated with the next formula:

$$E(x) = x_1\pi_1 + x_2\pi_2 + ... + x_n\pi_n \tag{5.12}$$

In the case where the probabilities are equal ($\pi_i = 1/n$), the expected value is equal to the arithmetic mean:

$$E(x) = \frac{x_1}{n} + \frac{x_2}{n} + ... + \frac{x_n}{n} = \frac{\sum_{i=1}^{n} x_i}{n} \tag{5.13}$$

The expected value of the outcome is not a risk measure. It aggregates all different outcomes into a single number. It is a commonly adopted measure of performance for decision-making under uncertainty. Based on the expected value criterion, the decision alternative to be selected would be strategy A, with 22 suites, as this decision/outcome combination results in the highest expected NPV.

5.5.2 Maximax

The maximax criterion represents the selection that an optimistic decision-maker would choose. With this criterion, the decision-maker selects the gives the maximum value for the best outcome in each state of nature. This means considering the lefthand column for strategies A and B in Table 5.7, and choosing the number of suites with the largest best NPV. In this case, strategy A with 26 suites would be selected.

Maximax is also called *The Optimist Criterion.* The optimist criterion attempts to describe the decision-making behaviour of people who are overly optimistic in their expectations. An optimistic decision-maker is attracted by large rewards and is willing to risk high losses in order to obtain them.

5.5.3 Maximin

The reverse approach to the maximax criterion is the maximin criterion, which is based on the assumption that the decision-maker is conservative about the future. With this criterion, the minimum payoffs for each alternative are compared, and the alternative that produces the maximum of the minimum payoffs must be chosen (i.e. the best worst-case). This

corresponds to picking the largest value of the righthand column in Table 5.7. and 2 suites would be chosen using strategy A.

Maximin is also called *The Pessimist Criterion.* The pessimist criterion attempts to describe the decision-making behaviour of people who are overly pessimistic in their expectations. A pessimistic decision-maker is averse to large losses and is willing to forego attractive gains in order to avoid a significant risk.

5.5.4 Minimax Regret

Regret is defined as the difference between the payoff of the best possible decision for a given state of nature and the payoff of the actual decision for that state of nature. It is, literally, a quantification of how much one regrets making the wrong decision and will be expressed in terms of lost NPV or increased cost, etc. For each decision that can be made, there will be a range of regrets for each state that may occur. The minimax regret criterion considers the worst possible regret for each decision and selects the decision that minimises this.

The minimax regret criterion is defined mathematically, using NPV as the payoff, as follows. The regret, R_{dk}, for each decision d and state k is defined by:

$$R_{dk} = \max_{d}(\text{NPV}_{dk}) - \text{NPV}_{dk}. \tag{5.14}$$

The worst regret for each decision is therefore

$$\max_{k} R_{dk} \tag{5.15}$$

From Table 5.8, each of the highlighted payoffs is the maximum for each alternative. In strategy A, the minimum among the best payoffs is when x is 26, where the minimum among the worst payoff is when x is 2. In order to balance both sides of the criterion, the minimax regret is the summation of the best and worst sides. The highlighted minimax regret occurs when x equals to 26, therefore, the decision should be to install 26 suites. As in strategy B, the minimax regret occurs when x equals to 12 as highlighted on Table 5.8.

Table 5.8: Minimax Regret Criteria using NPV

Strategy A ("wait-and-see")		**Strategy B ("here-and-now")**	
No. of Suites	Minimax Regret	No. of Suites	Minimax Regret
2	4848.41	2	4848.41
4	4183.09	4	4183.09
6	3605.41	6	3523.28
8	3002.89	8	2881.78
10	2412.92	10	2302.99
12	1854.99	12	2418.93
14	1337.68	14	2902.71
16	929.55	16	3386.50
18	552.92	18	3870.28
20	241.90	20	4354.07
22	288.59	22	4837.85
24	241.90	24	5321.64
26	**241.90**	26	5805.42

5.5.5 Hurwicz Criterion

The Hurwicz criterion compromises between the maximax and maximin criteria. It selects the decision that maximises a weighted average of the maximum payoff and the minimum payoff over all states of nature. A weighting parameter, $y \in [0, 1]$, allows the decision-maker to choose the level of pessimism or optimism represented by the criterion.

Values close to 1 give an optimistic criterion whereas values close to 0 are pessimistic, and with $y = 0$ or $y = 1$, the Hurwicz Criterion reduces to either the maximin or maximax criteria respectively.

The Hurwicz Criterion is defined mathematically as:

$$\max_{d}[y \max_{k} \mathrm{NPV}_{dk} + (1 - y) \min_{k} \mathrm{NPV}_{dk}] \tag{5.16}$$

Frohwein *et al.* (1999) stated that the Hurwicz criterion is only applicable to bounded distributions, i.e. cases where there exist finite minimum and maximum possible outcomes. The Hurwicz criterion discards the probability of experiencing an extreme event. However, y must be determined by the decision-maker and is completely subjective. The Hurwicz criteria for each of the two models is shown in Table 5.9. In this case, a typical pessimistic value of $y = 0.4$ was chosen. As with maximax or maximin, the alternative that yields the highest criterion is selected, therefore, 26 suites would be installed where they are required (strategy A), as highlighted in the table.

5.5.6 LaPlace (Equal Likelihood) Criterion

The LaPlace criterion is also called the equal likelihood criterion, which equally weights the possibility of occurrence of each state of nature. For example, if there are three states of nature, each has a 1/3 chance of occurrence. Then, each decision alternative will be assigned an "average" payoff value (see Table 5.10). If the probabilities of the states are unknown, or known to be identified, then the LaPlace criterion is identically equal to the expected value criterion. Using the LaPlace criterion for each alternative in Table 5.10, strategy A with 26 suites should be selected.

Table 5.9: Hurwicz Criteria using NPV

Strategy A ("wait-and-see")		**Strategy B ("here-and-now")**	
No. of Suites	Hurwicz Criterion	No. of Suites	Hurwicz Criterion
2	402.96	2	402.96
4	378.82	4	378.82
6	755.02	6	352.47
8	996.03	8	320.79
10	1232.02	10	265.10
12	1456.02	12	179.95
14	1663.83	14	62.29
16	1825.37	16	-114.79
18	1983.62	18	-332.47
20	2112.21	20	-497.39
22	2187.70	22	-778.30
24	2197.03	24	-1193.74
26	**2197.19**	26	-1677.52

Table 5.10: LaPlace (Equal Likelihood) Criterion using NPV

Strategy A ("wait-and-see")		**Strategy B ("here-and-now")**	
No. of Suites	LaPlace Criterion	No. of Suites	LaPlace Criterion
2	1050.37	2	1046.17
4	1647.61	4	1623.33
6	2155.10	6	2134.38
8	2597.44	8	2517.25
10	3012.27	10	2740.07
12	3282.56	12	2818.23
14	3484.36	14	2751.89
16	3604.53	16	2533.06
18	3674.79	18	2245.07
20	3711.29	20	1880.71
22	3712.31	22	1418.51
24	3715.44	24	952.07
26	**3707.94**	26	470.18

5.5.7 Summary of Decision-Making Criteria

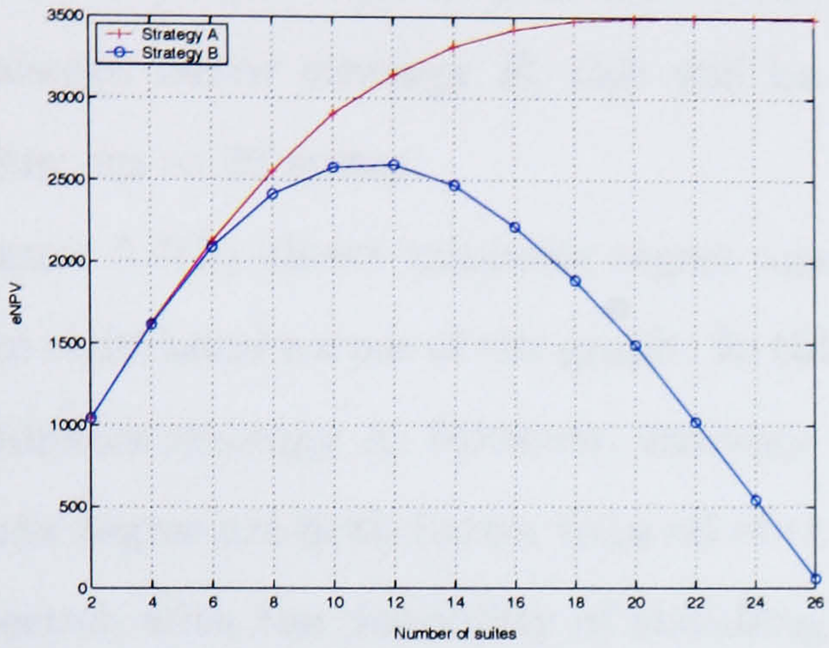
The decisions indicated by the decision criteria examined in the above methods can be summarised and presented as the diagrams in Figure 5.6. Figure 5.6(a) indicates the expected value criterion. In the figure, strategy A gives a better result as the eNPV values are always better than that of strategy B meaning a better profit return to be obtained. This is to be expected because in strategy A, suites can be added whenever there is sufficient demand for them, whereas in strategy B the decision has to be made at the beginning. Even if the correct decision is taken in strategy B, strategy A may still be because building the suites at the beginning incurs additional operating costs while the suites are idle. Decision-making using maximax is presented in Figure 5.6(b) which shows that better maximax values are obtained with strategy B when the number of suites is less than 14. Therefore, the decision-makers require better information in advance to decide to go for strategy A or B. For the maximin analysis in Figure 5.6(c), strategy A is chosen as it provides the best worst case. In Figure 5.6(d), the smallest value of minimax regret is used to choose between strategy A and strategy B. Strategy B has lower values when the number of suites is less than 6. This case is similar to the maximax analysis, where the decision-maker must know in advance whether a large capacity will be required in the future. Figures 5.6(e) and 5.6(f) are the Hurwicz and Equal Likelihood analyses, the results are very similar showing that strategy A is better.

The use of several decision criteria often results in a mix of decisions, with no one decision being selected more than the others. Hence, the appropriate criteria are dependent on the risk characteristics and the philosophy of the decision-maker.

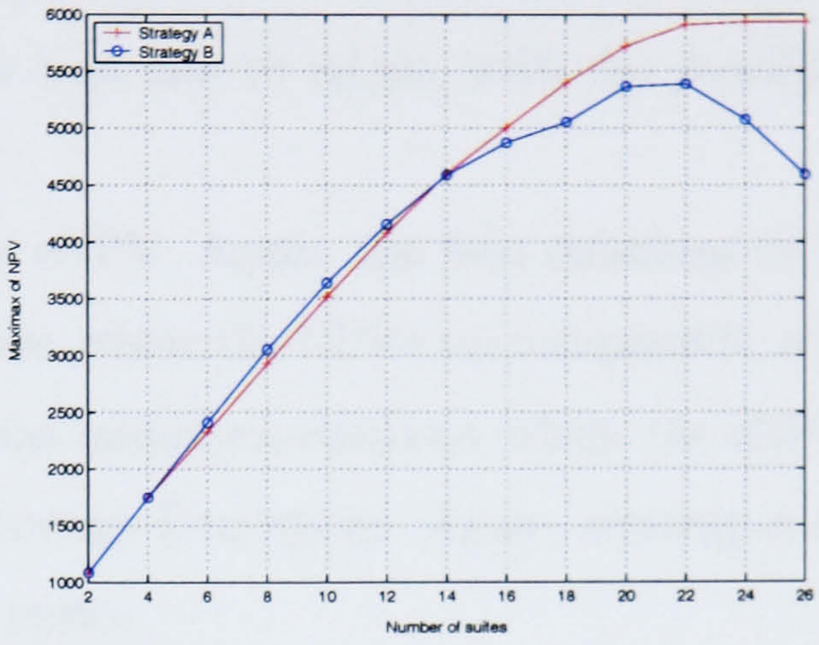
5.5.8 Pareto Analysis

Pareto analysis is a method of classifying items, events, or activities according to their relative importance. In this section, the Pareto curves in Figure 5.7 show the comparison of different risk factors against eNPV. The approach used here is to look for decisions that are consistently bad with all or most of the metrics. In this way, it is hoped that some solutions can be discarded regardless of the risk attitude of the decision taker.

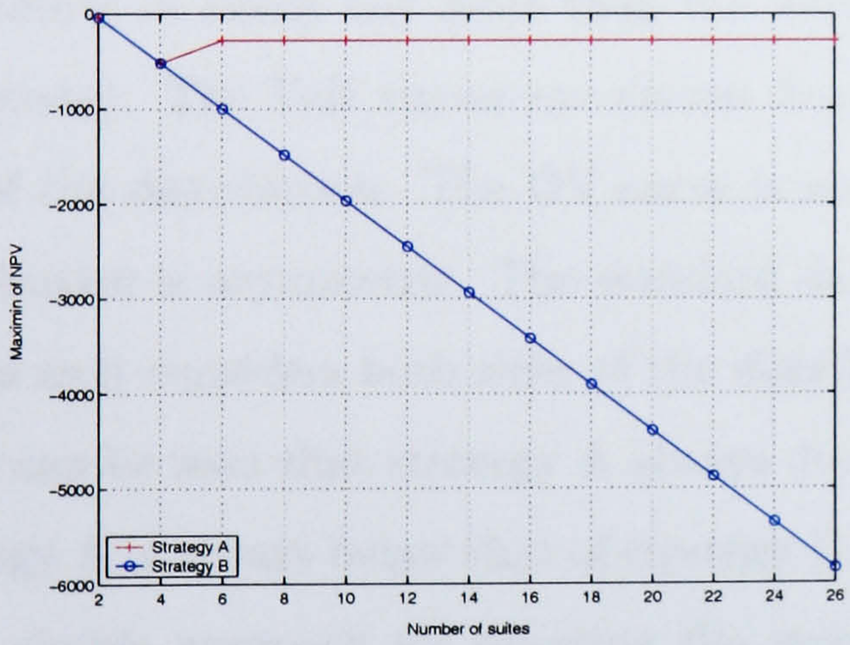
Figure 5.7(a) shows the relationship between eNPV and EDR. In the figure, the better



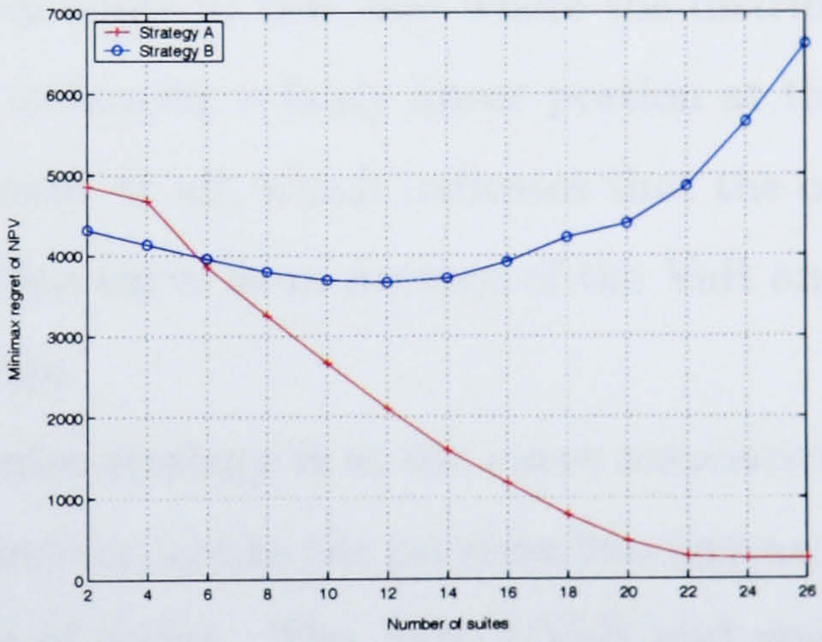
(a) eNPV



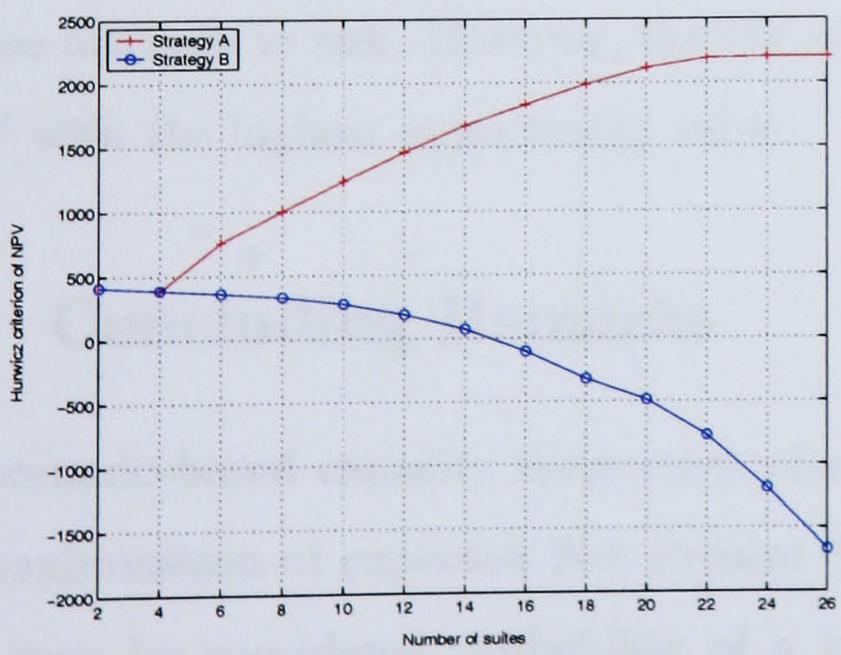
(b) Maximax



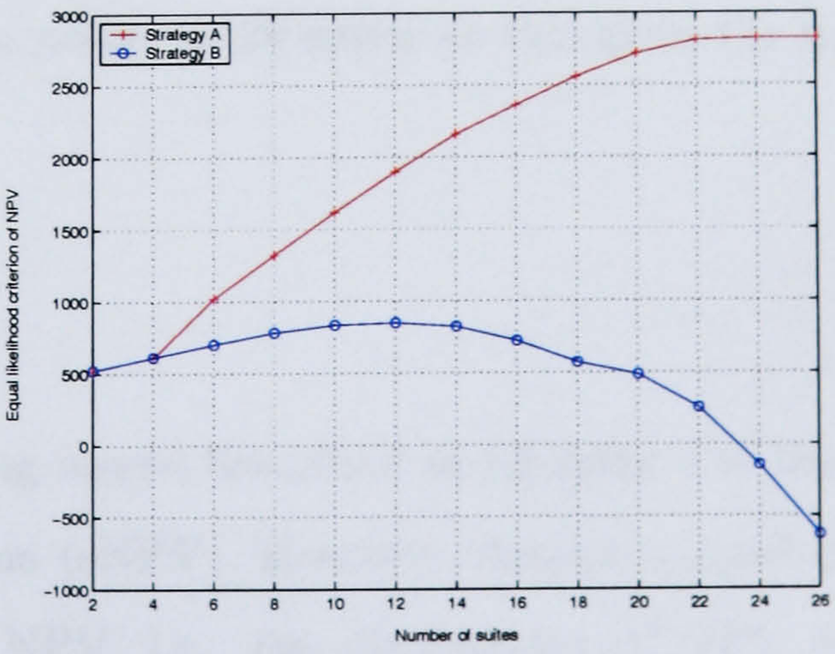
(c) Maximin



(d) Minimax Regret



(e) Hurwicz Criterion



(f) Equal Likelihood Criterion

Figure 5.6: Comparison of Decision-Making Criteria

solutions are towards the bottom right of the graph: high eNPV and low EDR. Since strategy A is always below strategy B, this will be the best one to adopt, with the possibility of installing up to 26 suites.

