A structured review of quantitative models in the blood supply chain: a taxonomic framework for decision-making

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This paper presents a structured review of the literature on quantitative modelling for the blood product supply chain. This is a widely researched topic, dating back to the 1960s, and several other reviews have been published over the years. However, this paper presents new relevant information for researchers, not only by including more recent models but chiefly because of the structured way in which the models are presented. The models are broken down into five categories. The first four categories represent the four stages (echelons) in the supply chain: collection, production, inventory and delivery. The final category contains ‘integrated’ models which cover more than one stage. Each section (other than integrated models, which are treated slightly differently) contains two distinct elements. The first element is a diagrammatic representation of decisions and relationships, broken down by hierarchy level (strategic – tactical – operational). The second element is a text description of the main features, contributions and gaps found in the analysed models. An additional element for each section is available online, namely a searchable table describing specific features of each echelon, together with a taxonomic key to assist the reader.

Keywords: blood supply chain; taxonomic framework; quantitative models; perishable inventory; blood collection; blood transfusion

1. Introduction

1.1 The blood supply chain

The blood supply chain comprises the processes of collecting, testing, processing and distributing blood and blood products, from donor to recipient. Blood products are transfused to patients as part of routine medical treatments or surgical operations and also in emergency situations. This means that availability of the right blood products is critical, since lives can be lost if no stock is available when it is needed. At the same time, blood is collected from human beings and the blood donation rate varies across different countries. According to the American Red Cross (2014) in the US, only 10% of all eligible people actually donate blood, and the World Health Organisation states that the figures for middle- and low-income countries are considerably lower (WHO 2014). This all means that decision-making for the blood supply chain is challenging, given the increasing demand for blood products as well as the decreasing population of donors (Seifried et al. 2011). Another important factor is cost; although blood itself is donated voluntarily in developed countries, many costs are incurred along the way, such as labour, testing, fractionation (separating whole blood into sub-products, of which there is potentially a vast range), storage and distribution. In general, an efficient blood supply chain should meet demand while at the same time reducing wastage and minimising costs. However, the limited shelf life of most blood products imposes strict constraints on this highly complex supply chain, which considerably increase the risks of shortages and outdating. Given the relevance, features and complexity of the system, it is necessary to develop robust methodologies to support the decision-making process at all stages of the blood supply chain.

The real world importance of the blood supply chain is self-evident, since human lives are at stake. The complexity of the supply chain is perhaps less obvious. According to Katsaliaki and Brailsford (2007), more than a hundred different products can be derived from blood, including products and sub-products, but red blood cells (RBC), plasma, platelets and cryoprecipitate are considered to be the most important. RBC represent 63.4% of the total transfused products, followed by plasma at 17.8%, platelets at 13.6% and finally cryoprecipitate at 5% (DHHS 2013). Moreover, these products can be processed to obtain sub-products such as irradiated or washed products for special treatments or as raw material for other products such as recombinant products.
Components are used in different situations: for instance, RBC are required in anaemia treatments, while platelets are required for cancer patients and plasma is required to treat patients with burns. This list represents one single example of the use of each component; however, each component can have many uses in distinct processes in health care. On the other hand, collecting blood requires a constant effort; in countries where donation is voluntary, many factors such as comfort, risks, convenience and accessibility can affect the decision to donate. However, obviously, in order to meet demand, enough blood must be collected. Matching supply with demand, in supply chain terminology, requires developing an infrastructure for collecting, processing and distributing blood and its products. Different configurations of the blood supply chain can be found both in the real world and in the literature, from internal blood banks in hospitals to multiple collection and processing and distribution centres supplying several demand points. The strategy followed can vary according with health care policies in different countries. However, the goal remains the same, that is satisfying demand for blood products at minimal cost and with minimal wastage.

In addition, special features of blood and blood products must be taken into account. Factors such as blood types, compatibilities and different shelf lives of blood products add complexity to blood supply chain systems and the decision-making process. There are eight main blood groups (A, B, AB and O, each of which can be rhesus positive or negative), and each group has a different proportion in the population. The proportions vary between ethnicities and geographical regions; for instance, in the UK, the proportions of type O positive and AB negative are 37 and 1%, respectively (Katsaliaki and Brailsford 2007), while in Colombia, the same blood types represent 56 and 0.3%, respectively (Beltrán, Ayala, and Jara 1999). Because there are some very rare blood types, very often the use of substitute products is required. However, there are specific restrictions and preferences in using them. Moreover, the shelf life of blood products is another important factor to be considered; platelets, RBC, plasma and cryoprecipitate have different shelf lives. Platelets are the most critical component with a shelf life of just 5 days, followed by RBC with 42 days and finally plasma and cryoprecipitate with one year. This means that if a blood product has not been transfused before the end of its shelf life, it must be discarded. Finally, it is important to note that blood products are not produced independently. There are different primary fractionation alternatives that generate from one to four products, as well as different methods of collection.

1.2 Previous reviews, overviews and frameworks

The blood supply chain has motivated researchers since 1960. Indeed, research in this field has contributed greatly to the development of effective methods for the management of perishable inventory (Nahmias 1982). A significant part of the related literature was developed in the 1970s and 1980s. Several reviews have been published covering distinct aspects of the blood supply chain. The first framework to classify the whole blood inventory problem is presented in Jennings (1973). This early work presents the problem by hierarchy level (strategic – tactical – operational) and shows the impact of the application of different blood inventory policies. Pierskalla et al. (1980) provide a detailed analysis of configurations of the blood supply chain in the US. This article also describes the functions and authority degree of each level. In a paper published in the same year, Page (1980b) reviews the computer software available at that time for supporting blood bank processes. This covers factors including origin, capacity, functionality, state of development and cost.

Some review articles focus on specific blood products. Blake (2010) presents an important overview and problem description of inventory of platelet concentrates. He introduces the problem from the point of view of producers and consumers, and then review the literature, ending with a short discussion of solution strategies. On the other hand, Stanger et al. (2012) describe the best practices in RBC inventory management. This article discusses the main models in the literature on this specific topic and presents the results of a study undertaken in the UK. An important finding is that good practices are related more with good training, electronic crossmatching and simple decision rules, rather than some of the complex algorithms proposed in the literature.

Nahmias (1982) provides a complete overview of the theoretical models in perishable inventory at that time. The models presented in this article are applicable to different types of perishable inventory; however, several examples are explicitly applied to blood stocks. The models are presented according to features such as type of demand, type of lifetime and queuing modelling approaches. Nahmias (2011) presents an updated review of this subject. This book also contains a specific chapter discussing the different models and approaches applied to the blood inventories problem. Prastacos (1984) presents a review discussing the main contributions from Operational Research to the blood supply chain. The model includes a general overview of the different stages and the kind of decisions in each of them. This review takes a similar approach to Nahmias (2011), although the number of papers and the model features presented in each article are not comparable.
In the last decade, Pierskalla (2005) and Lowalekar and Ravichandran (2014) published articles analysing the whole supply chain, describing advances and opportunities for further research. Pierskalla, one of the great pioneers in this field, provides a broad analysis including different network configurations, location, and allocation and distribution decisions as well as areas for further research such as donor scheduling, production planning and distribution. Lowalekar and Ravichandran (2014) present a complete overview of the state of the art of blood banks in India. In their paper, the literature is classified according to type of decisions in the blood supply chain. However, their classification is fairly general, compared with the present review where several distinct features are identified in each stage.