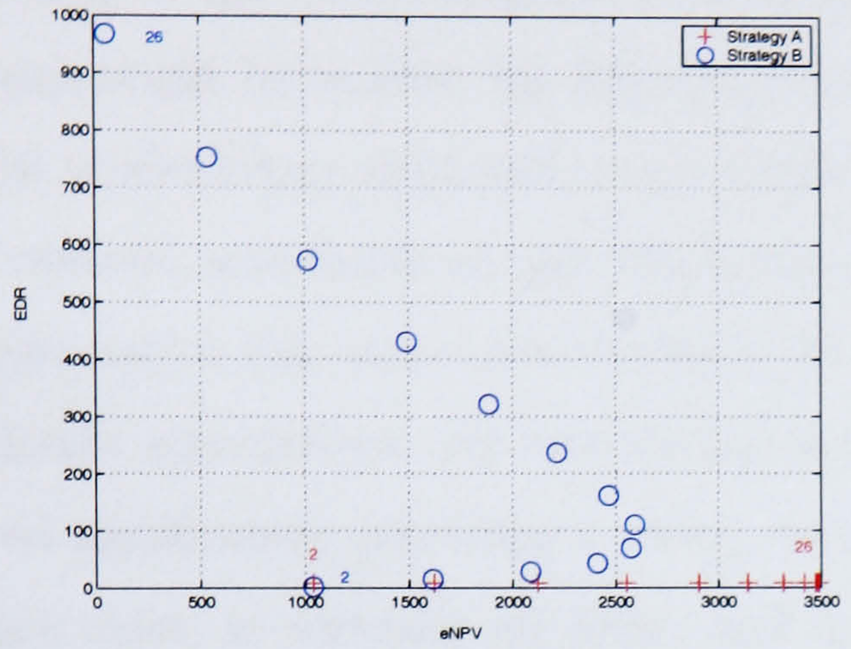
Figure 5.7(b) shows minimax regret against eNPV. Again, the best solutions lie in the bottom right hand corner of the graph. In this case, where the NPVs are comparable, strategy B dominates strategy A. However, strategy A has numerous solutions where the eNPV and minimax regret are both better than all of the strategy B solutions. Again, strategy A should be selected, with the possibility of installing 26 suites.

In Figures 5.7(c) to 5.7(f), the trends of the curves are similar. VaR and CVaR are almost identical, because they are calculated using the 99% confidence level (there is little probability of losing any more than the VaR, especially in this case where the distribution is discrete). The VaR curves are almost linear, indicating a fairly linear portion at the low end of the distribution. The OV curve is not linear at all, which indicates that the overall distribution is asymmetric. The standard deviation curve is an average of the VaR and OV curves as it considers both sides of the distribution.

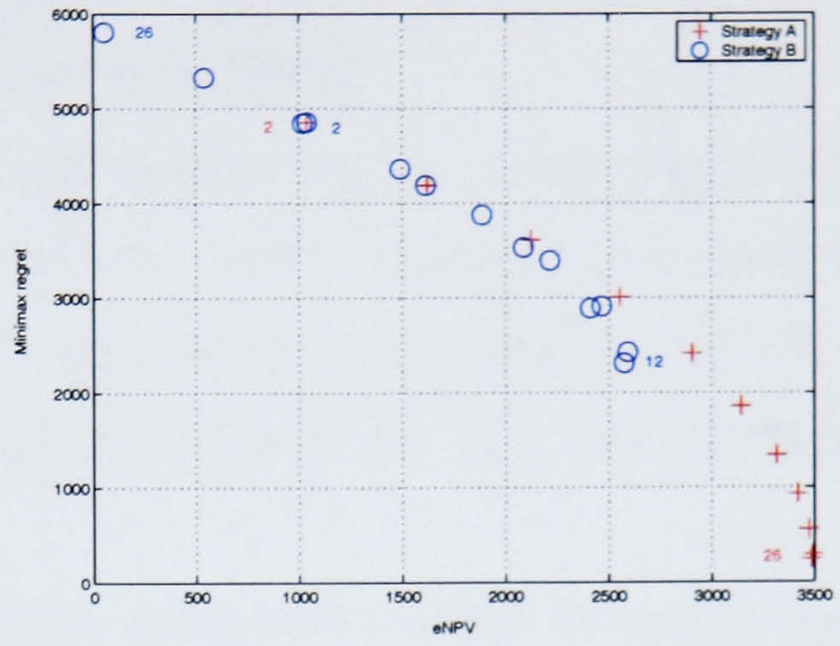
It can be seen that strategy A always dominates strategy B as the curve associated with strategy A is always below that of strategy B. However, unlike the previous two figures, there is no simple approach for selecting the number of suites. The VaR, CVaR and standard deviation curves do not suggest directly a solution, since 26 suites gives a high eNPV with a high risk and 2 suites gives a low eNPV with a low risk. The decision taken will depend on ones attitude to risk. However, the OV curve points to 26 suites as this gives the highest eNPV with the highest opportunity value.

5.6 Concluding Remarks

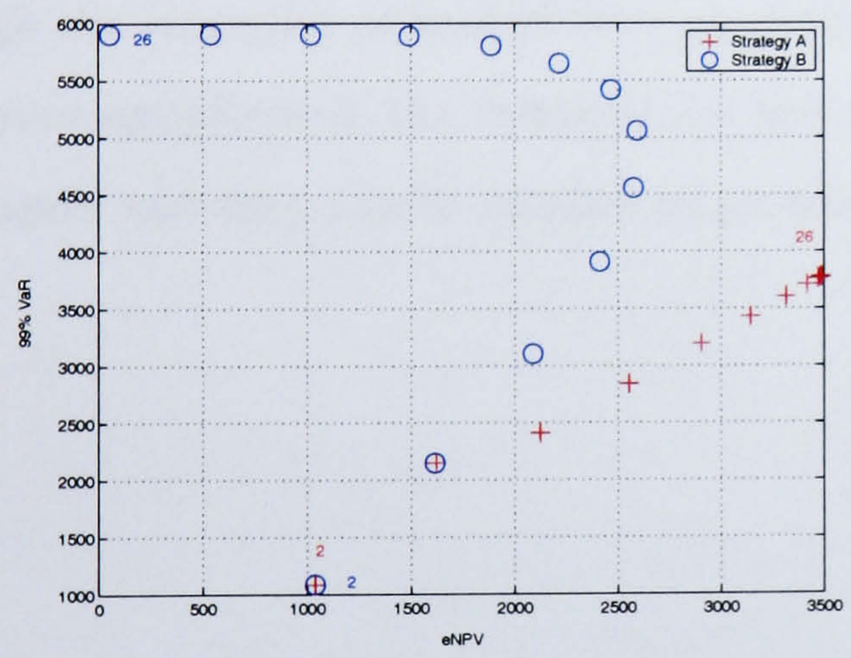
The scenario-based capacity investment planning model described in Chapter 4 is basically the maximisation of expected Net Present Value (eNPV). However, despite a good eNPV, there may be considered probability of a low NPV, i.e. the distribution of NPV is very broad, resulting in a risky decision. It is usually desirable to optimise the eNPV, subject to a constraint limiting the risk of the decision. For example, it may be demanded that the



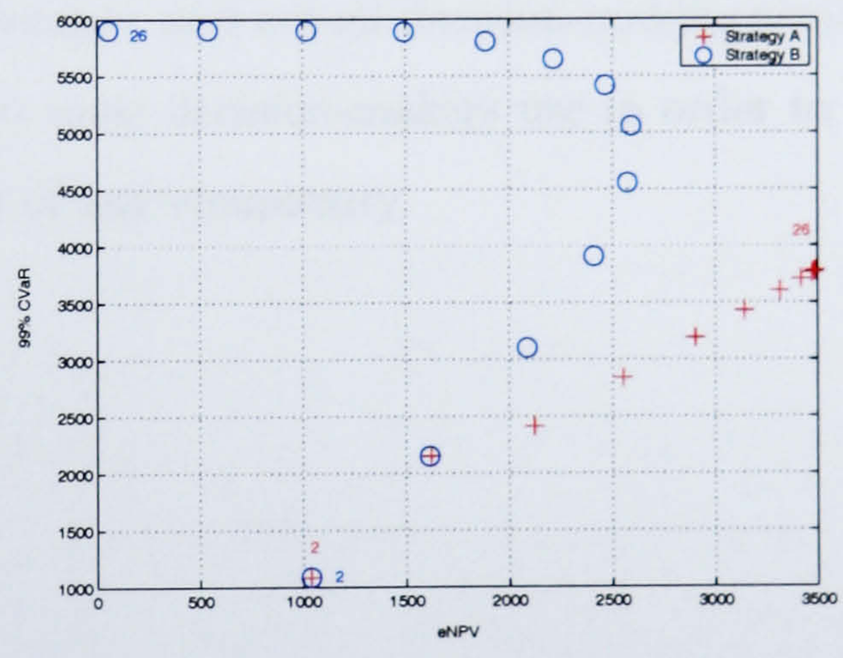
(a) EDR



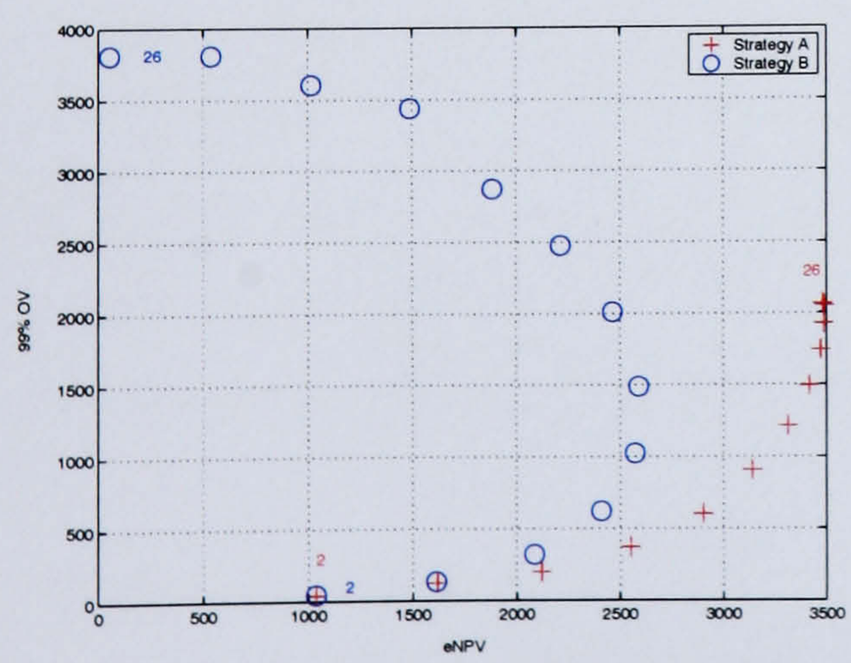
(b) Minimax Regret



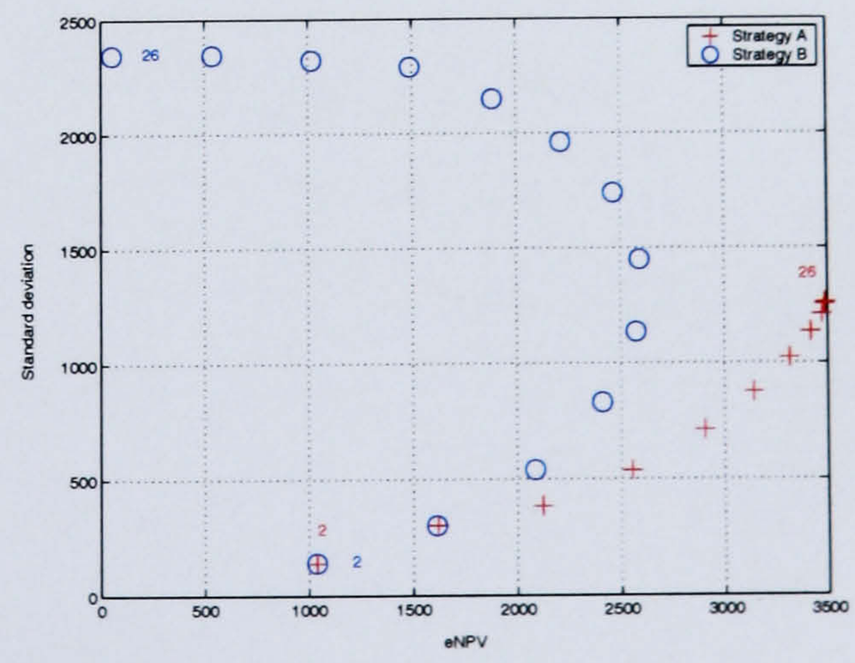
(c) VaR



(d) CVaR



(e) OV



(f) Standard Deviation

Figure 5.7: Comparison of Risk Criteria

probability of the NPV being less than an acceptable value does not exceed 10%. A similar approach might be to limit the Expected Downside Risk (EDR).

The methodology employed in the financial risk analysis section of this chapter allows a more realistic assessment of risk which may be relevant to the multiple vaccine case study. The cumulative risk curves were found to be very appropriate to visualise the risk behaviour of different alternatives. By introducing the tightening risk factor, RF, the actual EDR is reduced significantly, providing a robust result.

Risk exists in virtually all firms, and has been extensively studied in various business contexts. In the decision-making analysis section, we have demonstrated the concepts of decision-making with or without probabilities. We have used a payoff table approach. Although the examples presented here are rather simple, and actual decision-making situations are more complicated, the methods are the ones most decision-makers use in order to make a decision and they can be applied to problems of any complexity.

Chapter 6

Transmissive Disease Control and Vaccine Supply Chain Modelling

Despite the availability of a public health vaccination program, failure to supply sufficient vaccines on time to the potential recipients may increase the infection rate (and fatality rate where applicable) should there be an outbreak of a serious disease. Understanding the relationship between the vaccine supply chain and the population dynamics of transmissive diseases is critical in developing an effective overall vaccination strategy. Thus, the aim of this study is to develop a model that combines the supply chain and the disease dynamics in order to explore, via mathematical modelling, the impact of immunisation with a partially effective vaccine supply chain on the transmission dynamics of disease infection. The model addresses the question of whether such a vaccine could ever completely stop the spread of infection and determines the minimal vaccine efficacy and vaccination rate required to control infection in a population. Numerical results show that the vaccine supply chain strategies have great impact in controlling the spread of infectious diseases.

6.1 Introduction

Transmissive disease systems are made up of (1) populations of hosts that become infected, (2) the infectious agents that infect them, and (3) the media affecting the interactions of

hosts that transmit infection. The evolution, spread, and persistence of infectious diseases are facilitated by the mobility of contemporary society, for example through air travel, the continued growth in the world population and the steady rise in the number of densely populated urban areas. To control the spread of infection one must understand the transmission disease system and develop a good vaccination policy for the public. Transmission disease analysis is useful to understand how risk factors and contact behaviour generate patterns of infection in a population.

Mathematical studies of the transmission dynamics of diseases over the past decade have been focused on characterising the nonlinear dynamics of simple and complex models of disease transmission. Most of these studies are developed using the simple structured Suspectible-Exposed-Infected-Recovered (SEIR) model (e.g. Arino *et al.* (2004)). Typically, the difference between many studies is simply the SEIR model being applied to different transmission diseases. Ferguson *et al.* (1996) applied an SEIR model to measles; Kaplan *et al.* (2003) developed a similar SEIR approach for smallpox; Alexander *et al.* (2004) and Viboud *et al.* (2004) provided an analysis for influenza; and Donelly *et al.* (2003) applied it to Severe Acute Respiratory Syndrome (SARS).

Sufficient vaccine supply and a good vaccination policy are the most important factors in controlling the spread of diseases and the number of fatalities. However, according to a recent World Health Organisation (WHO) report (Tomich, 2002), the lack of vaccine supply in developing countries continues to leave these countries at threat. Vaccine shortages reported for the past two years represented a disaster for manufacturers and health care providers, and caused inconvenience and confusion for the public. The vaccine shortages left some people vulnerable to preventable diseases. While catch-up efforts have temporarily alleviated these recent shortages, the conditions that led to the supply crisis continue to concern public health experts and all those who are involved in the development, production, delivery, and regulation of vaccines.

To control a sudden outbreak of an infectious disease, the population needs to be immunised quickly. Failure to supply sufficient vaccines on time may increase the infection rate. The relationship between the vaccine supply side and the population dynamics of transmis-

sive diseases is critical in developing an effective vaccination strategy. The aims of this work are (1) to develop a model that captures both the supply chain and the disease dynamics, (2) to explore the impact of different supply chain strategies on the infection rate, and (3) to determine the vaccination rate required to control the infection.

The chapter is organised as follows. Section 2 reviews some of the technical literature related to the concept of the supply chain modelling and policy analysis. A mathematical model for the transmission dynamics of a typical infectious disease is formulated and normalised in Section 3. A sample vaccine structure is described in Section 4. The computational results obtained from the model are then discussed in Section 5. Finally, discussion and concluding remarks are given in Section 6.

6.2 Review of Supply Chain Modelling and Policy Analysis

As supply chains are very complex systems, the effects of policy changes on their behaviour is very difficult (if not impossible) to ascertain without using some form of modelling approach. Supply chain models are typically used to analyse and/or simulate raw material purchasing, products pricing, ordering, production management, inventory management, etc. Considering the complexity of a supply chain, there is no model that can capture all aspects of supply chain processes. To compromise between model complexity and realism, a model builder should define the objectives of the supply chain model in such a way that it is sufficiently representative without being too tedious to solve.

Simulation models (e.g. Julka *et al.* (2002*a*), Biswas and Narahari (2004)) allow a more realistic capture of the supply chain characteristics and dynamics and they provide a means to evaluate the impact of policy changes carried out by one or more supply chain nodes. Therefore, simulation can be described to be the first step towards optimisation.

There are two major types of analytical supply chain models: (1) Deterministic (non-probabilistic) analytical model (e.g. Cohen and Moon (1990), Applequist *et al.* (2000)), and (2) Stochastic (probabilistic) analytical model (e.g. Pyke and Cohen (1993), Sabri and Beamon (2000)). Deterministic analytical models (e.g. for process planning and scheduling) take into account only the certain and exact elements and assume that product demands

are known. However, in an increasingly competitive environment, there are many random or uncertain elements in the supply chain such as customer demands, lead times, and production fluctuations. The stochastic models take into account some or all these uncertain and random elements.

6.3 SEIR Model with Vaccine Supply Chain

SEIR is the oldest and best known mathematical model of disease transmission dynamics (see, e.g., Ferguson *et al.* (1996)). It comprises four sub-groups of a population: Susceptible (S), Exposed (E), Infected (I) and Recovered (R). Here we have extended the model to account for Vaccinated (V) and Dead (D) people. In order to derive the equations of the mathematical model, it is first assumed that there is no possibility of two concurrent outbreaks. In this case, the model does not consider the effects of partial cross-immunity between different diseases. The equations describe the transitions between the different situations using discrete time steps and by expressing the number of cases at a given time, $t + 1$, in terms of those at the preceding time, t. The transfer model is illustrated in Figure 6.1. A description of the model parameters is provided in Table 6.1.

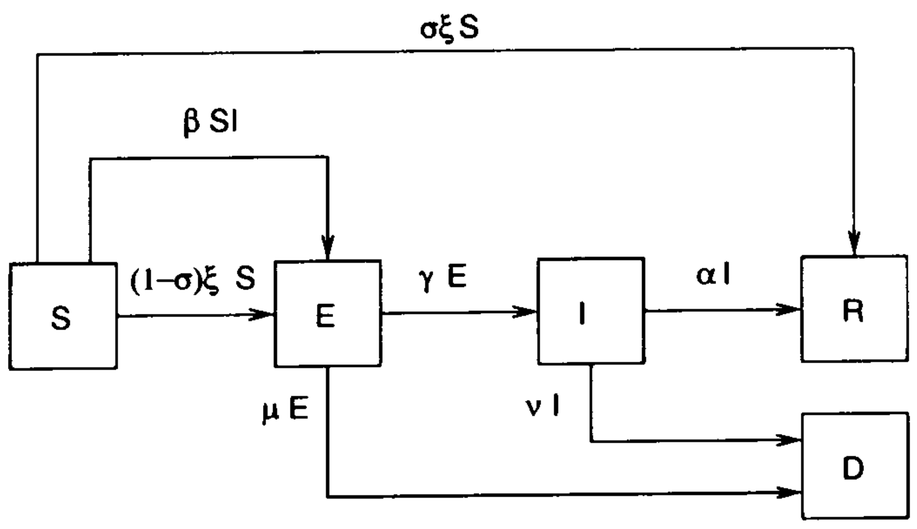


Figure 6.1: Transfer Diagram of the SEIRD Model

For diseases conferring long-lasting immunity following infection, the number of S decreases with time. Before the outbreak of a first transmission disease attack case, S is near 100% of the population because all of the population is susceptible, hence, E, R, and D are 0 while I is a small proportion. When an epidemic starts to spread, the S population is reduced through vaccination (ξS) and infection (I) with time. It is assumed that over this

Table 6.1: Model Parameters and Descriptions

Symbol	Parameter	Value	Reference
N	total population $[person]$	100000	—
β	contact probability $[person^{-1}day^{-1}]$	0.00001	Kaplan *et al.* (2003)
ξ	vaccination rate $[day^{-1}]$	variable	Alexander *et al.* (2004)
σ	vaccine efficacy [-]	0.9	Bedford and Elliman (2000)
γ	infection rate $[day^{-1}]$	0.1	Kaplan *et al.* (2003)
α	recovering (immune) rate $[day^{-1}]$	0.1	Kaplan *et al.* (2003)
μ	death rate due to exposure $[day^{-1}]$	0.01	Alexander *et al.* (2004)
ν	death rate due to infected $[day^{-1}]$	0.01	Alexander *et al.* (2004)

timescale there is no recruitment of individuals (either by birth or immigration).

The exposed population, E, consists of people who have been exposed to the disease or who have been infected but are not yet infectious. E can increase in two ways. First, if susceptible people (S) have not been vaccinated, they will become exposed (at the rate βSI) by coming into contact with an infectious person (I). Note that the I population does not decrease by this interaction: an infected person cannot return to being exposed. Second, if they receive the vaccination but it is inefficacious, they immediately become exposed (at the rate $(1-\sigma)\xi S$). This immediate transition from failed vaccination and the lumping of exposed and newly infected populations into one are simplifying assumptions in the original SEIR model.

E is reduced through two routes. Either infected people may die (reducing E and increasing D at a rate of μE) before reaching the infectious stage, or they become infectious at the rate γE. Finally, the infectious population, I, is reduced either through death (νI) or by individuals recovering by themselves (reducing I and increasing R at the rate αI).

The population of vaccinated individuals (V) is affected by different public health vaccination policies and the supply chain managed by the vaccine suppliers and public health institutions. Since the vaccine does not confer immunity to all recipients, vaccinated individ-

uals may become infected because the vaccine efficacy (σ) is less than unity.

The details of the transitions between the five groups of populations can be described mathematically by the following equations:

$$S_{t+1} = S_t - \beta S_t I_t - \xi_t S_t \tag{6.1}$$

$$E_{t+1} = E_t + \beta S_t I_t + (1-\sigma)\xi_t S_t - \gamma E_t - \mu E_t \tag{6.2}$$

$$I_{t+1} = I_t + \gamma E_t - \alpha I_t - \nu I_t \tag{6.3}$$

$$R_{t+1} = R_t + \alpha I_t + \sigma \xi_t S_t \tag{6.4}$$

$$D_{t+1} = D_t + \mu E_t + \nu I_t \tag{6.5}$$

To demonstrate the applicability of the disease model, different vaccine supply chain strategies are modelled. Here, a new variable to represent the cumulative number of people vaccinated up to time t, V_t, is introduced. The number of people who are vaccinated is the product of total population, N, and the cumulative rate of vaccination ξ_t.

$$V_t = \xi_t N \tag{6.6}$$

During the study of the SEIR model, it was assumed that only one vaccine was produced. This minimised the complexity of having different vaccines to cure the population. Furthermore, since the model monitors the dynamics of the human populations, it is assumed that all the model parameters and variables are positive. It was also assumed that all susceptible people are required to receive vaccines, in some cases, people do not know whether they have already caught the disease during an outbreak, so the vaccine demand is approximately equal to the whole population.

6.4 Vaccine Supply Chain Structure

The vaccine supply chain consists of a supplier, a manufacturer, a warehouse, a hospital and/or clinics/surgeries and patients who require vaccination. The vaccine supply chain is modelled based on dynamic material balances and orders for the vaccine. Safety stock is introduced to correspond to the minimum amount of vaccine to be stored in the warehouse to buffer against any unexpected increase in the demand. It therefore represents the lower bound of the inventory level.

In designing the vaccine supply chain, each node operates an inventory control policy to manage the stockpile. The control policy can either be one of the Re-Order Point (ROP) techniques, or one of the MRP/DRP that creates orders according to a future prediction of stock levels based on a demand forecast. In this work, the stock level of the *warehouse* is controlled by a Re-Order Quantity (ROQ) policy reviewed at every time step. ROQ is one of the ROP techniques in which a fixed quantity, Q, is ordered when the stock level drops to or below the safety-stock level. Note that no demand forecasts are required with ROQ: this is a key difference between the ROP and DRP techniques.

The stock levels of the manufacturer, and the hospital used in the following models are controlled by DRP. A time phased order point approach is often used whereby the planned orders are driven by actual requirements by date. The overall intent of DRP is to schedule inventory replenishment to meet predicted demand at branch warehouses within the customer service guidelines and inventory levels specified by management policies. Basically, at each storage location in the supply chain, the following material calculation (see Martin (1983)) is performed:

$$P_{it} = F_{it} + X_{it} - S_{i,t-1} \quad \forall i, t \tag{6.7}$$

where

P_{it} = production or receipt of vaccine i in day t

$F_{i,t}$ = demand forecast of vaccine i in day t

X_{it} = inventory level of vaccine i in day t

S_{it} = safety stock level of vaccine i in day t

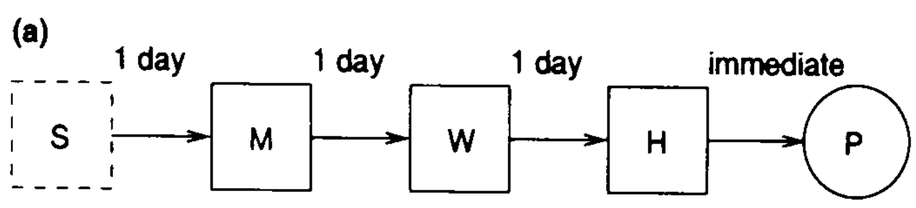
The efficiency of supply chains can in general be improved by e.g. reducing the number of stages, reducing lead-times, using alternative supply chain policies, etc. The number of stages may be reduced if the corresponding facility has already had sufficient stocks to fulfil the customers. In this work, we consider two vaccine distribution strategies case studies: *centralised* (vaccines supplied by 1 hospital) and *decentralised* (vaccines supplied by 12 clinics/surgeries). Each case is further differentiated by a number of different supply chain structures.

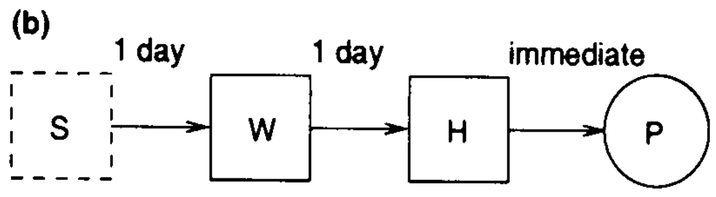
6.4.1 Centralised Model

The characteristic of the centralised model is that, for our sample population, the vaccines are only provided by a single hospital. The vaccine supply chain is simple; it is linked by one supplier, one manufacturer, one warehouse and one hospital, then to the patients who requires vaccination. In Figure 6.2, the four supply chain structures considered are illustrated where one stage is successively removed from Figure 6.2(a) to 6.2(d). The supply chain policies and parameters of each node are listed in Table 6.2. Figure 6.2(a) to 6.2(c) are termed "reactive", as the supply chain has to react to an outbreak and provide sufficient vaccine without prior warning, and Figure 6.2(d) is termed "proactive", as an outbreak is anticipated and vaccines are manufactured and supplied to the hospital in advance. The proactive case is the benchmark for the supply chain to try to achieve.

Table 6.2: Replenishment Control Policy of the Centralised Model

Node	**Supplier**	**Manufacturer**	**Warehouse**	**Hospital**
Policy Type	-	DRP	ROQ	DRP
Safety Stock Level	-	2 days	1000	2 days
Order Quantity	-	10000	20000	10000
Initial Stock Level	100000	0	0	0





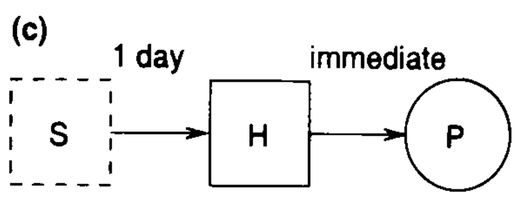


Figure 6.2: The four centralised supply chain structures in this study: (a) 3-node, (b) 2-node, (c) 1-node, (d) proactive.

6.4.2 Decentralised Model

Once an outbreak occurs or government introduces a vaccination program, the demand for vaccination at the hospitals may be greater than the supply of vaccines. Due to the heavy demand, hospitals may run out of vaccines meaning that the people may suffer a higher chance of becoming infected. A recent innovation is for patients to visit their local clinics to receive the vaccination as an alternative to going to the hospital. In Britain, the general practitioner (GP) is always the initial point of contact for most routine health care (Pooley *et al.* (2003)). The benefits of receiving vaccination in local clinics are accessibility, less time to wait for vaccination and a smaller contact probability between individuals.

The vaccine supply chain for this decentralised model is slightly different from the vaccine supply chain of the centralised model as illustrated in Figure 6.3. Instead of one single hospital, 12 clinics (Clinic A to Clinic L) are able to provide vaccines for the local population. The effect of reducing the number of nodes, varied as shown in Figure 6.3(a) to 6.3(d), is also examined in this section.

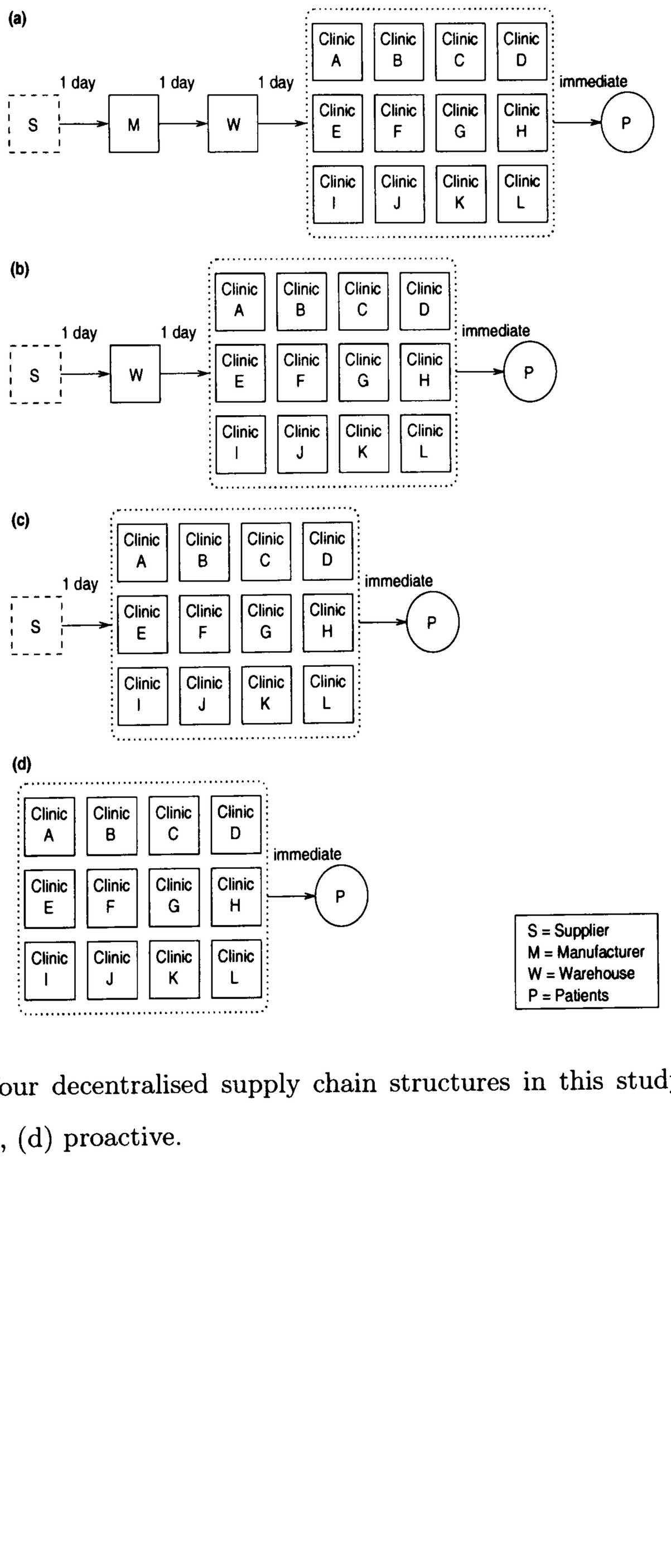


Figure 6.3: The four decentralised supply chain structures in this study: (a) 3-node, (b) 2-node, (c) 1-node, (d) proactive.