Finally, Beliën and Forcé (2012) published a literature review of the blood supply chain, which covers papers published up to 2010. Beliën and Forcé cover very diverse aspects of the topic, not just quantitative models, and classify models in eight general categories without detail about specific features of the supply chain. There are significant differences between the Beliën and Forcé paper and this review, in addition to including papers published up to 2014. This review has a different focus; we only consider quantitative models, and we present the main features of each model according to the relevant supply chain echelon. This means, for example, that in the collection stage, 14 distinct features of collection processes are included. There are similar numbers of different features in the production, inventory management and distribution echelons.

1.3 Paper selection process
The selection criteria for this review fall into two main categories. Firstly, we include papers that consider quantitative models for any stage of the blood supply chain. Secondly, papers from other knowledge areas such as perishable inventory and multi-type production with explicit application to the blood supply chain are also included. The search process included research articles, executive reports, proceedings, thesis and reports that meet any of the two points mentioned previously, published between 1963 and September 2014.

2. Review
In order to help the reader and present the information in a structured way, the literature and analysis of the blood supply chain will be presented according to the main echelons of the blood supply chain depicted in Figure 1. In reality, the system is not as linear as this. It is a highly complex process, since blood is transported not only between blood centres and hospitals but also between blood centres, in countries where there are regional or even national systems. Generally, however, after the production stage blood products are transported from a blood centre directly to the hospitals it serves, based on each hospital’s request for replenishment, and are then stored in the hospital’s blood bank as ‘unassigned inventory’ until needed for a named patient. In order to assign blood units to a donor, different procedures to check compatibility can be used. On the one hand, electronic crossmatching, also known as type and screen (T&S) procedures, consist of computer-aided checking. In this case, there is no ‘assigned inventory’ for a specific patient. On the other hand, crossmatching is the process of checking that the recipient’s blood is compatible with the donated blood: this is more complex than merely matching the ABO Rh groups. The blood is then assigned to that patient and becomes ‘assigned inventory’. Frequently, more blood is crossmatched than is actually required, since many doctors prefer to err on the side of caution. The application of these policies depends on several factors such as antibodies found in the patient’s blood, probability of transfusion and internal policies of the institutions. In terms of safety, according to Georgsen and Kristensen (1998) and Chow (1999), T&S is comparable to crossmatching procedures. However, the most important effect of electronic crossmatching is in the performance of the blood bank. Blood units are always ‘at hand’ inventory and can be used to transfuse other patients. This decreases the probability of expiration of a unit and helps blood managers to control inventories better, as well as decreasing stock out probabilities. Using crossmatching, unused blood can be returned to the hospital blood bank, although not normally to the distribution centre. Different countries have different returns policies, and these may also vary by blood group. An additional complication is mismatching, where patients can be transfused blood of a different type to their own: this can be done in emergency situations or to improve inventory planning in small institutions where the rarer blood types are less frequently required. Again, there

![Figure 1. Echelons of the blood supply chain.](image-url)
are many different policies for this. Thus ‘Distribution’ occurs at least twice: it covers transportation of processed products from blood centres to hospital blood banks (or indeed other blood centres), as well as from the hospital blood bank to the operating room, care unit or ward where the recipient is located. Similarly, ‘Inventory’ covers storage at blood centres and also within hospital blood banks, both assigned and unassigned. We have used the simplistic framework in Figure 1 as a helpful means for categorising the models, but in practice, the third and fourth stages are intertwined. This of course greatly adds to the complexity of the blood supply chain in the real world and the challenges of modelling it.

2.1 Collection

The collection stage comprises the processes of procurement of blood and blood products. This is the first echelon of the blood supply chain, and its purpose is to obtain the quantity of blood and blood products required to meet demand. Decisions in this stage are mainly related to the management of blood collection: location and capacity decisions, collection methods and donor management. Figure 2 presents a schematic representation of the decisions in this stage. Decisions at the top of the figure are strategic, with tactical decisions in the middle and operational decisions at the bottom. Relationships between decisions are represented by blue arrows. The flow depicted in the bottom of the figure is the general process in the collection stage; this flow is represented by red arrows and the inputs/outputs are represented by grey boxes. Typically, blood is collected at donor centres, which can be at either fixed or mobile locations, and is then transported back to a processing and testing facility (a ‘blood centre’) and is stored there awaiting onward distribution. In most cases, whole blood is collected from donors, but occasionally a process called aphaeresis is used. Here, the donor’s blood is passed through a machine which extracts the required component (e.g. plasma, platelets or RBC) and then returns the blood to the donor. Other collection decisions include the type of bag to be used. This decision is made at the moment of collection and has several impacts in the production process. Different types of bag sets can be used, from one single bag up to quadruple bag sets. The type of bag set to be used depends on what products are required to be produced from one unit. Fractionation processes use centrifugal forces to separate the different components, and this is done in different stages where each product is extracted in ‘satellite’ bags. For instance, a triple set is used to obtain one unit of RBC and one unit of plasma, but a quadruple set can be used to obtain one unit of RBC, one unit of plasma and one unit of platelets, or one unit of RBC and one unit of cryoprecipitate.

Figure 2. Decisions by hierarchy level in the collection stage.
Figure 2 depicts decisions and relationships in the collection stage. At the highest (strategic) level, decisions such as location, capacity definition and staff definition reflect the long-term strategy of the organisation. These decisions are characterised by their importance and because they will affect other lower level decisions. Tactical level decisions are aimed at middle-term planning. At this level, decisions such as definition of policies, planning of collection campaigns and allocation of staff and collection points can be found. Finally, operational level refers to decisions that must be made daily or even in shorter time periods. This level comprises decisions such as scheduling, decisions on collection methods according to each donor and routes of collection. This classification presents a general idea, however depending on the specific blood supply chain decisions can be classified in a different way.

Several different modelling approaches can be found to support decisions in the collection echelon. The problems studied include, for example, donor arrival estimation, planning for emergencies, donor motivation and behaviour, different collection strategies and capacity planning.

Prediction and classification of donor arrivals improve the collection process. One of the very earliest studies in the collection stage is presented by Cumming et al. (1976). A forecasting model is developed to improve blood collection plans and eliminate shortage and overstocking. The model includes transfusion and issuing sub-models, taking into account preferences in the use of the blood as well as differences in the use of the blood during a period of time of seven days. However, this model has several aspects that make it less applicable in procurement situations, since the main issuing policy used is first-in-first-out (FIFO) and the weights or probabilities of use of the blood vary according to the time of the year. On the other hand, Melnyk et al. (1995) present a classification of donors based on survival analysis. This classification is used to track and measure all the activities in the collection process. The aim of this study was to improve the layout of the collection facilities and increase the satisfaction of donors, which is very important in encouraging people to donate regularly. This kind of approach could be used to understand and study other aspects in the blood supply chain such as survival rates of blood units.

Additional blood is required in disasters and emergencies. Glynn et al. (2003) and Sonmezoglu et al. (2005) use log linear models, logistics regression and chi square tests to compare indicators such as volume and reaction rates during both normal and disaster periods. Both studies show that disasters considerably increase the volume of collections since these events have a major impact on the motivation of donors. However, it is not always convenient to collect a large quantity of blood in a very short period of time. Moreover, risks are increased since adverse reaction rates for first-time donors are usually higher than for regular donors. Additionally, Boppana and Chalasani (2007) develop Markov chain models to determine the optimal acquisition rate of blood during emergencies. However, a debatable point about this article is that it assumes independence between shortage and outdate rates, whereas other studies such as Jennings (1973) and Sirelson and Brodheim (1991) show that these variables are related. An et al. (2011) present an evaluation of collection strategies in catastrophic scenarios. This paper evaluates situations such as in an epidemic, where the donor population decreases while at the same time demand increases. Finally, Jabbarzadeh, Fahimnia, and Seuring (2014) present a robust optimisation model to design a blood supply chain in case of emergency. The model supports decisions such as location and amount of permanent and temporary facilities, allocation of donors, amounts of blood to be collected and inventory. The model is solved using a robust optimisation methodology that considers scenarios designed by combination of critical parameters such as injury to death rate, hospital admission and blood transfusion rate.

The configuration of collection sites, the allocation of staff and donor scheduling strategies have been also studied. Pratt and Grindon (1982) and Brennan, Golden, and Rappoport (1992) evaluate different configurations of collection points for different donor arrival rates. However, Brennan, Golden, and Rappoport (1992) extend this work, taking into account staff allocation and work rules. Both articles use simulation as an approach and measure the impact of changes in conditions using indicators such as the time taken in different stages in the collection process. Michaels et al. (1993) study strategies based on different ways of scheduling donors. This study also proposes several scenarios about donors arriving late, inclusion of walk-in donors and batching donor arrivals.

Other studies in the collection stage concern factors that affect the motivation of donors. Godin et al. (2007, 2005) use regression to determine the relevance of variables such as intention, perception of control, anticipated regret, moral norm, age and past behaviour to understand motivation and determine key factors between first-time and regular donors. Yu et al. (2007) present a similar study based in China, using several methodologies such as decision trees and k-median. On the other hand, Custer et al. (2004) use Monte Carlo simulation and decision trees to evaluate different aspects of blood collection such as cost, collection and deferral policies. These models could help operations managers and decision makers improve collection, for instance, by improving the location of collection facilities and advertising strategies. Bosnes, Aldrin, and Heier (2005), Schreiber et al. (2005) and van Dongen et al. (2014) present studies aimed at studying the behavioural variables that affect donor arrivals, their commitment to future donations and the management of donors. Finally, a similar study is presented by James and Matthews (1996) who use survival analysis to study the key factors in donation cycles.
Other researchers have studied collection policies and collection methods and their impact on the performance indicators of the blood supply chain. Lowalekar and Ravichandran (2010) develop a simulation model to evaluate different collection policies. Those policies have been studied from an inventory theory perspective; however, the same models can also inform collection decisions. Policies are studied with both fixed and variable quantities to be collected and varied times between donations. One of the main conclusions of this work is that it is not necessarily convenient to collect as much blood as possible. Alfonso et al. (2013, 2012) also develop a simulation model aimed at determining the capacity and staff required. The methodology firstly consists of a representation using Petri Nets to define the main events in the model. After this, the model is represented using discrete event simulation (DES) in order to include stochastic elements such as arrivals, processing times and donor behaviour. Two recent papers by Alfonso and Xie (2013) and Alfonso, Augusto, and Xie (2014) present mathematical models for collection planning. The aim of the first model was to minimise products obtained from external suppliers. This model considers important features, such as the regional donation capacity, and optimises the quantity of blood to be collected each week. The second paper incorporates daily planning for the same self-sufficiency objective. Finally, Madden, Murphy, and Custer (2007) evaluate the impact of two different collection methods of RBC, using fractionation and double red blood cells donation by aphaeresis (2RBC): fractionation produces just one unit of RBC while 2RBC produces two units. This paper evaluates both methods under different policies such as European Travel Deferral, which is aimed at deferring donors who are ineligible to donate for various reasons, because of travelling and living in the UK and certain European countries during specific periods when Creutzfeldt-Jakob Disease (CJD) or variant Creutzfeldt Jakob Disease (vCJD) were active.

Donor classification models have also been used to support decision-making processes in the collection stage. The aim of classification was to identify important features of the donor population. For example, the proportion of men and women, the type of donor and age are all variables that should be taken into account in collection planning, since aspects such as donation cycles are different for men and women. Studying donor behaviour also provides important information about reasons for donation. Using such studies, researchers have identified critical variables in donor motivation, such as distance to the donation point and waiting times. Examples are presented by Lee and Cheng (2011) and Testik et al. (2012). In the first paper, the authors use data mining methodologies to classify donor behaviour. In the second paper, the authors use classification and queuing theory to determine staff requirements hour by hour. This is an important approximation to improve collection planning and support decision makers.

Ghandforoush and Sen (2010) develop a nonlinear integer programme to support the daily process of platelet production planning. The objective is minimising the costs of collection, production and shortages. Capacity constraints in collection and transport are included; however, there are no inventory variables. The model does not consider a time index, and the shortages are calculated using a historical rate. Optimisation models are also used by Gunpinar (2013). In one of the several models presented in this thesis, the author minimises the distance of collecting blood units from remote donors. This model describes a problem rarely studied and can serve as a basis to develop other collection strategies such as home collections.

Finally, other important features of the blood collection stage are also considered in some of these papers. Apheresis collection processes are considered in Custer et al. (2005), Madden, Murphy, and Custer (2007) Bosnes, Aldrin, and Heier (2005), and Alfonso et al. (2013, 2012). The latter three papers also consider appointments in the collection stage. In addition, collection policies are studied in Lowalekar and Ravichandran (2010), Alfonso and Xie (2013) and Alfonso, Augusto, and Xie (2014). On the other hand, ABO Rhesus groups in the collection stage are only considered by James and Matthews (1996). None of the models described in this section consider decisions about the types of bag to be used or payment for donation. These features, together with additional detailed information about the models such as the size of the problem and the type of study, can be found online at http://dx.doi.org/10.1080/00207543.2015.1005766.

As we have seen, the literature on collection models is diverse; however, there are still several areas which need further research. Examples of these are different collection alternatives, optimisation of cost, location of mobile collection centres and planning considerations such as periodicity in regular donors. All those aspects have not been addressed and represent opportunities to continue expanding knowledge in this area.

2.2 Production

Production is the stage where a unit of blood is received at the blood centre and is then tested and possibly fractionated (broken down into components). This stage is concerned with replenishing inventories of blood products during normal and emergency periods. A large body of knowledge has been developed on inventories; however, the analysis is frequently focused on specific products and does not consider other products and sub-products generated during the fractionation processes. In this level, decisions are related to how to exploit the fractionation alternatives and advantages of collection methods to improve the performance of the blood supply chain.
Figure 3 is a schematic representation of the decisions in the production stage. Like for Figure 2, there is a hierarchical relationship among decisions. Strategic decisions in production planning usually refer to determination of location and capacities, as these kinds of decisions are not easily reversible. Decisions such as staff allocation, production master plans and facilities layout are classified as tactical and are affected by strategic decisions. Finally, operational decisions in production in the blood supply chain refer to daily planning such as scheduling of staff, paths for blood fractionation, timetabling and scheduling for testing. This is one of the most frequently studied levels in industrial supply chains; however, given the special features of blood, these models are not easily applicable to the blood supply chain.

There are relatively few publications concerned with production decisions. However, in this section, the literature concerned on blood products production is reviewed, including aspects such as production alternatives, single product production, platelet production, modelling approaches and models to study the impact of reducing shelf life.