Table 6.3: Replenishment Control Policy of Decentralised Model

Node	Supplier	Manufacturer	Warehouse	Clinic (A-L)
Policy Type	-	DRP	ROQ	DRP
Safety Stock Level	-	2 days	1000	2 days
Order Quantity	-	10000	20000	10000
Initial Stock Level	100000	0	0	0

6.4.3 Demand Modelling

The demand on the vaccine providers is dominated by the susceptible population requiring vaccination during a sudden outbreak. Kaplan *et al.* (2002) suggested that the queuing distribution can be modelled by a lognormal-like distribution.

Anon (2002) and Haynes *et al.* (1999) stated that distance may be the main barrier to susceptible individuals immediately seeking vaccination at a hospital. The authors compared travelling times to the nearest hospital with travelling times to the GP. The numerical data shows that the perceived difficulty in accessing a hospital is significantly larger than accessing a GP: according to the Office for National Statistics, 20% of adults say that they have difficulty getting to hospital. Peak vaccination demands for clinics are assumed to be earlier than the hospital due to the convenience of visiting the clinic, hence the demand distribution is shifted to the left in the decentralised case.

However, a small clinic may have insufficient capacity and long lines of patients waiting for vaccinations. More patients require more space as they wait to receive treatment. If too many patients are in the clinic, they cause congestion, crowding, and confusion. We assume that they then go to second nearest clinic in order to be vaccinated.

It can be suggested that variations in vaccine demands in different clinics, and in the way that vaccines are received, will be closely related to the characteristics of the population in the local area. Areas with high levels of deprivation and/or a high proportion of small children may make heavier demands upon the vaccination program. However, in order to simplify this case study, it is assumed that clinics have different demand patterns but the

same total demand (=size of population served by the clinic). The vaccine demand for each clinic is estimated by dividing the total population by 12. In these case studies, we assume a total population of 100000. The demand profiles are estimated using different lognormal distribution as shown in Table 6.4. The demand profiles for the clinics and hospital are shown in Figure 6.4. The population in area 1 generates the latest but the highest peak demand. while area 12 generates the earliest but the lowest peak demand; the hospital shows a much later peak in demand, in line with the discussion above. Note that the profiles in Figure 6.4 are only the demands for vaccine and the number of people actually vaccinated will depend on the availability of vaccine in the hospital or clinics.

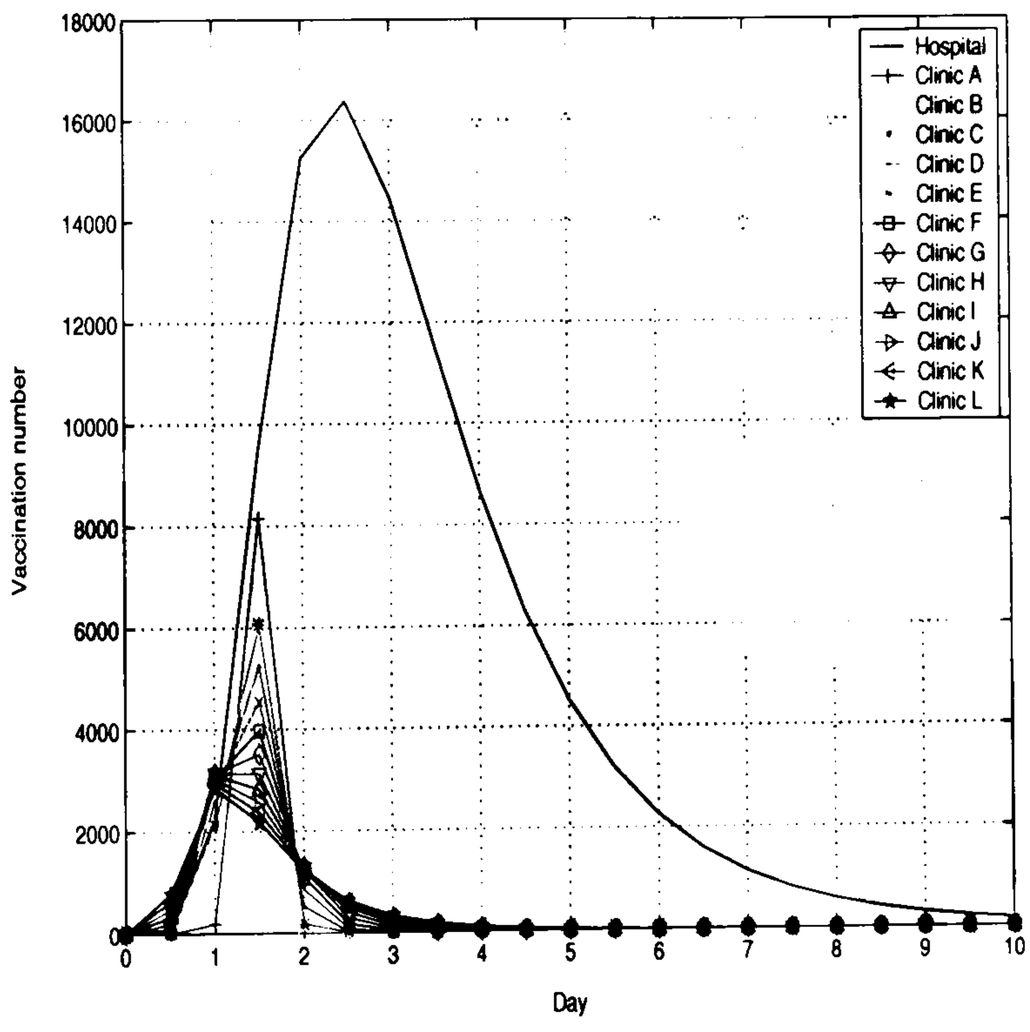


Figure 6.4: Lognormal Distribution of Vaccination Number

6.4.4 Supply Chain Modelling

Each node of the supply chain is modelled using a material balance, to track the vaccine inventory, and a control policy to determine when to order stock from a supplier node. A typical material balance is shown below.

$$X_{t+1} = X_t + P_t - Y_t$$

Table 6.4: Sample Data

Clinic(Area)	Population Size	Mean time to visit clinic	Standard Deviation
A(1)	8333.33	1	0.05
B(2)	8333.33	1	0.10
C(3)	8333.33	1	0.15
D(4)	8333.33	1	0.20
E(5)	8333.33	1	0.25
F(6)	8333.33	1	0.30
G(7)	8333.33	1	0.35
H(8)	8333.33	1	0.40
I(9)	8333.33	1	0.45
J(10)	8333.33	1	0.50
K(11)	8333.33	1	0.55
L(12)	8333.33	1	0.60

Where X_t is the inventory position at time t, P_t is the production or receipts of vaccine at time t and Y_t is the delivery of vaccine to a downstream node at time t. The deliveries will be equal to the demands, unless there is insufficient inventory, in which case all available vaccine is delivered.

Transportation between the nodes is modelled using a fixed lead time.

Finally, for the hospital or clinic nodes determine the vaccination rate based on the demand for vaccines and the available inventory. This vaccination rate determines the vaccination rate, ξ_t, in the disease model.

6.5 Computational Results

The basic inputs that were altered in the vaccine supply chain were (i) the supply chain structure, i.e. 3-node, 2-node, 1-node, and proactive, and (ii) the inventory control policies, i.e. ROQ, DRP. The results of the study are presented as individual performance measures. The performance measures related to the SEIR model are mainly the peak infection level and the total number of deaths. The results in terms of these measures are presented in the following subsections.

Both the supply chain and the SEIR models were implemented in Microsoft Excel.

6.5.1 Effects of Reducing the Number of Nodes

The vaccines are usually supplied to the hospital via the manufacturer and a warehouse, but in the case of a sudden disease outbreak, a long period of time is usually required to manufacture and deliver the vaccines to the hospital. In order to minimise the delays in delivering vaccines, hospitals may store some amounts of vaccine to cover sudden demand.

In this section, the effect of reducing the number of nodes is examined. The benefit of performing this investigation is to give a broad view of how important the hospital or its upstream nodes are to satisfying the demand. The investigation starts from a full 3-node vaccine supply chain (including manufacturer, warehouse, and hospital) and finally a 0-node (also called proactive), which means the hospital has enough vaccine stockpile for all the

patients who require vaccination (i.e. the outbreak is anticipated and sufficient vaccine is manufactured well in advance).

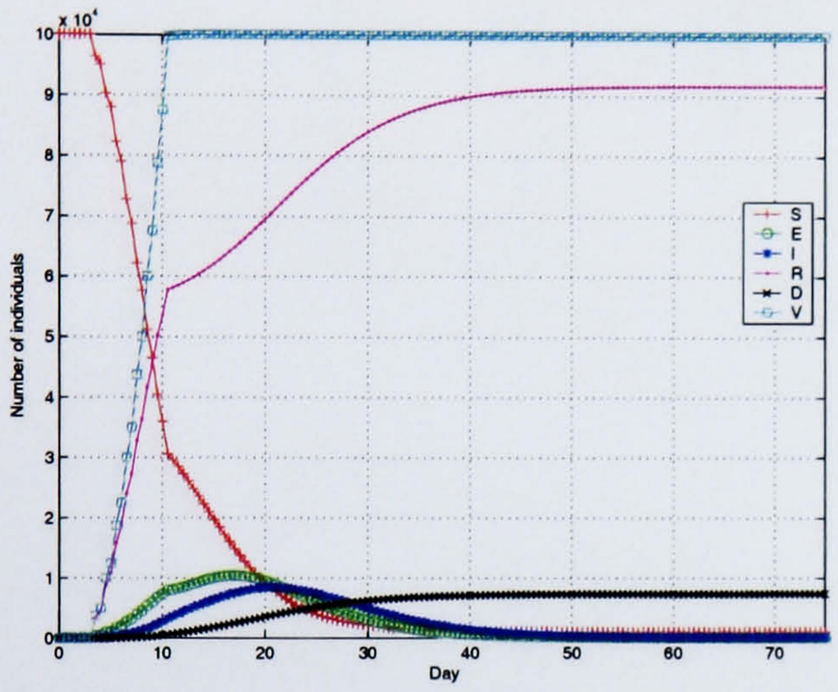
The effects of reducing number of nodes of the centralised model are shown in Figure 6.5. Figures 6.5(a) and 6.5(b) show that the vaccine supply rate is insufficient in these cases. The main reasons are the transportation lead-time and low order quantities.

The effects of reducing the number of nodes of the decentralised model are shown in Figure 6.6. Similar effects to the centralised case can be seen.

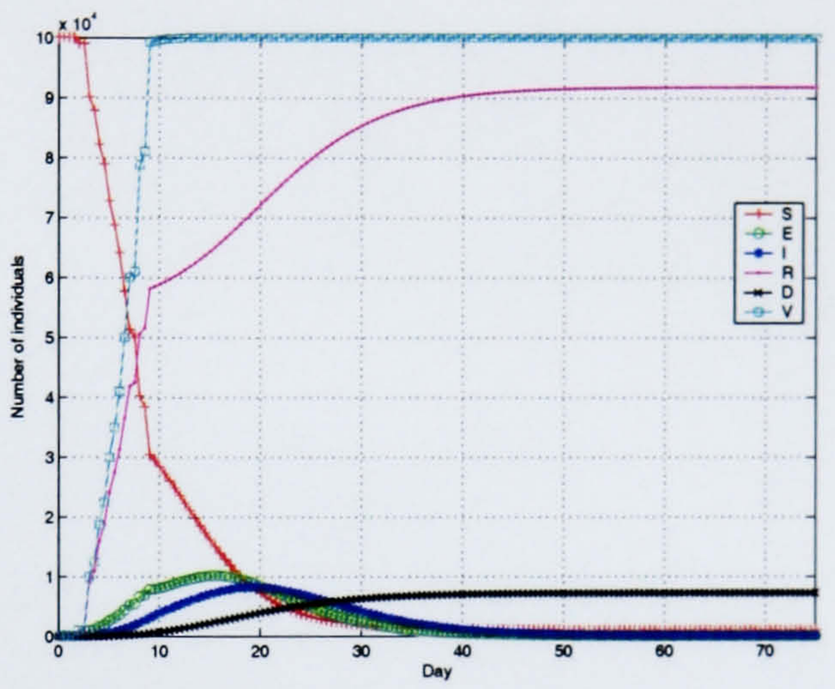
Although the exact peak infection level and the total number of deaths are not shown clearly in Figures 6.5 and 6.6, the differences in those performance measures are significant and are in Figure 6.7 and Table 6.5. Table 6.5 shows that the peak infection level and the number of deaths decrease when the number of nodes decreases. In Figure 6.7, the supply chain performance deteriorates sharply from 1-node to 2-node. The longer lead time results in the clinics (and to a lesser degree the hospital) running out of vaccine. With 2-node and 3-node supply chains, there is little difference between the centralised and decentralised models. This indicates that the supply-chain performance significantly affects the performance of the clinics. The clinics run out of vaccine early on, when the demand is the highest, so the patients wait about the same length of time for a vaccination as they would with the hospital.

Table 6.5: Key Metrics of the Centralised and Decentralised Models

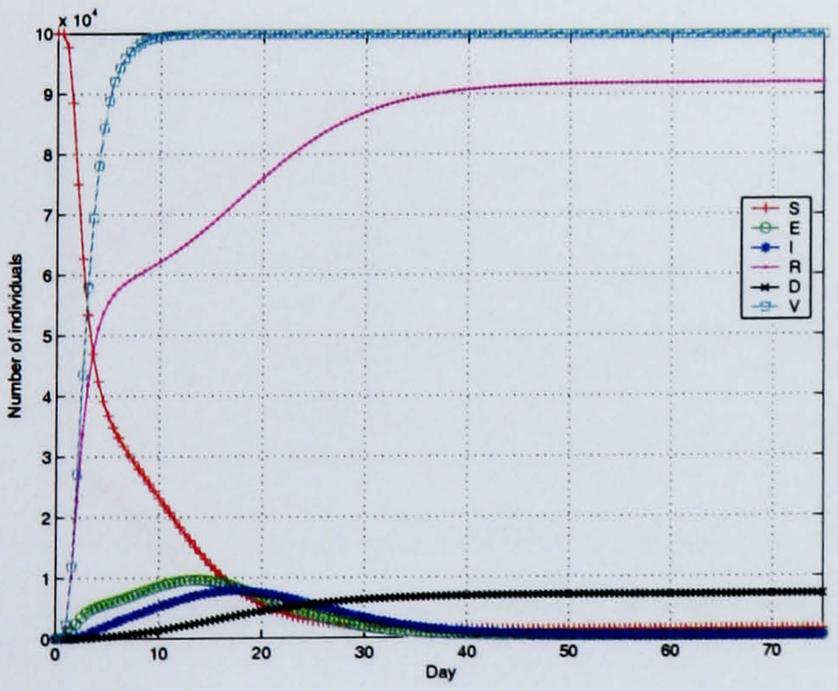
Model	**Scenarios**	**Peak Infection Level**	**Number of Deaths**
Centralised	3-node	8361	7382
	2-node	8203	7276
	1-node	7709	7075
	proactive	7709	7075
Decentralised	3-node	8262	7324
	2-node	8209	7314
	1-node	5877	5833
	proactive	5877	5833