Very few researchers consider several products simultaneously and the production alternatives to generate them. The first studies in production components are presented by Deuermeyer and Pierskalla (1978) and Deuermeyer (1979) who develop an analytical model to minimise the production costs of RBC and platelets. In this paper, production decisions are associated with different production processes and are characterised according to the initial inventories of each product. This article introduces the idea of optimisation of production, since there are different alternatives to process a unit of blood. However, the model is too simple to be relevant now, since current fractionation processes includes alternatives with more than two products. In addition, the model does not consider other features such as compatibilities and availability of donors.

In the case of a single product, production orders are derived directly from inventory levels. Sirelson and Brodheim (1991) develop a simulation model to support production decisions for platelets based on the inventory on hand. The authors develop profile graphs, where inventory levels are associated with accepted shortage and outdating rates. They also point out that inventory policies can be designed using only the mean demand as a single parameter and that shortage and outdate rates are related mainly to the base stock. This model is interesting, but demand for platelets can vary over time and the inventory policies defined could become obsolete. Katz et al. (1983) propose a platelets production function. This equation is based on historical demand and deviations for each day as well as planned inventory and service level. This approach is similar to non-perishable inventory theory. Finally, Ledman and Groh (1984) develop production planning rules based on demand mean and variability and collection schemes. This report presents important concepts that have been less studied, such as different collection policies.

Given their short shelf life, platelets are regarded as highly perishable and several publications have dealt with the associated inventory problems. Haijema, van der Wal, and van Dijk (2007) develop a Markovian model to represent decisions on production and inventories of platelets. The model includes multiple periods as well as weekend breaks. Ordering, shortages and production are integrated in a general cost function to be optimised. This article considers two
types of demand and different issuing policies to meet them as well as order-up-to policies. The first solution approach the authors tried was dynamic programming, but it was unsuccessful because of the problem size and number of states. Therefore, the problem was addressed using simulation and local search algorithms which gave near optimal solutions. Haijema et al. (2009) and van Dijk et al. (2009) present articles based on the same model. The first paper includes breaks such as Christmas, New Year and Easter. In the second paper, the model is used to introduce changes and study different scenarios. The scenarios studied by the authors consider differentiation of blood types and changes in shelf life, as well as the crossmatch ratio and issuing policies. Uncertainty in demand and arrivals of donors are also considered. In the case of platelets, the authors state that differentiation between ABO Rh groups can be ignored. This work is important since there is a real application which was implemented in Holland; in addition, the model is easily replicable. The heuristic presented gives a good approximation to the solution of this kind of problem; the problem’s size and structure would normally make it intractable by exact methodologies.

Other studies have used different modelling approaches for production planning. For example, Baesler et al. (2011) present a simulation model to study capacity and support decisions on capacity expansion. Most of papers in the literature assume infinite capacity in collection and processing and do not consider internal processes. However, Baesler et al. analyse the problem of resources used and internal waiting times and queues through simulation. Decisions about fractionation equipment and medical staff are made according to utilisation rates. This model could be extended to planning and scheduling collection campaigns based on capacity in order to avoid dissatisfaction of donors because of long waiting times.

In addition, features such as fractionation alternatives, ABO Rh groups, special periods and different types of demand have been considered by some researchers. Fractionation alternatives are the least frequently studied. Of all the articles presented in this section, only Deuermeyer and Pierskalla (1978), Ledman and Groh (1984) and Baesler et al. (2011) considered this feature. In terms of type of products, the models presented in this section are mainly focused on platelets, with the exception of Deuermeyer and Pierskalla (1978) and Baesler et al. (2011) who also consider other products such as whole blood, RBC and plasma. On the other hand, ABO Rh groups are considered by Ledman and Groh (1984), Haijema, van der Wal, and van Dijk (2007), Haijema et al. (2009) and van Dijk et al. (2009). The latter three papers, and also Katz et al. (1983) and Sirelson and Brodheim (1991), also consider special periods such as weekends in their models. With exception of Deuermeyer and Pierskalla (1978) and Baesler et al. (2011) all these models include a periodical review inventory system. Finally, different types of demand are included in Haijema, van der Wal, and van Dijk (2007) and van Dijk et al. (2009). Further detailed information on additional features such as the size of the problem, horizon planning and type of data can be obtained online at http://dx.doi.org/10.1080/00207543.2015.1005766.

2.3 Storage and inventory

Inventory is the stage of the blood supply chain that has received the most attention in the literature. From 1960 onwards, researchers began to develop new methodologies to study inventory policies for blood products. The perishable nature of blood products, together with special features such as crossmatching and mismatching, considerably increases the complexity of this problem, and has stimulated many theoretical developments in this area which have had wide applicability beyond the blood supply chain.

Figure 4 shows the relationship between decisions on inventory. The figure is general; however, the complexity of platelets inventory can be greater than that of other blood products since the shelf life is much shorter. Decisions in this echelon have been mainly related with definition of inventory policies; however, some of the models presented in the literature are focussed on specific decisions and do not consider constraints and features such as availability of donors, proportionalities and compatibilities that could affect decisions at this stage. Decisions in this stage can also be classified according to hierarchical levels. Again, long-term planning is associated with strategic decisions such as network design. In addition to location decisions, this stage also covers decisions such as information systems, which play a very important role in inventory management. Tactical decisions in this stage refer to inventory policies definition and staff allocation. Mismatching and crossmatching policies can be also defined in this level, although these policies can be altered in emergency situations where they become more operational decisions. In the lowest level, decisions are related to daily quantities to order, how to meet special orders and what specific products should be issued in order to fulfil demand.

Methodologies such as analytical models, statistical approaches, Markov chains, queuing theory, optimisation, simulation and combinations thereof have been proposed to address this problem. However, even now there is no practical theory to calculate optimal policies for some blood products.

One of the earliest approaches to the study of blood inventory problems was analytical modelling. Two analytical models to evaluate different aspects of blood inventory management are presented in Cohen (1976) and Nahmias and
Pierskalla (1976). Cohen’s paper is aimed at finding optimal ordering policies for any perishable product, taking blood as an example. This model considers important features such as perishability and backlogging; however, results are presented just for three periods and the current shelf life of RBC is 42 days. Even platelets have a longer shelf life period than 5 days. Nahmias and Pierskalla (1976) present a model considering two types of demand and two different policies to meet demand. Pierskalla and Roach (1972) evaluate FIFO and last-in-first-out (LIFO) policies, finding that, in most of the scenarios evaluated, FIFO outperforms LIFO, according to key performance indicators such as shortage, outdate, assigned inventory and cost. Finally, other examples of analytical models can be found in Chazan and Gal (1977) who find bounds for the expected outdating rates; Jagannathan and Sen (1991) who study the impact on shortage and outdate rates of changes in crossmatching parameters; and Pegels et al. (1977) who use a single blood centre model to evaluate different strategies such as using frozen RBC and improving inventory control and donor scheduling.

Other articles also present analytical procedures to determine inventory and ordering rules. This approach is aimed at finding functions and profiles to support the decision-making process. Sapountzis (1985) develops characteristic curves to determine outdating probabilities for each RBC type in hospitals. Omosigho (2002) presents a general formula for calculating the probability of use for perishable products. According to Omosigho (2002), in the specific case of the blood supply chain, this probability can be assumed to be the crossmatching ratio. Telles et al. (2013) present a typical inventory model for blood products. However, blood is treated as a normal product since special features are not considered. Blake et al. (2010) discuss the convenience of using cost as objective for platelets inventory policies. In this work, the authors also present a simplified methodology for ordering platelets, based on service levels. This methodology was applied to different sized hospitals, finding that it works better in hospitals with more stable demand. Finally, Zhou, Leung, and Pierskalla (2011) present an analytical model to define optimal inventory policies for platelets. The model extends analytical policies to three periods and also includes different replenishment modes, such as normal and optional.

Markov chains and statistical approaches have been widely used for many years to study the performance of blood inventory systems. Pegels and Jelmert (1970) use a Markov chain model to assess two different issuing policies and calculate its impact on blood inventory. However, this model is criticised by Jennings and Kolesar (1973) who argue that the model is not clear about transition probabilities and even that it is not a Markov chain model. On the other hand, Brodheim, Derman, and Prastacos (1975) use a Markov chain model to represent the behaviour of an inventory system and distribution policies. The model assumes stationary demand and is aimed at calculating shortage and outdating rates as well as bounds and inventory parameters. This approach is also used by Mole (1975) to generate profile curves of

Figure 4. Decisions by hierarchy level in the inventory stage.
shortage/demand versus wastage/replenishment for two different demand distributions. Statistical methods are used by Frankfurter, Kendall, and Pegels (1974) to try to predict the behaviour of inventory based on the main variables of the system. Similar methods are proposed by Critchfield et al. (1985) who use time series forecasting methodologies such as moving average, Winter’s methods and exponential smoothing to predict the use of platelets concentrates in a blood centre. The results were less accurate than empirical prediction, but the authors highlight that reductions in outdates were obtained using the method. Finally, Silva et al. (2013) propose seasonal ARIMA models (SARIMA) to forecast demand of blood products as well as arrivals of donors. The paper specifies an automatic procedure to be applied without human intervention.

Queuing theory has also been applied, modelling blood collection as arrivals and demand as a service. Some models include transient features such as impatient donors who are not prepared to wait more than a given time. Goh, Greenberg, and Matsuo (1993) develop a queuing model to evaluate two policies, unrestricted and restricted ways of meeting demand, in an inventory system with two stages. The unrestricted policy allows fresh blood to be used to meet demand for either fresh or old blood, whereas the restricted policy does not allow fresh blood to be used to meet demand for old blood. Moreover, Kopach, Balcıoğlu, and Carter (2008) present an elaborate queuing model that considers various costs in addition to shortage and outdate rates. The model also considers two types of demand and several strategies to meet each type. However, such models often include strong assumptions that can make them less applicable in practice. For example, assumptions about the distribution of donor arrivals and demand over time can affect the results, since donor arrivals can be affected by policies such as the maximum quantity collected, and demand can also vary over the time period. In addition, these models do not include the crossmatching ratio and the crossmatching period, which are very important features in the real world setting.

Given the complexities of the system, simulation has been one of the most important approaches to modelling the blood inventories. One of the earliest simulation models was presented by Elston and Pickrel (1963) who use Monte Carlo simulation to evaluate scenarios for blood inventory management. This work showed that indicators such as the inventory level, the expiration percentage, the age of the blood and shortages, could be improved. This approach is also used by Cohen and Pierskalla (1975) and Vrat and Khan (1976), to evaluate different aspects on blood inventory. In Cohen and Pierskalla (1975), the methodology is used to evaluate issuing and crossmatch period policies. The cross-match release period is the length of time a unit of blood is stored in assigned inventory before it is returned back to unassigned inventory, normally because the patient is deemed to be in no further need of it. The metrics to evaluate the different scenarios are units transfused, shortages, outdates, cost and assigned and unassigned inventory. The model presented by Vrat and Khan (1976) has similar metrics but in this case, crossmatching features are not considered. Brodheim, Hirsch, and Prastacos (1976) develop profile curves to define inventory levels based on shortages and mean demand. The proposed curves are a simple and effective way to support blood bank managers. The use of substitute products has been studied in Cumming et al. (1977). Using simulation, the authors evaluate the use of frozen RBC in avoiding shortages; however, this practice is not common at this time. A similar study was published by Friedman, Abbott, and Williams (1982), who study the impact of both reducing non-type O inventory to exploit the compatibilities of this blood type and also an extension of the shelf life from 21 to 35 days. Currently, it is widely accepted that shelf life of RBC is 42 days, but recent evidence suggests it is preferable use ‘young blood. Recent studies such as Fontaine et al. (2010) and Blake et al. (2013) have evaluated the impact of reducing the actual maximum shelf life of RBC in blood bank indicators. Pereira (2005) uses Monte Carlo simulation to evaluate an alternative to crossmatching called T&S, which does not assign inventory to patients. According to this paper, T&S outperforms crossmatching on all the key performance indicators. However, to date, T&S has still not been completely accepted by medical staff, despite some successful cases as presented by Georgsen and Kristensen (1998). Finally, Kamp et al. (2010) present a system dynamics (SD) model to evaluate strategies under critical scenarios such as pandemics, when demand increases but the donor population decreases. However, SD has been less used than other techniques to study the blood supply chain.

Optimisation has rarely been used in blood inventory. Given the complexities of this kind of problem, the use of optimisation seems to be impractical. The size of the problems and the nature of the variables can affect the quality of solutions obtained. However, this also depends on the specific application. A goal programming model is proposed by Kendall and Lee (1980) to allocate blood units to hospitals considering the remaining shelf life. The criteria to evaluate the solutions in this model are availability stock levels, fresh blood availability, age of blood, rate of outdating and cost. Recently, Gunpinar (2013) and Gunpinar and Centeno (2015) present optimisation models aimed at minimising total cost (purchase cost, holding cost, wastage cost, outdate cost and outdated cost). The models seek to generate an inventory plan considering internal parameters such as capacity and lead time. Finally, other articles such as Britten and Geurtze (1979), Erickson et al. (2008) give results of application of decision rules; however, not much information is given about the methodologies used to define the parameters.
When two or more methodologies are combined, models can be more robust and different features can also be included. Statistical methods, economic modelling, simulation and inventory theory are combined by Cohen and Pierskalla (1979) to calculate a single equation to define optimal inventory policies. The aim of the model was to support the decision-making process of blood bank managers. Cohen, Pierskalla, and Sassetti (1983) use the same model to estimate the impact of extending the shelf life from 21 to 35 days. Recently, Li and Liao (2012) develop a model using the Taguchi method, combined with neural networks and genetic algorithms, to estimate optimal parameters in a blood supply chain. This methodology enables optimal minimum and maximum inventories to be found, as well as optimal donor arrival rates. This approach seems to be promising, since it can evaluate many different configurations in reasonable times. However, the model did not include important features such as crossmatching. Duan and Liao (2013) apply sample average approximation to include uncertainty in an optimisation model aimed at minimising the expected outdate ratio. The model also considered maximum shortage constraints as well as centralised and decentralised inventories. Duan and Liao (2014) combine DES and heuristic methodologies to generate an inventory plan, considering compatibilities and reduction of the shelf life of blood products. Finally, a recent publication developed by Blake and Hardy (2014) presents a simulation framework to evaluate inventory policies in both supplier and customer. Using response surfaces generated by simulation the methodology fits regressions to establish equations that can represent the surfaces. The equations are combined in a weighted non-linear function that is finally optimised to generate changes for inventory policies that satisfy objectives such as outdated, shortages and the numbers of normal and emergency orders.