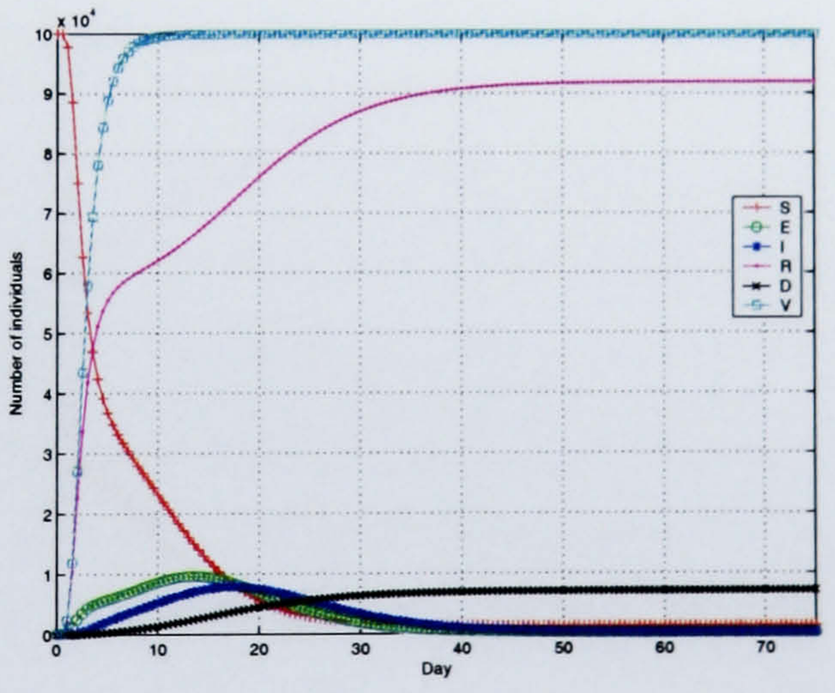
(a) 3-node



(b) 2-node

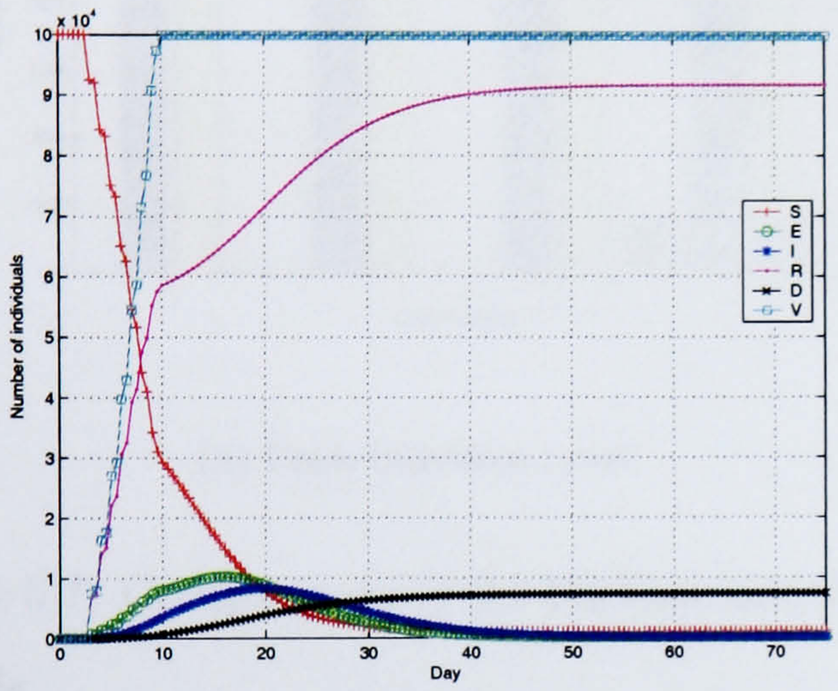


(c) 1-node

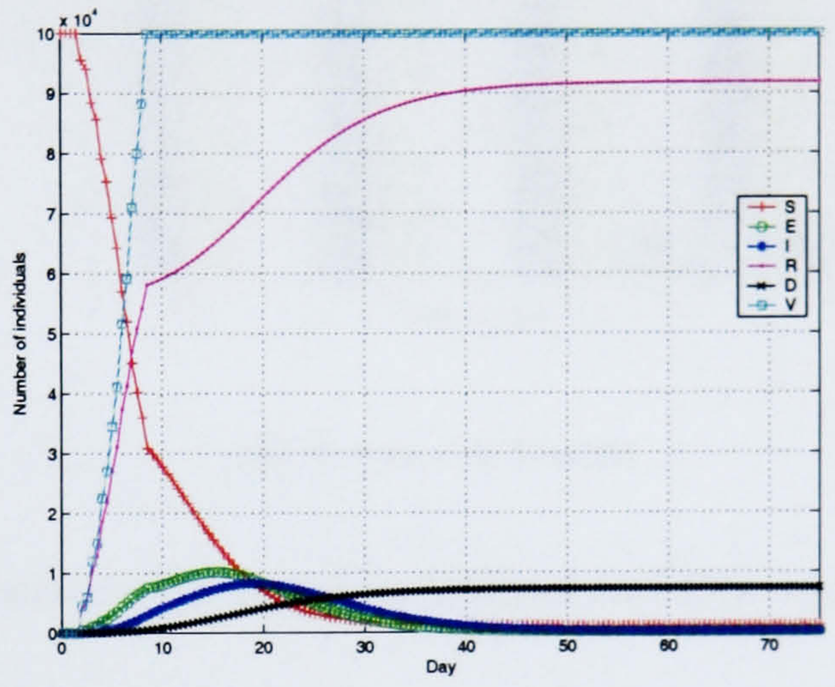


(d) proactive

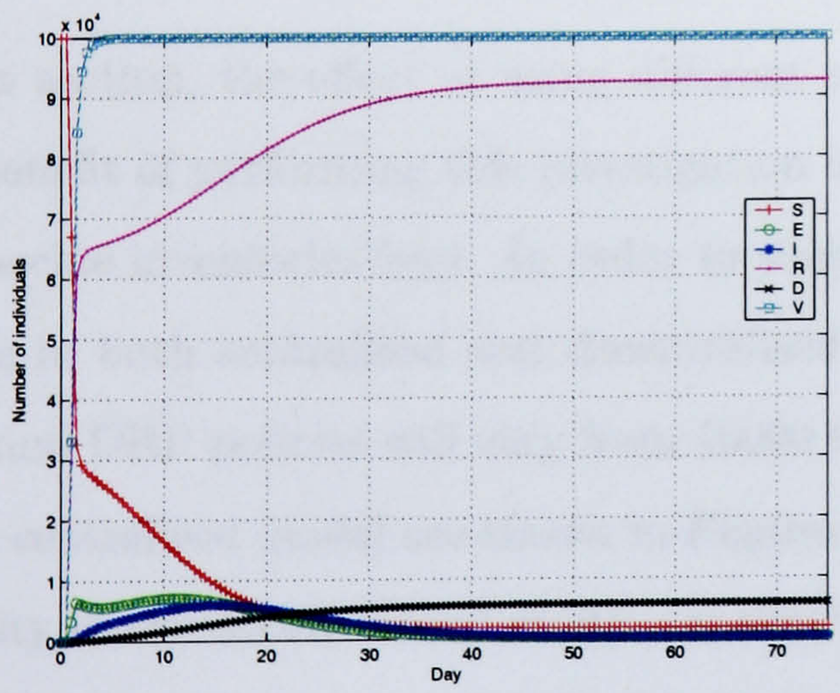
Figure 6.5: Effects of Reducing Number of Nodes of the Centralised Model



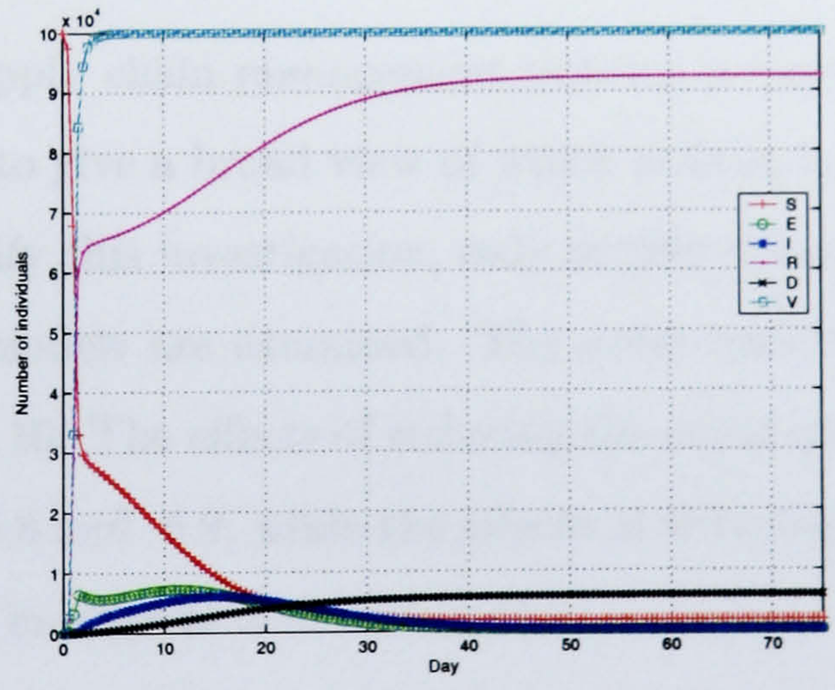
(a) 3-node



(b) 2-node

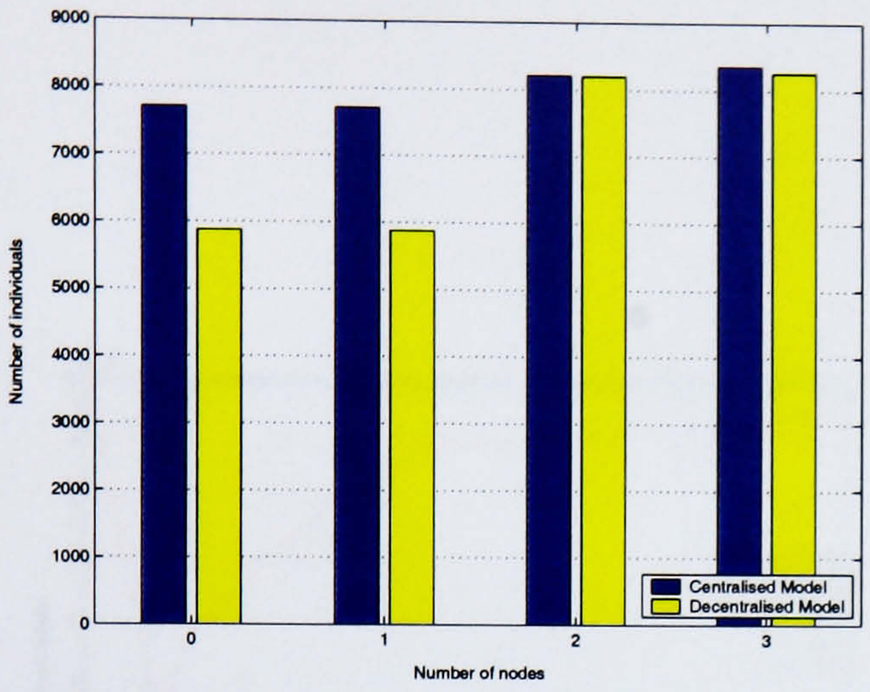


(c) 1-node

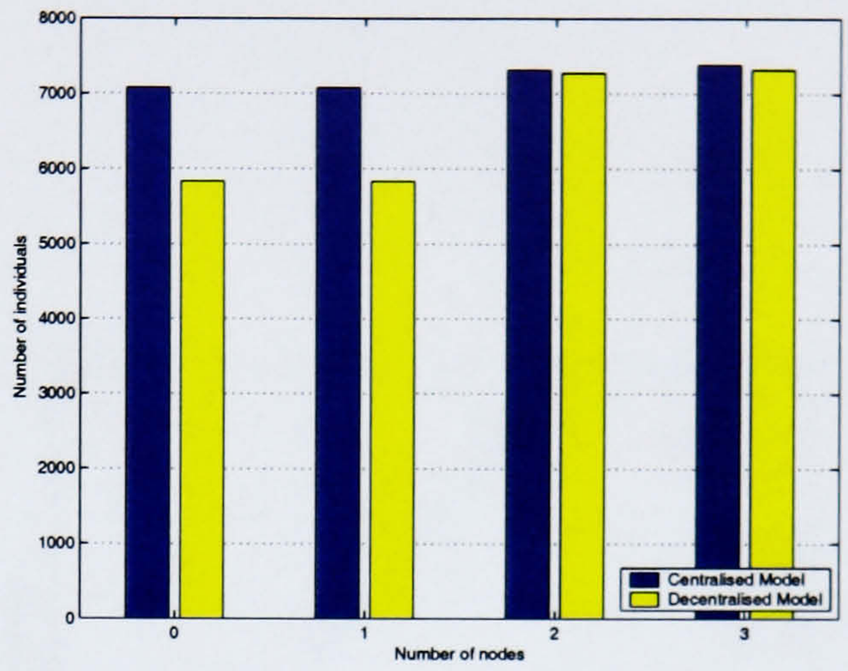


(d) proactive

Figure 6.6: Effects of Reducing Number of Nodes of the Decentralised Model



(a) Peak Infection Level



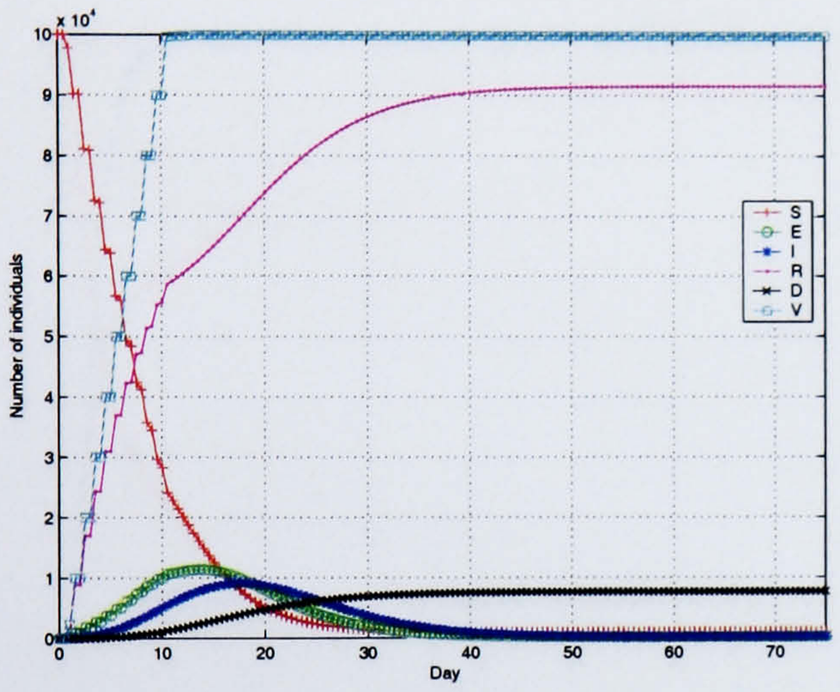
(b) Number of Deaths

Figure 6.7: Comparisons of the Performance Measures between Centralised and Decentralised Models

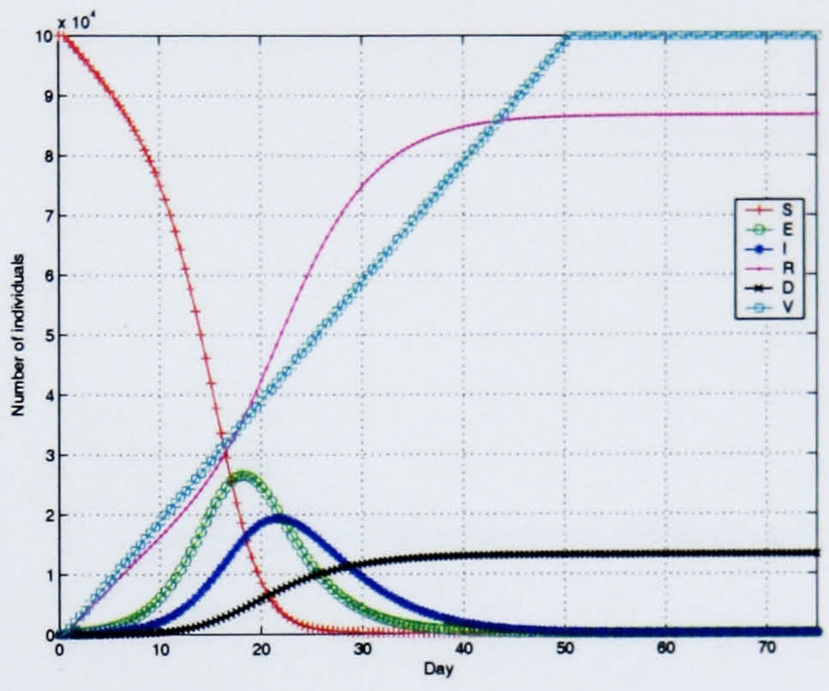
6.5.2 Effects of Using Different Supply Chain Management Policies

In this section, the effect of using different supply chain management policies is examined. The benefit of performing this investigation is to give a broad view of which policies manage the vaccine inventories best. In order to simplify this investigation, only supply chains with 1-node in both centralised and decentralised models are examined. The order quantity for ROP and DRP policies will vary from 10000 to 10. The effects of reducing the order quantity in the centralised model are shown in Figures 6.8 and 6.9, while the effects of reducing order quantity in the decentralised model are shown in Figures 6.10 and 6.11.

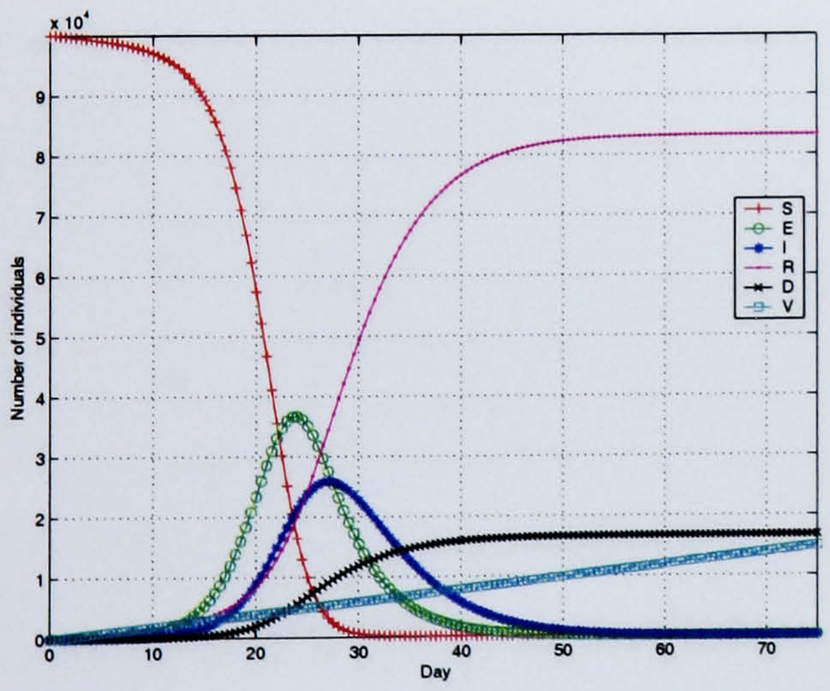
Although the exact peak infection level and the total number of deaths are not shown clearly, the differences in those performance measures are significant and are shown in Figure 6.12 and the exact numbers are listed in Table 6.6. In Figure 6.12, the ROQ lines in both centralised and decentralised models are below the DRP lines, indicating that ROQ is more reliable to use than DRP. Table 6.6 shows that the values of peak infection level and the number of deaths increase when the order quantity decreases.