Most of the models presented in this section concern whole blood or RBC inventories. However, papers such as Critchfield et al. (1985), Blake et al. (2010), Zhou, Leung, and Pierskalla (2011), Duan and Liao (2013) focus on platelets inventories while other papers such as Gunpinar (2013), Silva et al. (2013) and Telles et al. (2013) consider multiple products in the models. ABO Rh groups are explicitly considered in articles such as Elston and Pickrel (1963), Jennings (1968), Frankfurter, Kendall, and Pegels (1974), Vrat and Khan (1976), Brodheim, Hirsch, and Prastacos (1976), Fontaine et al. (2010), Duan and Liao (2013) and Blake and Hardy (2014). In terms of inventory strategies, most models include typical periodical and continuous review policies. However, other authors such as Blake et al. (2010) and Blake and Hardy (2014) present a more elaborate policy combining periodical and continuous review systems. Other policies based on expected outdates and the age of the blood products are presented in Duan and Liao (2013, 2014). With the exception of a few publications at the early stages of research on inventory policies, the articles use FIFO as the issuing policy. On the other hand, emergency orders are included in some models, such as Kendall and Lee (1980), Erickson et al. (2008), Kamp et al. (2010), Zhou, Leung, and Pierskalla (2011) and Blake and Hardy (2014). Finally, other features such as the crossmatch ratio and crossmatch release period were included and studied in the 1980s and 1990s, for example Cohen and Pierskalla (1979), Britten and Geurtze (1979) and Jagannathan and Sen (1991). However, policies such as type and screen avoid the complications for inventory planning generated by these features. Further information on the features presented here can be also found online at http://dx.doi.org/10.1080/00207543.2015.1005766, together with information about the models such as problem size, type of information and type of study.

2.4 Distribution

Collection, production and inventory are all independent of the configuration of demand points in the blood supply chain. However, distribution processes can vary considerably: in places where there is a regional blood service, blood can be transported from one blood centre to another if there is a shortage in one location and an over-supply in another. Moreover, distribution also includes the internal transfer of blood products from a hospital blood bank to the point of care. Generally, hospitals provide daily requests for blood from their local blood centre, based on historical data, forecasts and clinical knowledge. There are published tables specifying how much blood is typically required for each type of major surgery. In most countries, emergency requests can also be placed and additional supplies are then ‘blue-lighted’ using a fast vehicle, for example if there is a major incident. The goal is to deliver the correct quantity of the correct product to the patient at the moment it is required.

Figure 5 presents a general schematic representation of distribution decisions. Distribution decisions can be found throughout the supply chain: even the collection stage includes decisions about how to pick and distribute whole blood to the blood centres. The framework presented in Figure 5 corresponds mainly to the process of transporting ‘finished’ product from inventories in blood centres to hospitals to be transfused to patients. However, models and methodologies can be extended to other areas that contain distribution decisions. Long-term decisions in the distribution stage relate to the strategy for product delivery: choice of types of vehicles, capacity and staff. These decisions will affect tactical decisions such as routing and allocation. Planning in the short term implies scheduling of vehicles, packing, transhipments between different points and meeting time window constraints. The distribution stage in the blood supply chain must handle complex situations, since in some cases, it is not desirable to maintain inventory in low demand hospitals for
scarce products such as AB-negative RBC. The inventory must be kept in blood centres and will only be dispatched to hospitals in emergencies, at very short notice.

The analysis of the literature for this aspect includes location decisions as well as allocation and distribution strategies. Papers that cover different aspects such as crossmatching strategies, blood products allocation, facility location and delivery strategies are analysed and presented, highlighting the contributions and important aspects.

Blood is a raw material produced by donation from human beings. In many countries, donation is voluntary and donors need to be assured that their blood is used to good purpose. Collecting blood requires an enormous effort, which means that its spoilage and wastage need to be reduced as much as possible. Yahnke et al. (1972, 1973) study the effect of returning unused blood from the hospital to the blood centre, and find that this practice can decrease the outdate rate; it should be noted that today this practice is not allowed in most developed countries. The authors also propose a different indicator aimed at measuring the impact on each hospital. This indicator is called the effective outdate rate, and its objective is to avoid returns of very old blood. Dumas and Rabinowitz (1977) propose two policies to reduce the outdating rate. The first policy uses double crossmatching to increase the probability of use and reduce the outdate rate. Under this policy, each unit is assigned to two different patients and each patient is assigned two different blood units. Unfortunately, this policy was not well received by physicians. However, the other proposed policy is widely used now and is focused on the use of substitute products (mismatching). Provided the compatibility criteria are met, demand can be satisfied by the use of more common products. Nowadays, there are even preferences in the use of each substitute product. Finally, Sapountzis (1984, 1989) develops optimisation models to reduce outdating rates based on the activity level of each hospital and inventory allocation under both deterministic and stochastic demand.

Allocation strategies are also aimed at decreasing wastage and shortages. Prastacos (1978), Brodheim and Prastacos (1979) and Prastacos and Brodheim (1980) develop models to reallocate the blood inventory of several hospitals in a region at the end of each planning period. In the first paper, analytical methods were used to calculate optimal values of two different strategies, rotation and retention. The objective optimised is the sum of the shortage and wastage costs. The second paper is similar, but in this case, the author uses mathematical programming to determine the policies which minimise the use of fresh blood. Furthermore, Prastacos and Brodheim (1980) develop a model to minimise the transshipments considering pre-schedule deliveries, a fixed quantity of old blood returns and rotation and retention policies according to the age of the blood. Finally, a formalisation of the models developed is presented in Prastacos (1981). In this paper, the myopic policies presented in previous articles are compared with optimal policies, permitting the
generation of bounds to measure the goodness of the myopic strategy. The authors found that there is not much difference from optimal policies. The main reason to develop myopic policies is that these are easier to implement in practice than the optimal inventory policies presented in other publications.

Location decisions are typically considered as strategic in any supply chain. In the blood supply chain, these kinds of decisions are also very important, since the distance between donors, blood centres and demand points can play an important role in the improvement of different indicators in the blood supply chain. Or and Pierskalla (1979) present an integrated mathematical model to locate blood centres and allocate hospitals to them, which aims to minimise the distance travelled. The paper also contains two algorithms to solve this model. The objective function is only concerned with distance: costs are not considered. Another contribution in location models is presented by Jacobs, Silan, and Clemson (1996) who developed an integer linear programming model to evaluate location alternatives and decisions such as allocation of donors to collection points, allocation of collection points to blood centres and quantities of blood to be collected. The model’s main objective is the minimisation of distance, meeting assignation, capacity and demand constraints. Şahin, Süral, and Meral (2007) present two models to support decisions on location and allocation in Turkey. The first model minimises the weighted distance between demand points and blood centres. The second case minimises the number of blood stations considering distance covering constraints. The models are modifications of the well-known $pq$-median and set covering models, and both were solved using optimisation software without any additional solution methodology. Other articles also aimed at locating facilities are presented by Cerveny (1980), Price and Turcotte (1986) and more recently Çetin and Sarul (2009). These articles present heuristics and combined methodologies to determine the location of a facility. The main objective was to minimise distance; however, in Price and Turcotte (1986) other criteria such as accessibility and space availability are also considered.

Routing-scheduling models and vendor managed inventory (VMI) have been applied to reduce shortages and distance indicators in the distribution stage. Federgruen, Prastacos, and Zipkin (1986) present two models for allocation and routing inventory problem aimed at minimising shortage cost, transport cost and outdate cost. Sivakumar, Ganesh, and Parthiban (2008) develop a mixed methodology combining the vehicle routing problem and the analytic hierarchy process to study an allocation-routing problem in a blood supply chain in India. Recently, Hemmelmayr et al. (2009) presented a model to improve the assignment of hospitals to the routes planned by a blood bank. The model is based on VMI methodologies which imply that hospitals do not define the quantities and delivery dates, but instead the blood bank will programme the deliveries based on stationary deterministic demand. Since demand is deterministic shortages are not considered. The model aims to minimise the distance travelled and considers time constraints.