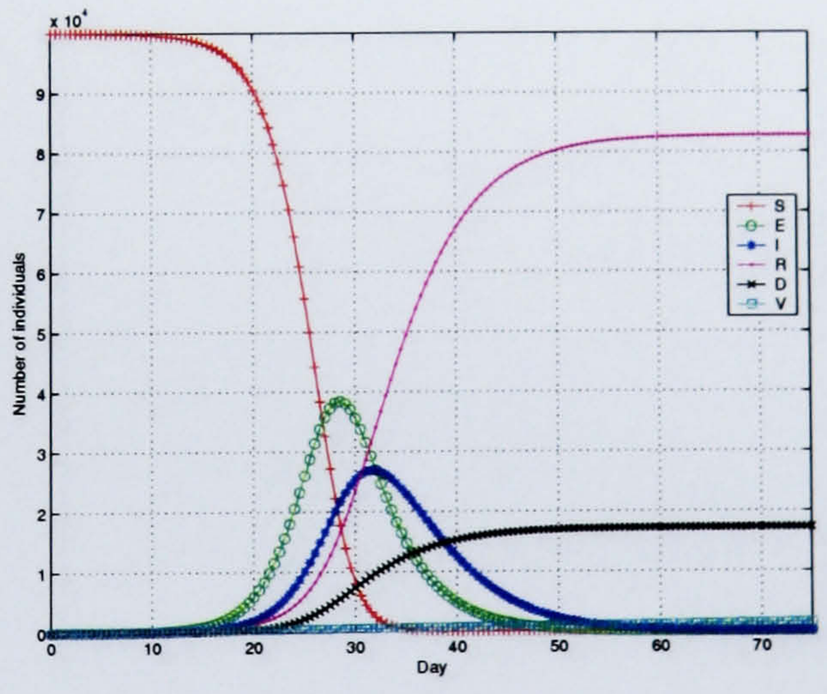
(a) ROQ = 10000



(b) ROQ = 1000

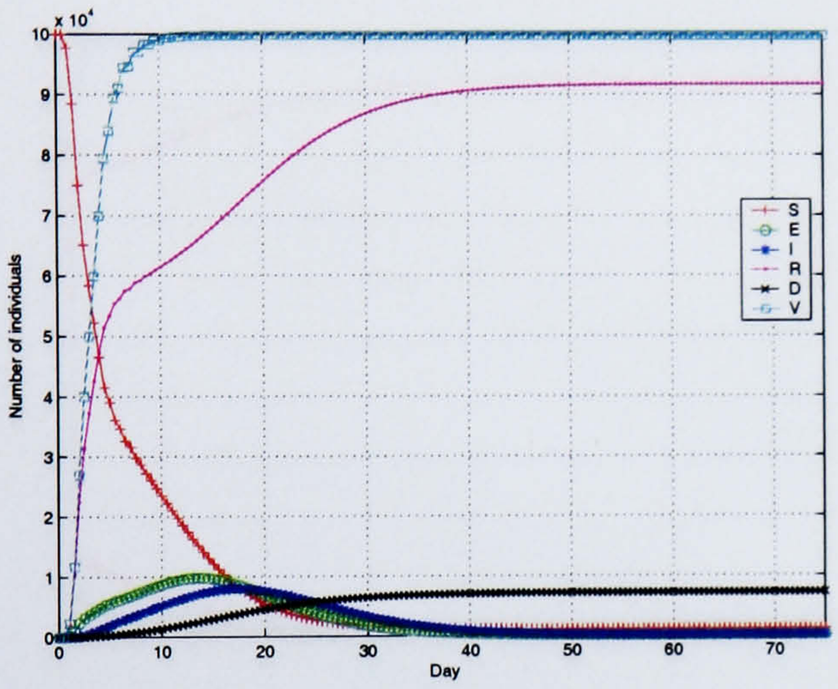


(c) ROQ = 100

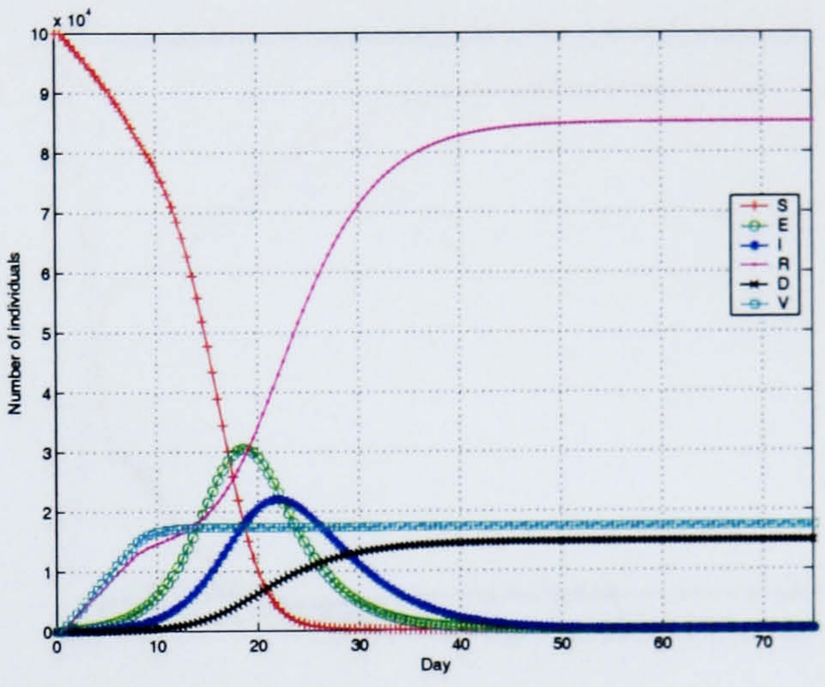


(d) ROQ = 10

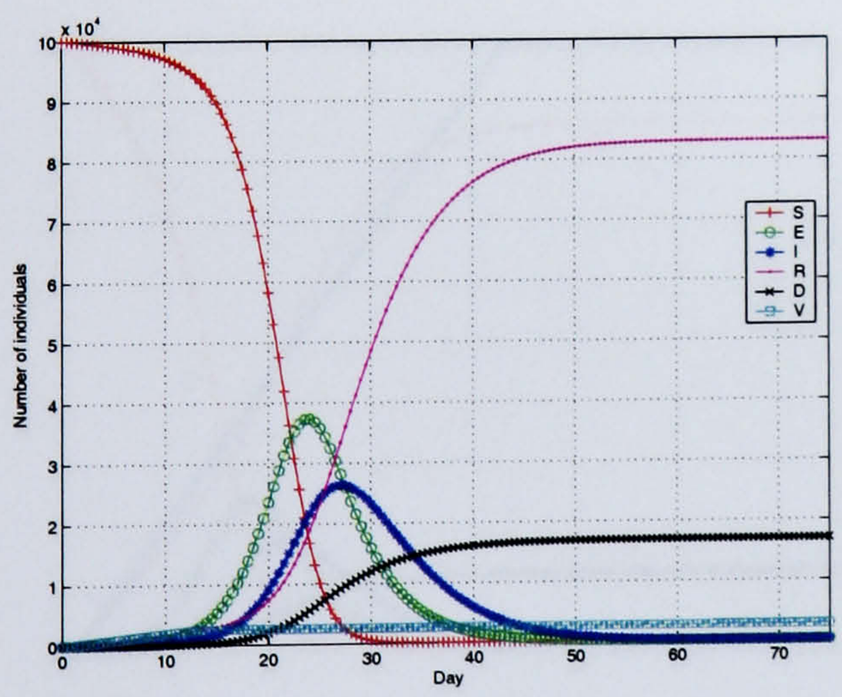
Figure 6.8: Centralised Model: ROQ



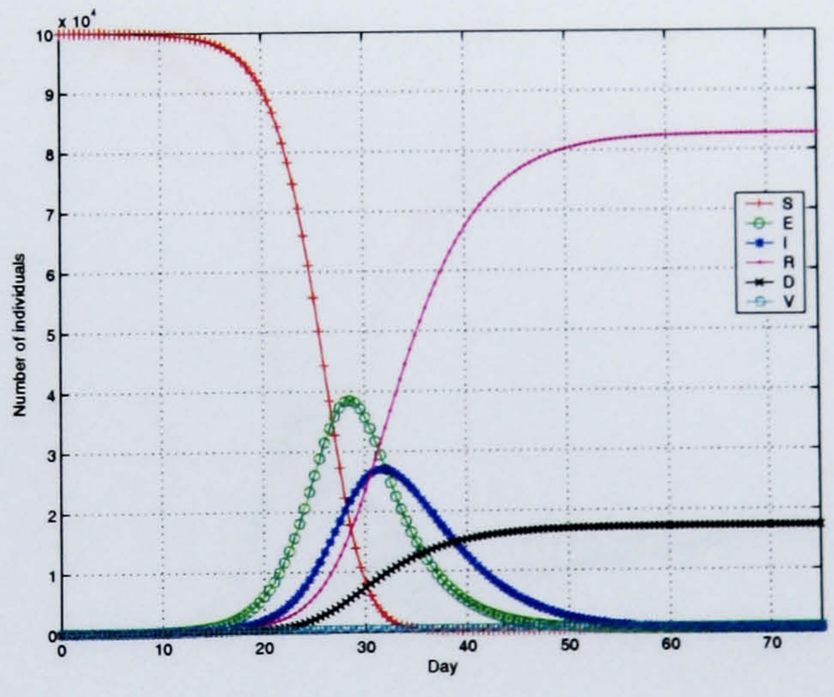
(a) DRP = 10000



(b) DRP = 1000

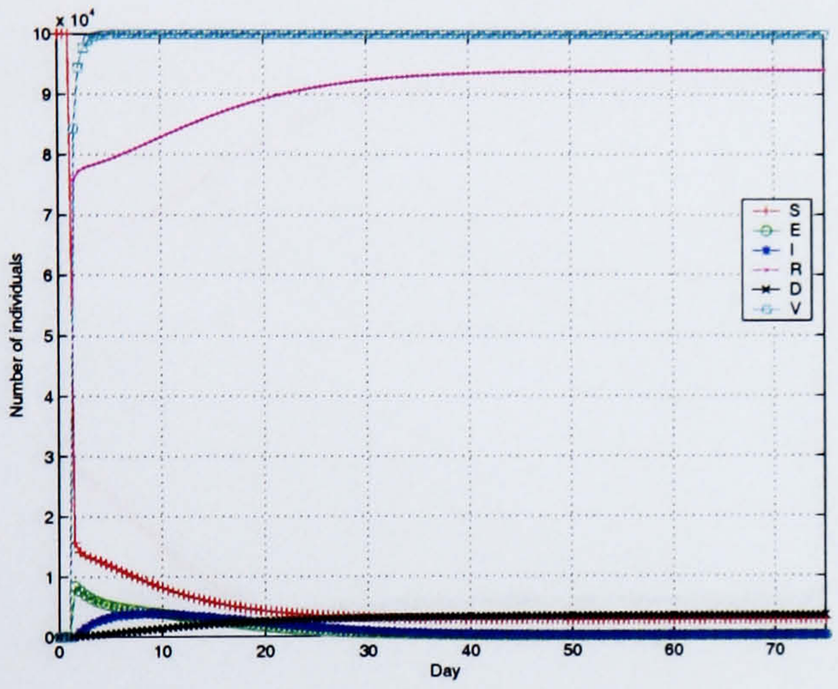


(c) DRP = 100

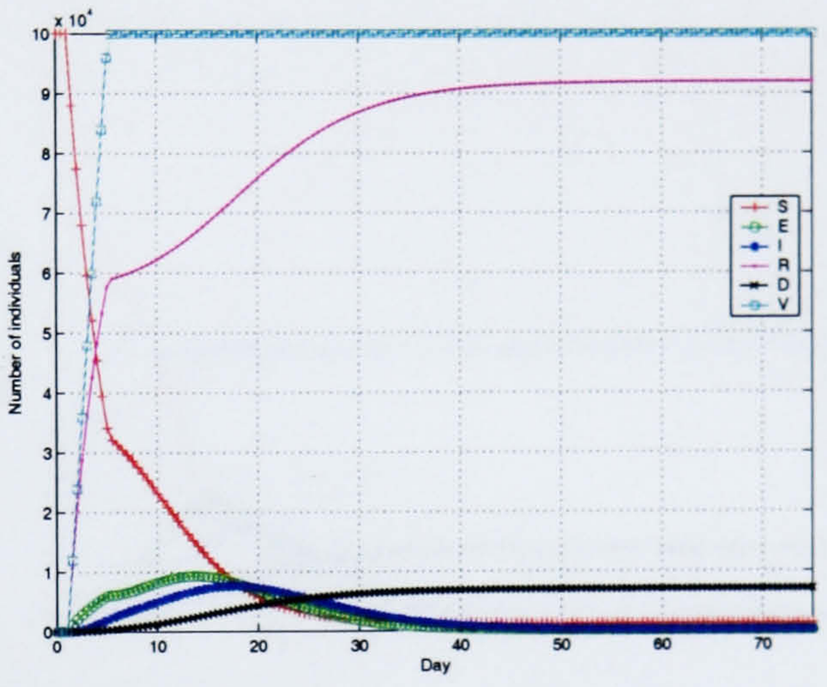


(d) DRP = 10

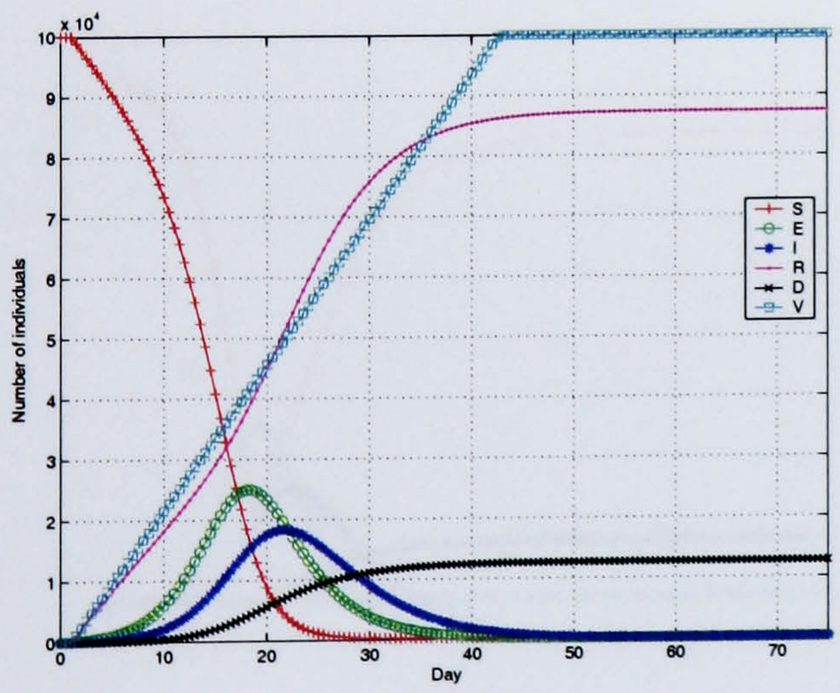
Figure 6.9: Centralised Model: DRP



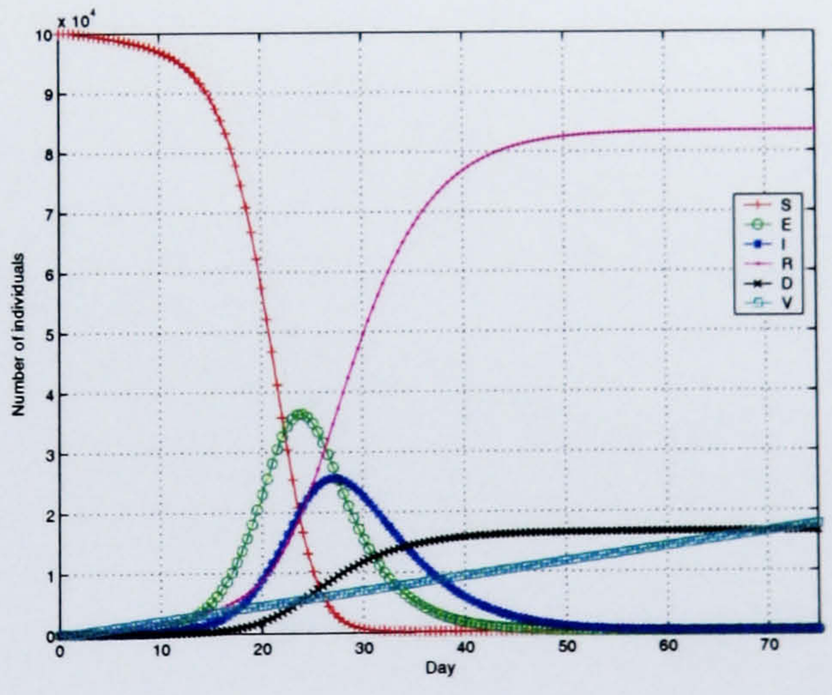
(a) ROQ = 10000



(b) ROQ = 1000

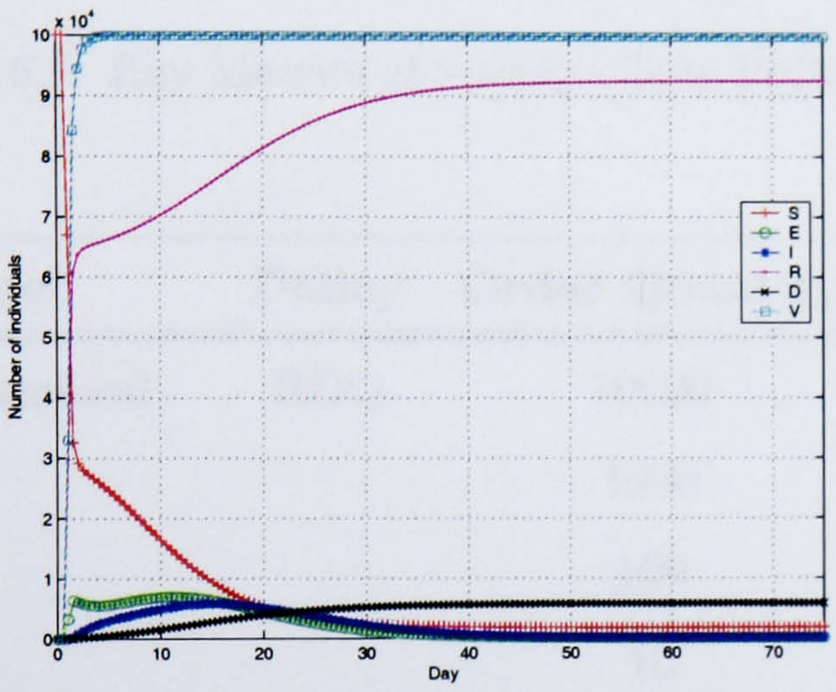


(c) ROQ = 100

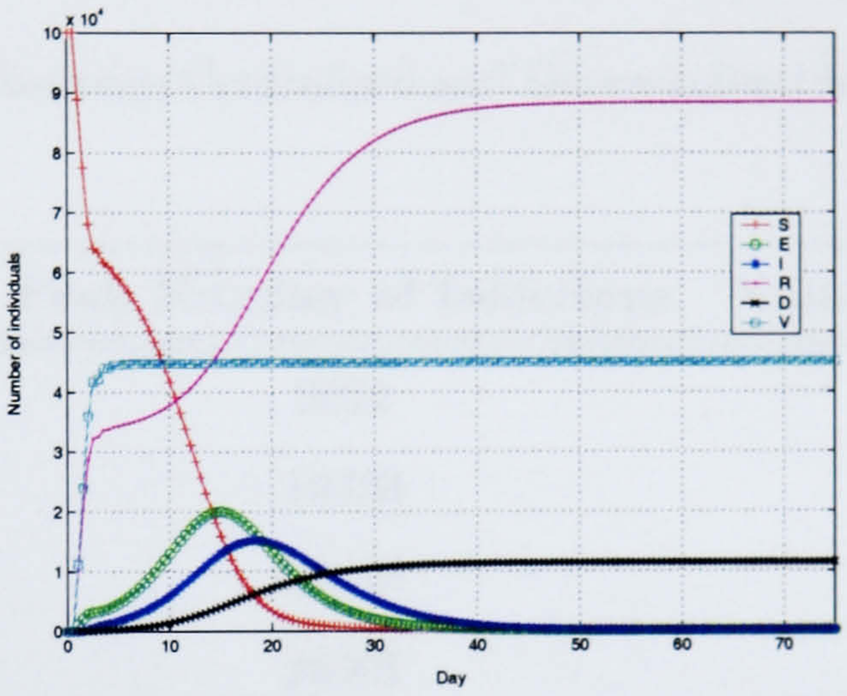


(d) ROQ = 10

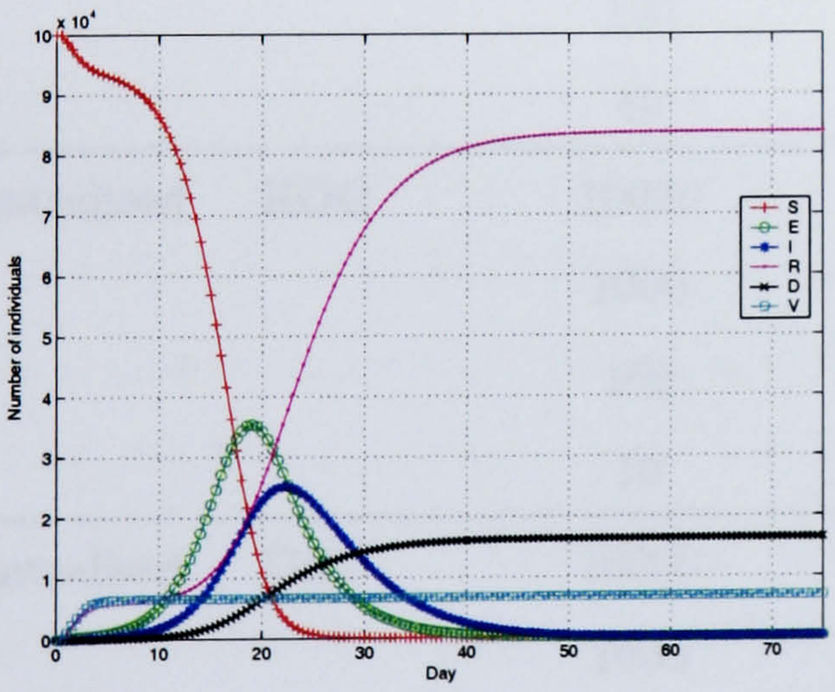
Figure 6.10: Decentralised Model: ROQ



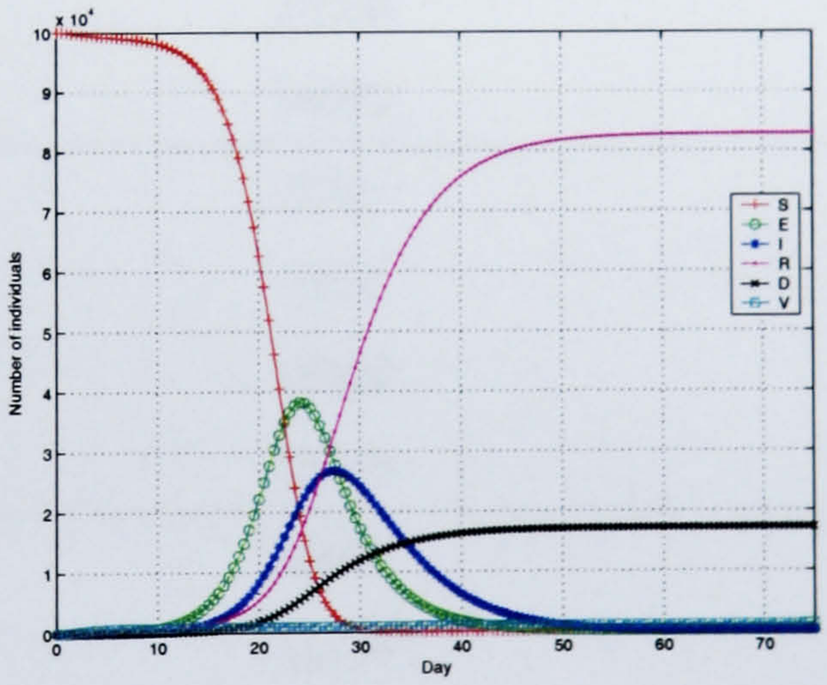
(a) DRP = 10000



(b) DRP = 1000



(c) DRP = 100

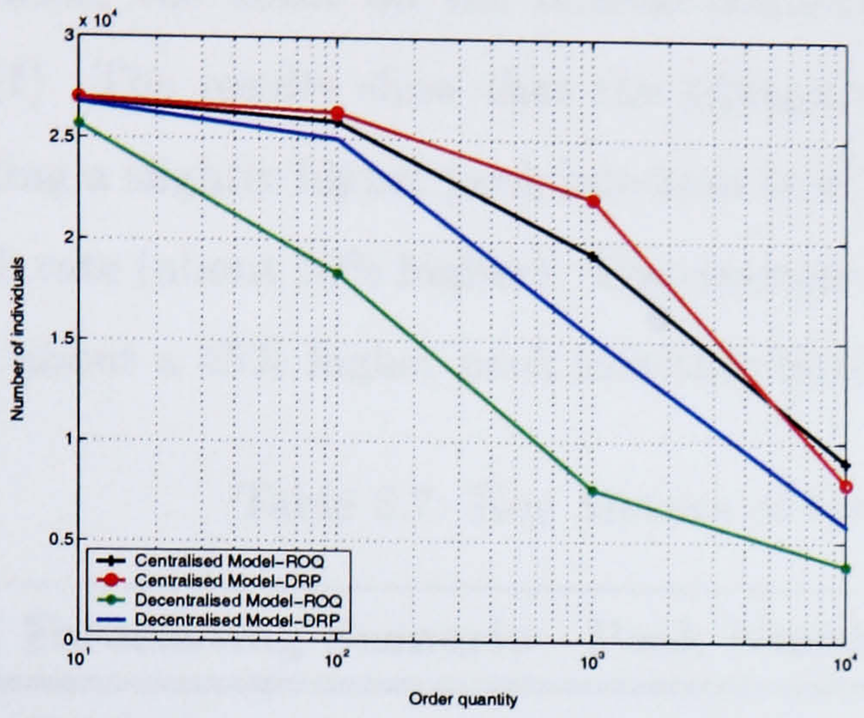


(d) DRP = 10

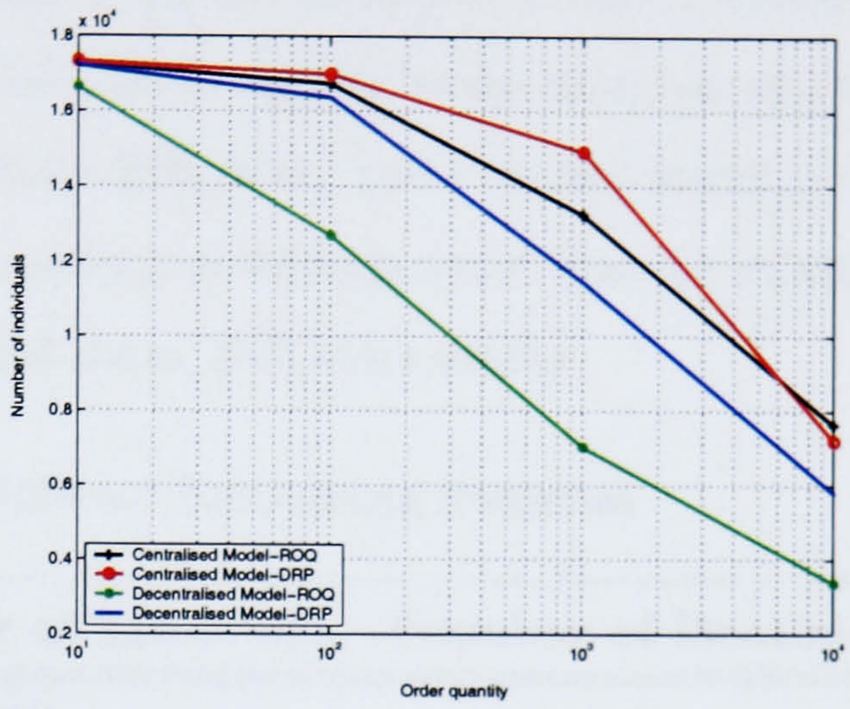
Figure 6.11: Decentralised Model: DRP

Table 6.6: Key Metrics of Supply Chain Policy between Centralised and Decentralised Models

Model	Policy	Order Quantity	Peak Number of Infections	Number of Deaths
Centralised	ROQ	10000	9022	7639
		1000	19333	13254
		100	25846	16730
		10	26901	17274
Centralised	DRP	10000	7901	7177
		1000	22050	14893
		100	26266	16962
		10	26942	17297
Decentralised	ROQ	10000	3795	3359
		1000	7581	7012
		100	18292	12668
		10	25639	16625
Decentralised	DRP	10000	5807	5778
		1000	15178	11435
		100	24991	16352
		10	26755	17201



(a) Peak Infection Level



(b) Number of Deaths

Figure 6.12: Comparisons of the Supply Chain Policies in the Centralised and Decentralised Models

6.5.3 Effects of Demand Forecast Error

Greater forecast errors for vaccine demand may increase the number of deaths in sudden outbreaks as they may result in sub-optimal supply strategies.