Finally, some models include emergency (blue light) orders. Gregor, Forthofer, and Kapadia (1982) study distinct distribution strategies such as changing the number of vehicles and redefining inventory levels to minimise several objectives including the reduction of emergency orders. Hemmelmayr et al. (2010) present an improved version of their previous model. In this case, demand is considered as stochastic and the model includes several forms to meet demand in case of emergencies. The solution methodology proposed is a combination of sample average approximation and metaheuristics. The methodology proposed is robust and can be used to address other problems in the blood supply chain. Banthao and Jittarnai (2012) develop a mathematical model to locate blood banks using distance coverage policies. This model is similar to presented by Çetin and Sarul (2009) but in this case, the objective is minimisation of the total cost: normal ordering cost plus emergency ordering cost. As a final point, few of these models consider the possibilities of meeting demand using substitute products, which can be a practical alternative in case of shortages and emergencies.

Other important features such as the use of substitute products, returns and transshipments are included in some of the papers presented in this section. The use of substitute products is studied in Dumas and Rabinowitz (1977) while returns are allowed for example in Yahnek et al. (1973), Dumas and Rabinowitz (1977), Prastacos (1978), Prastacos and Brodheim (1980), Gregor, Forthofer, and Kapadia (1982) and Federgruen, Prastacos, and Zipkin (1986). Transshipments or interchange of blood products is considered in the models presented by Yahnk et al. (1973), Prastacos and Brodheim (1980), Şahin, Süral, and Meral (2007) and Sivakumar, Ganesh, and Parthiban (2008). Finally, some distribution models such as Hemmelmayr et al. (2010), Sapountzis (1984, 1989) and Gregor, Forthofer, and Kapadia (1982) also consider blood types in the distribution strategy. A complete presentation of the features mentioned for each article of this section, together with additional information such as problem size, type of data and type of products considered, is available online at http://dx.doi.org/10.1080/00207543.2015.1005766.

2.5 Integrated models

Features of the blood supply chain such as perishability, blood types and uncertainty of supply and demand affect decisions at all echelons of the blood supply chain. These features add complexity to the decision-making process and
differentiate the blood supply chain from other supply chains, and from other perishable products. Figure 6 presents a general schematic of the features and their relationships with each echelon of the blood supply chain. This figure also presents the main performance indicators of the blood supply chain such as outdating rate, shortage rate and cost. A less frequently studied indicator is the number of donors required to meet demand. Since demand for blood products is increasing and the donor population is decreasing, this indicator may play an important role in blood bank management. Figure 6 relates the main features of the blood supply chain and the indicators and stages directly impacted by each feature. This figure also illustrates the complexity of the blood supply chain and shows why it is different from industrial supply chains.

The majority of the literature in the blood supply chain is focused on individual echelons and does not consider relationships between the different stages. For example, models for collection often do not consider production and distribution policies. Models for inventory management very often assume that there are no limitations on the number of units that can be collected. However, recent publications on the blood supply chain often aim to connect donors with patients, considering flows of blood and blood products throughout the supply chain. Different methodologies have been used, such as simulation, optimisation and hybrid approaches to study and improve the blood supply chain.

One of the main methodologies to represent and study the blood supply chain is discrete event simulation (DES). Page (1980a) presents one of the first articles using DES to study the blood supply chain, evaluating distinct strategies such as heuristic procedures for inventory allocation, forecasting of inventory levels and recycling of old blood to reduce the cost per unit transfused. Rytillä and Spens (2006) develop a DES model to study inventories and distribution policies measured through indicators such as outdating, cost and back orders. This model also includes different aspects of the supply chain such as compatibilities, integration between hospitals and blood centres, and the crossmatch release period. Although the authors mention the optimisation of inventory policies, they do not provide much information about what methodology they used. An important point in this article is that it was developed in conjunction with medical staff, who helped to implement several proposals derived from the model. Katsaliaki and Brailsford (2007) use DES to provide a complete representation of the blood supply chain, including collection, production, inventory and distribution stages. This DES model is based on the National Blood Service in the UK, specifically on the processes developed in typical hospitals in Southampton. Changes in policies are proposed to improve the supply chain, mainly based on inventory and distribution stages, with other echelons represented to study the flow of the blood along the complete supply chain. A similar study is presented in Yegül (2007); in this paper the author develops a more generic model.
considering collection points, blood centres and hospitals. The model developed allows transhipments and incorporates heuristic mismatching rules. This work is aimed at evaluating different scenarios of the structure of the blood supply chain in Turkey. Finally, Baesler et al. (2014) also present an integrated DES model. This paper is aimed at developing heuristic mismatching rules. This work is aimed at evaluating different scenarios of the structure of the blood supply chain considering collection points, blood centres and hospitals. The model developed allows transhipments and incorporates inventory policies considering emergency collection campaigns. Reorder points are estimated to minimise wastage and outdating rates, with a decision rule to start an extra collection campaign. The model considers several stages of the blood supply chain, but is mainly focused on collection stage.

Another simulation paradigm used to study the blood supply chain is Monte Carlo simulation. Lowalekar and Ravichandran (2011) and Simonetti et al. (2014) present studies based on this methodology to support decisions. In the first paper, the authors model the collection and production stages. In collection, different strategies are studied, including fixed and variable collection quantities. In the production stages, the authors evaluate different fractionation rates and develop profile curves to help the decision-maker to define policies. Their model includes several blood products; however, collection methods such as apheresis are not considered since these methods are not common in India. The second paper combines DES and Monte Carlo simulation to study different issuing policies, evaluating availability and shortage indicators. The results show that FIFO, newest and oldest policies differ considerably on the availability of units. However, other indicators such as outdating are not significantly different. On the other hand, the model includes a new idea about mismatching policies, creating a decision rule for preferences in the use of substitute products. Finally, the models consider a decision rule to mismatch blood products. This process consists of a table of preferences in the use of substitute products; these preferences are often used in blood banks, but it is the first time that they have been explicitly included in a model.

Mathematical programming and data mining combined with geographical information systems (GIS)-based analytics are used by Nagurney, Masoumi, and Yu (2012) and Delen et al. (2011), respectively, to model the blood supply chain. The model developed by Nagurney, Masoumi, and Yu (2012) is claimed to be the first attempt to use mathematical programming to optimise the whole blood supply chain. This model considers the blood supply chain as a network problem, defining different nodes, arcs and flows to represent the entities and relationships of this supply chain. The article also includes algorithms to generate optimal flows throughout the whole supply chain as well as optimal results of basic instances. An extension of this work is presented in Nagurney and Masoumi (2012). The main differences are the inclusion of discarding cost along the supply chain and the consideration of the arc capacities as decision variables. However, both articles are focused on a strategic perspective and do not consider important features of the blood supply chain such as the crossmatching period, compatibilities and multiple products. Finally, Delen et al. (2011) present an application of several methodologies such as data mining, GIS-based analytics and optimisation to improve the blood supply chain in the armed forces. This application is interesting since the blood demand and the blood supply chain in the armed forces have several differences from a typical blood supply chain, such as emergencies arising from combat, resource limitations and geographical constraints. However, the article is focused on the software developed and does not describe in depth the models and methodologies used. Finally, Abdulwahab and Wahab (2014) propose a combination of methodologies such as news vendor problem, linear programming and approximation dynamic programming to address the platelets inventory problem. The paper highlights that there is no need to resize the problem, as previous studies have described. Another important contribution is the inclusion of blood types and use of substitute products.