In this section, different scenarios are examined to compare different forecast errors and more importantly to test the responsiveness of the vaccine supply policy. In this study, only centralised supply chains with 1 node using a DRP policy are examined. The initial stock allocation is zero and the safety stock is two days' worth of demand forecast. The effect of forecast error is examined using three different types of forecasting strategy: Exact, Triangle, and Constant. In the exact case, the demand forecast is exactly equal to the demand, thus providing a best-case scenario. In the triangle and constant cases, the forecasted demand profiles are triangular and constant respectively, with the total forecast equal to the total demand. The exact, triangle and constant forecasts are shown in figures 6.13(a), 6.13(c) and 6.13(e), along with the actual demand. These subfigures also show the corresponding safety-stock level (two days' forecast), vaccine ordered from the supplier and the actual stock level predicted by the simulation. Given the performance of the supply chain in the three

scenarios, the effect on the disease transmission is shown in figures 6.13(b), 6.13(d) and 6.13(f). The results show that the triangular forecast is slightly worse than the exact one, yielding a slightly higher peak infection level (about 20% more) and a correspondingly higher death rate (about 10% higher). The constant forecast is noticeably worse than the triangular, with about a 45% higher peak infection level and about 25% more deaths.

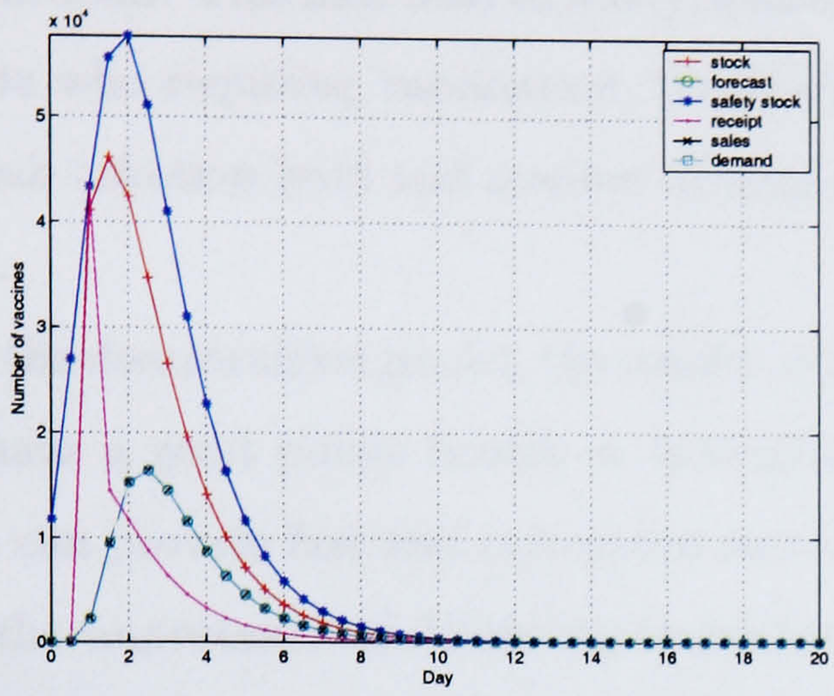
Table 6.7: Key Metrics of the Different Forecasting Scenarios

Forecasting Scenario	**Peak Number of Infections**	**Number of Deaths**
Original	7708	7075
Triangle	9210	7766
Constant	13322	9738

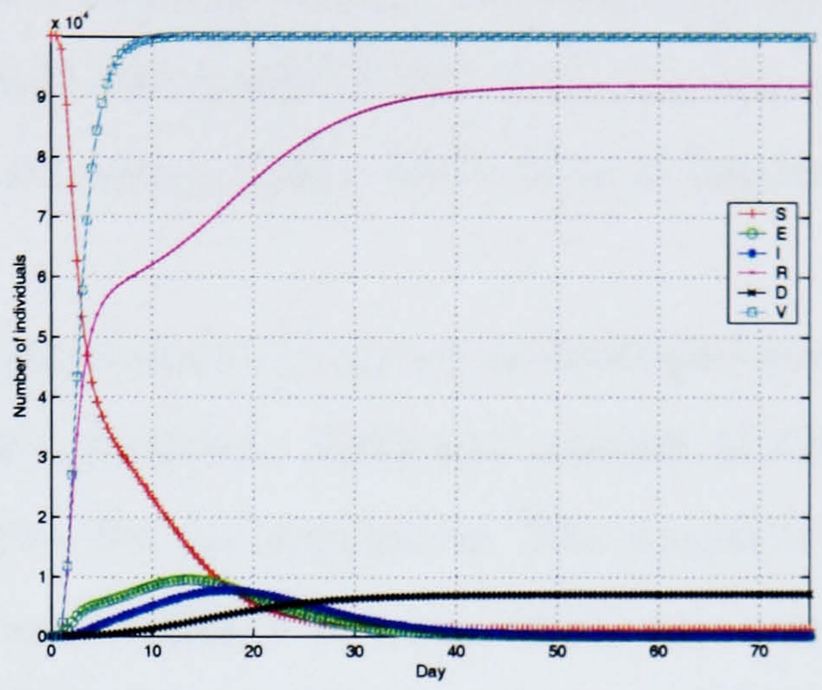
6.6 Discussion and Concluding Remarks

This work evaluates the impact of the vaccine supply chain on the control of the rate of infection of transmissive diseases, using a mathematical model. The model is generic, in that it can be applied to any disease with known infection rate γ and vaccine efficacy σ. It accounts for transitions between the various subpopulations as shown in Figure 6.1. In fact, this model extends the classical model for transmissive diseases, such as including the effects of different supply chain policies and structures.

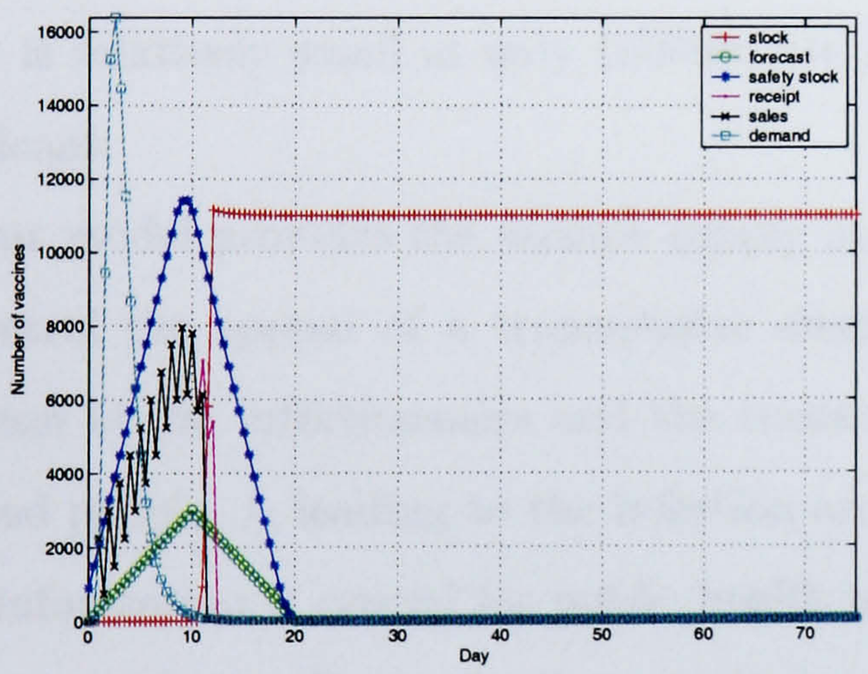
The centralised model developed is representative mainly of countries that do not have a good public health or immunisation program. Although the currently available models for transmissive diseases lack sufficient structural details of the vaccine supply chain, they consist of the main nodes in the realistic vaccine supply chain. In developing countries, insufficient numbers of GPs and clinics reduce the efficacy of a public health or immunisation program. People may receive vaccines only when a sudden outbreak occurs or foreign medical teams visit. Since developing countries may not have appropriately stocked clinics or any health stations, people may need to queue at the hospitals or the main health stations to receive



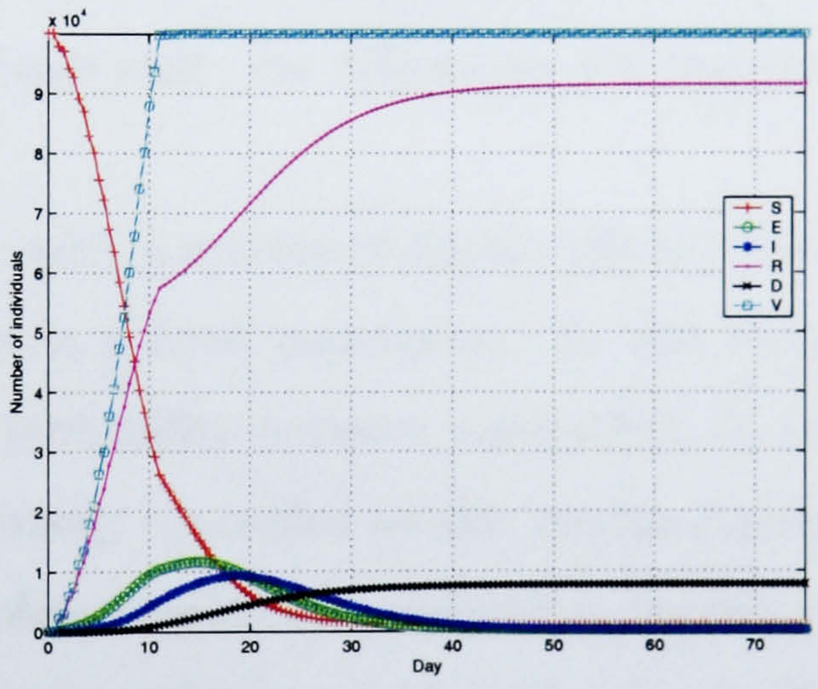
(a) Supply Chain Dynamics: Original



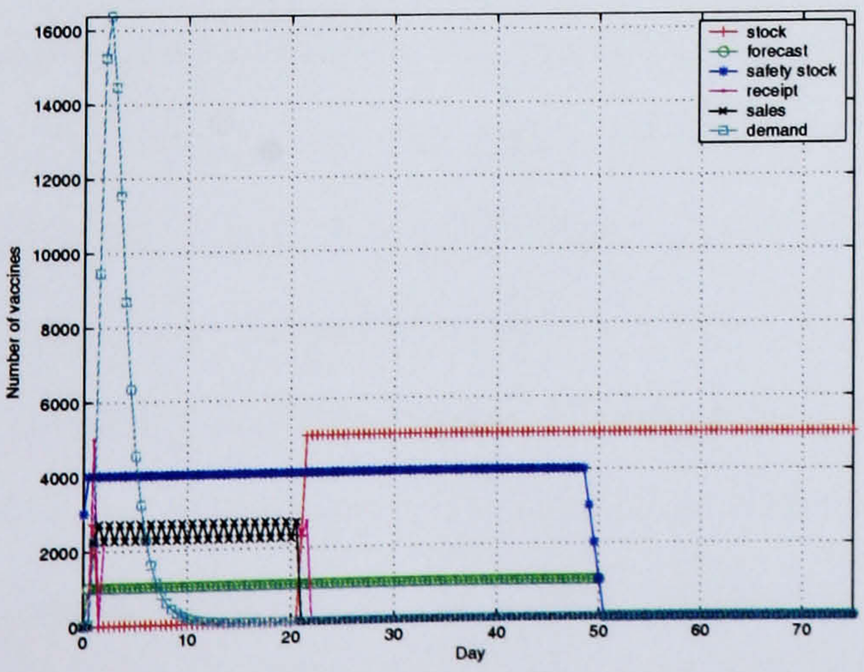
(b) SEIR Model: Original



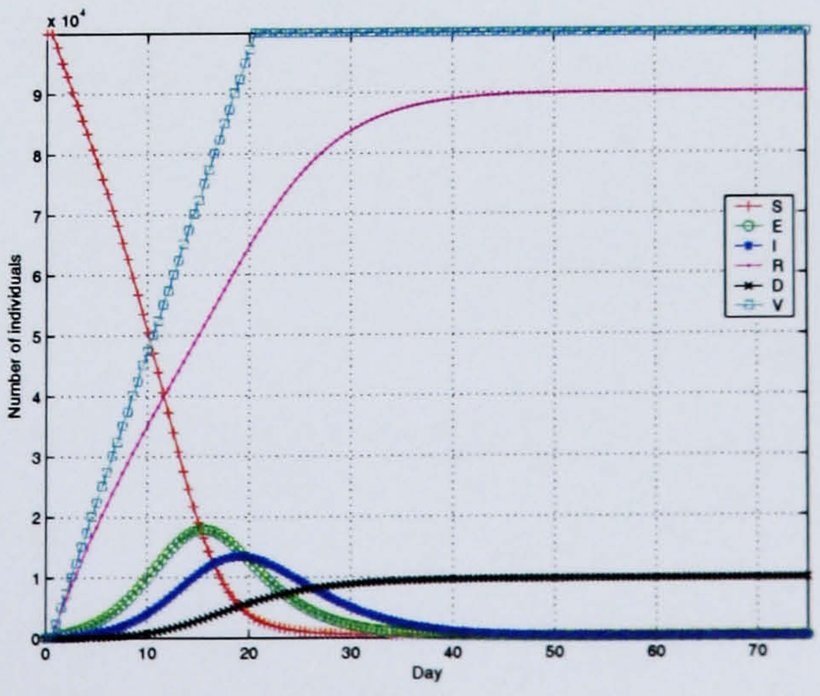
(c) Supply Chain Dynamics: Triangle



(d) SEIR Model: Triangle



(e) Supply Chain Dynamics: Constant



(f) SEIR Model: Constant

Figure 6.13: Forecasting Error

immunisation. This may lead to heavy demands or delays to delivery sufficient vaccines to the patients who requiring vaccination, therefore from the results obtained in previous section, the peak infection level and number of deaths are always higher than those in decentralised model.

In the decentralised model, the results resemble mainly the status in developed countries: they have a good public health or immunisation program. Sufficient number of GPs and clinics can provide fast and responsive vaccination for the population. The results obtained show the importance of delivering immediate and sufficient vaccine, which can reduce the peak infection level and the number of deaths. Although the differences in the peak infection level and the number of deaths between the centralised and decentralised model are not large, lives are the most important concern. It is also noted that the population size used in the study is relatively small at only 100000. On a large scale, the differences will become more significant.

Our model provides the vaccine supply rate, with a vaccine of known efficacy, necessary to control the spread of a transmissive disease in a fixed population. In this study, the duration of the infectiousness and the contact probability between susceptible, S, and the infected people, I, leading to the infection are mainly controlled by the vaccine supply rate. This information is crucial for public health implementation of transmissive diseases control measures with insufficient vaccine supply or with the aid of a vaccine with a lower efficacy.

Chapter 7

Conclusions

In this thesis, several optimisation and simulation techniques were applied to the vaccine supply chain problem. Vaccine supply chain problems are considered to be complex because most of the vaccine manufacturing plants involve many process tasks and lengthy quality control steps. In order to describe the structure of the vaccine production industry and its supply chain network, some key literature on supply chain management and supply chain modelling was reviewed. The techniques used in this thesis included supply-chain scheduling, capacity planning and supply-chain modelling, and the computational experiments were concerned with the impact of operating policies on the performance of the supply chain.

7.1 Contributions of This Thesis

The main contribution of this thesis is to give a thorough treatment of the detailed scheduling of the manufacturing processes, through to capacity planning and risk management, and finally to the effect of supply-chain performance and various supply strategies on the spread of an infectious disease through a population.

Scheduling was considered in Chapter 3, where an influenza vaccine production scheduling problem was described. Due to its complexity, it was solved using both heuristics and optimisation techniques. In order to improve the current operating strategy, modifications to cleaning tasks were suggested and debottlenecking was performed to reduce the utilisa-

tion rate of the most utilised equipment items. The approaches used were well suited to the influenza vaccine supply chain problem.

A capacity planning and design model under uncertainty was developed in Chapter 4 in order to enable analysis of multiple-vaccine supply chains over a long horizon. It successfully measured the relative value of the financial techniques using various performance metrics, more specifically to create models that can guarantee long-term profitability and sustainability for vaccine supply-chain systems and to find optimal inventory control policies and parameters so as to minimise costs and maximise fulfilment of customers' requirements. A stochastic analysis was also used to find the expected value of the Net Present Value (NPV) of vaccine production under various scenarios.

In Chapter 5, an extension to the capacity planning model using financial risk analysis was also developed. Many traditional risk measurements and decision-making methods were applied to the results obtained from the capacity planning model. Additionally, it presented some descriptive methods for decision making, and some concepts and basics of decision making using a payoff-table approach were demonstrated. Although the examples presented were rather simple, and actual decision making situations are more complicated, the methods were the ones most decision makers employ and they can be applied to more complicated problems.

Finally, in Chapter 6, a vaccination model was developed to provide an understanding of the relationship between the vaccine supply side and the population dynamics of infectious diseases. The work provided a new concept to account for the impact of the vaccine supply chain on the control of the rate of infection of transmissive diseases. Different supply-chain strategies were performed to compare the efficiency in terms of peak infection and death numbers. Moreover, approximated models were built to estimate the differences in supply-chain behaviour between the developed and developing countries.

7.2 Potential Directions for Future Work

The objective here is to provide a broad view to how a future vaccine supply chain can be modelled and analysed. There are a large number of possible generalisations and extensions

of this work.

7.2.1 Directions for Scheduling Research

Inventory Management

The potential area for further research in connection with the complex influenza vaccine manufacturing facility may be the investigation into inventory management. In Chapter 3, there was no provision made for external intermediate storage, so any delays between adjacent tasks must be accommodated by holding the material in the upstream process equipment item. However, in some cases, external storage is required for the intermediates if the subsequent equipment item is not yet ready to process the intermediates and the delays would adversely affect the production rate/efficiency.

Distribution Management

Another potential area for future work can be to focus on the distribution management. Since the influenza vaccine manufacturing facility produces vaccines for most of the countries in the world, distribution and logistics management is an important aspect to examine. Since oil and petrol prices increase every year, an efficient distribution and transportation strategy can significantly reduce cost.

7.2.2 Directions for Capacity Planning Research

Model Aggregation

Model aggregation is a relatively new term in the statistical literature and it is generically used to describe any procedure that combines a family of concurrent estimators of a given parameter. In a sense, model aggregation is also equivalent to linear interpolation of models, where the interpolation is performed using equal weights. Thus, any situation where models are interpolated can be viewed as a form of aggregation.

Aggregation remains attractive because of its simplicity. It is useful to reduce the number of equations and constraints, hence the computational processing time is significantly reduced.

Of course, the value of the model must not be diminished too far due to the aggregation.

Production Formulations

Consider the production constraints in Chapter 4, the changeover equation was assumed to provide an estimated value of the amount of time for all products being produced. In the model, the estimated value maybe bigger than that in the real case.

Equation 4.8 gives the correct bound on T_{ptk} when $P_{tk} \geq A_{tk}$ but if $P_{tk} > A_{tk}$ the second term on the right hand side of equation 4.8 changes sign and causes T_{ptk} to be greater than the available time $H_t A_{tk}(1 - L^{sq})$. To remedy this, we need to introduce a new variable, R_{tk}, that is equal to $\tau(P_{tk} - A_{tk})$ when $P_{tk} \geq A_{tk}$ and equal to zero otherwise. This is shown matematically in equations 7.2 to 7.4.

$$\sum_p T_{ptk} \leq H_t A_{tk}(1 - L^{sq}) - \tau(P_{tk} - A_{tk}) \qquad \forall t \in T_2, k \tag{7.1}$$

$$\sum_p T_{ptk} \leq H_t A_{tk}(1 - L^{sq}) - R_{tk} \qquad \forall t \in T_2, k \tag{7.2}$$

$$R_{tk} \geq \tau(P_{tk} - A_{tk}) \qquad \forall t \in T_2, k \tag{7.3}$$

$$R_{tk} \geq 0 \qquad \forall t \in T_2, k \tag{7.4}$$

Multi-site Capacity Planning

The capacity planning model proposed in the thesis was for a single-site, it is possible to extend it to a multi-site problem if it takes into account transportation between the sites. Multi-site capacity planning can also consider the sharing of available suites in other sites rather than investing a new suite in the current site. Also the effect of different tax and duty regimes could be indicated.

Multi-Attribute Decision-Making

Since there are many different types of decision-making analyses, it is often the case that the best decision to take depends on the risk metric employed. Therefore, a scoring approach is suggested in order to provide a better understanding for the decision makers: i.e. they would provide a range of scores for each metric based on its importance to their business, and would take a decision based on the sum of the metrics weighted by the scores.

7.2.3 Directions for Disease Control and Supply Chain Modelling Research

In order to make the transmissive disease model more realistic, different occurrences of transmissive diseases to a localised population can be considered.

In terms of the SEIR model, potential improvements can be made by adding a recirculation of subpopulation R back to subpopulation S. In practice, even when the population was recovered, a new transmissive disease may arise, thus shifting the subpopulation R back to subpopulation S. The diseases will continue to exist, and the public health or immunisation program can never finish. The SEIR model should capture the circulation by the addition of the following terms in existing formulae, where ω is the rate at which immunity to the infection is lost:

$$S_{t+1} = S_t - \beta S_t I_t - \xi_t S_t + \omega R_t \tag{7.5}$$

$$R_{t+1} = R_t + \alpha I_t + \sigma \xi_t S_t - \omega R_t \tag{7.6}$$

However, the limitation of this model of transmission dynamics of disease infection is that the contact probability between the population who are infected and the susceptible population is often difficult to predict, i.e. it is difficult to determine the value of β.

If a concurrent outbreak occurs due to two or more viruses, the SEIR model dynamics may not predict the infection rates correctly, as people infected with one disease may be more susceptible to the other(s). One direction for future work might be to look at extending the SEIR model to account for simultaneous outbreaks.

Different levels of supply chain performance have been used in this thesis when measuring the peak number of infected people and the number of deaths during an outbreak. It would be interesting to see if direct relationships can be obtained between the supply-chain performance metrics and the infection levels. By studying several types of disease, it may be possible to categorise them according to what level of supply-chain performance is required for a certain level of control of the disease. Thus, the correct immunisation strategies may be determined without direct simulation of the particular vaccine/disease combination.

In Chapter 6, only ROQ and DRP inventory control policies were applied to the SEIR model. However, there are many other supply chain replenishment control policies that can be applied, such as Basic Stock Control (BSC), Line Requirements Planning (LRP). Vendor Managed Inventory (VMI) and Just-In-Time (JIT). Different types of policy affect greatly affect the supply-chain performance, therefore affecting the rate of disease transmission and ultimately the death levels.

In the current model, we assumed all people need to be vaccinated, however, to obtain a more accurate result, the model can be improved by accounting for the exposed, infectious and dead populations.

7.2.4 Integrating Scheduling and SEIR model

The work in this thesis considered a number of relevant problems, but in isolation. Future work might seek to combine these into a single problem, linking the scheduling and SEIR models together. One approach might be to generate the vaccine output volumes from the scheduling results and use these as the supply level to the SEIR model in order to identify the effects of any delay in supply or any extra demands in the SEIR model.

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