Multi-objective approaches and simulation optimisation methodologies have also served to evaluate different aspects. Firstly, Kendall (1980) use multi-criteria methods to find the best configuration of blood supply chain planning. Using predefined options, the article develops a trade-off methodology to find the best combination of policies in different aspects such as collection, budget, acceptable shortages and outdates, and inventory levels. Currently, there are more robust multi-objective methodologies; however, few articles consider more than one objective. Finally, Lang (2010) uses a combination of simulation and heuristic methodologies to evaluate the impact of both transhipment and substitution. Both concepts are very important to the goal of reducing outdating and shortage rates since they present alternatives to supply demand. Although these concepts are not new, very few models consider these aspects.

In addition, some papers present discussion on important features of the blood supply chain such as considerations about the duration of shelf life of RBC and its impact. Recently, Blake et al. (2013) published an article which studied the impact of reducing the shelf life in three scenarios: 28, 21 and 14 days. In the 1970s, research on transfusion was aimed at extending the shelf life, and the result of this is that currently the shelf life of RBC is usually 42 days. However, as Blake states ‘there is a body of literature that suggests poorer clinical outcomes when older RBCs are used’. (Blake et al. 2013, 1). Under this premise, Blake et al. developed a simulation model to evaluate shorter RBC shelf life, taking into account inventory, outdating, shortage and emergency indicators. This kind of model could be useful to measure the impact of the use of substitute products, since there have not been studies specifically designed to measure the impact of this important feature of the system. Papers discussed in previous stages such as Fontaine et al. (2010) and Duan and Liao (2014) also consider reductions in the shelf life of the RBC.
Integrated models are aimed at studying more than one stage in the blood supply chain. However, it is almost impossible to represent every single feature of each echelon in one single model. Some features such as blood type are independent of the echelon analysed. Most of the models presented in this section, with the exception of Kendall and Lee (1980), Delen et al. (2011), Nagurney and Masoumi (2012) and Nagurney, Masoumi, and Yu (2012), consider blood types as a feature in the models developed. One of the less frequently studied features is fractionation. Of all the articles presented in this section, only Lowalekar and Ravichandran (2011) and Baesler et al. (2014) considered fractionation. On the other hand, many of the models described in this section include the collection stage. Kendall and Lee (1980) and Abdulwahab and Wahab (2014) represent collection amounts as stochastic parameters associated with probability distributions or expected values. The latter three papers, together with Kendall and Lee (1980), Katsaliaki and Brailsford (2007), Yegül (2007), and Lang (2010), considered inventory policies explicitly in the models presented. Distribution features such as issuing policies, mismatching policies, crossmatch rate and crossmatch period are included in some models discussed in this section, with the exception of Baesler et al. (2014) and Lowalekar and Ravichandran (2011) who mainly focus on the initial stages of the blood supply chain and do not consider distribution aspects. Finally, transshipments and interchange of products are included in the models presented by Page (1980a), Rytilä and Spens (2006), Yegül (2007), Lang (2010), Delen et al. (2011) and Blake et al. (2014). Additional information about each model presented in this section can be found online at http://dx.doi.org/10.1080/00207543.2015.1005766.

3. Conclusions
The blood supply chain remains a very active research area. There is renewed interest in research in this field, judging by the number of recent publications. In this review, we present a structured taxonomy of the state of the art of quantitative models as well as a decision-making framework in the blood supply chain. In this final section, we shall discuss aspects such as less frequently studied decisions, modelling needs, modelling approaches and potential future changes in the blood supply chain.

We have already identified that in each echelon there are some decisions which have been rarely studied to date. In the collection stage, the literature has mainly focused on donor behaviour and the location and configuration of blood collection points. However, we found very little discussion on the allocation of donors to different collection methods. We found no models studying the relationship between efficiency and the cost of different collection methods. Production is perhaps the least well explored stage of the blood supply chain. There is a considerable body of the literature on inventory control, but very few articles that consider the process of fractionation, where blood products are derived from whole blood as a result of separation processes that generate at least two products. This means that it is not necessarily efficient to manage inventories of different blood products independently. The majority of the literature concerns the inventory stage. Recently, inventory research has focused on platelet concentrates. However, the question of centralised or decentralised inventory has been rarely studied, and more research into the best use of substitute products is required. Finally, we found widespread application of location and allocation methods in the distribution stage. However, problems such as product allocation to production centres, blood transshipments, substitute products and collaborative schemes need more attention.

We found very few examples of integrated models and inclusion of multiple features. Most of the literature focuses on one single echelon. This can lead to a myopic view of the blood supply chain. Collection methods and goals are not governed by production policies. Inventory policies often do not consider the supply constraints. Production does not consider the age of the inventory. Those are all examples of problems by considering echelons individually. On the other hand, features such as the crossmatching rate and release period, mismatching and multi-products are not typically considered at the same time, leading in some cases to unrealistic and impracticable solutions. We argue that there is a clear need for modelling the entire process flow in the blood supply chain. This can help to identify bottlenecks as well as evaluate policies from a whole-system perspective. At the very least, integrated models would recognise the existence of constraints in the preceding and succeeding echelons. Of course, such models are challenging to develop and call for the use of mixed methodologies.

Recent publications tend to use more than one methodology to address blood supply chain problems. In the early years, analytical procedures and Markov chains were commonly used for inventory control problems, whereas statistical methods were used to study donor behaviour and forecast demand. However, the complexity inherent in each stage of the blood supply chain means that it is often necessary to combine methodologies. One popular combination is simulation plus optimisation. Using these approaches in combination enhances the possibilities of making practical improvements to the system. Both methodologies have advantages and disadvantages, but these are largely complementary and using them jointly, robust decision models can be created. This interaction of techniques can be achieved in different
ways. The combination of Monte Carlo simulation with optimisation is a technique often used in stochastic optimisation. On the other hand, the optimisation of simulation parameters is also used. In the case of the blood supply chain, this combination can be an interesting hybrid methodology to generate efficient solutions. Simulation can be used to represent, in a realistic way, the system features and flows of donors, blood, blood products and information throughout the whole supply chain. Moreover, optimisation can be used to define the parameters of the whole supply chain such as collection and production policies.

Recent scientific developments such as type and screen and the proposed shorter shelf life of RBC will also create a need for new research. Changes in the features of the blood supply chain can affect performance both positively and negatively. Type and screen provides a very efficient alternative to crossmatching since there is no physical assigned inventory. Crossmatching is one of the features of the blood supply chain that contributes to increased outdated rates, since it leads to unrealistic inventory levels. On the other hand, studies such as (Blake et al. (2013)) consider the impact of reducing the shelf life of blood products, which in the case of RBC may lead to improved clinical outcomes. This change could greatly affect the performance of the blood supply chain, since RBC is the main blood component in terms of demand. Those changes as well as other changes such as deferral policies and mismatching preferences impact the blood supply chain in different ways. It is clear that this field will continue to be a fertile area for research for many years, leading not only to improvements to patient outcomes in the real world, but also contributing to methodological developments in modelling.

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