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# A systematic review of simulation models in medicine supply chain management: Current state and emerging trends.

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ABSTRACT

Simulation modelling has widely been applied in healthcare supply chain management, focusing on blood and vaccine supply chains with less attention on the medicine supply chains. This study presents a systematic review of studies applying simulation methods, namely agent-based modelling, discrete event simulation, and system dynamics, to address problems in the medicine supply chain. We adopt the Search, Appraisal, Synthesis, and Analysis (SALSA) approach to collect data from three databases (Scopus, Web of Science, and PubMed) from 2000 to 2023. 320 journal publications qualified for the initial screening and filtration and were extracted for further analysis. Only 31 studies met the inclusion criteria, with the first publication identified in 2010 and the last in 2023. The paper shows the usefulness of applying simulation in identifying medicine supply chain bottlenecks pertaining to stockouts (19%, n = 6), and falsified or counterfeit (16%, n = 5). System dynamics was the most applied approach with 42% (n = 13) and 6% (n = 2) employing a hybrid simulation approach. 32% (n = 10) of the studies reported verification and validation at either a conceptual or operational level with insufficient data from the real-world system reported as a challenge. The study suggests a gradually increasing interest in simulation applications in medicine supply chains informing decision-making. Combining multiple simulation approaches is recommended to address complex medicine supply chain issues, such as availability. In order to understand the usefulness of the model in decision-making, more effort is needed to validate developed models.

## 1. Introduction

Supply chains involve the interaction of different agents of suppliers, manufacturers, retailers, distributors, health facilities, and customers. Individual rules govern these agents with a decision made by one affecting everyone else in ensuring improved service delivery. Key activities in the supply chain include planning, sourcing, making, delivering, and returning [1]. Healthcare supply chains (SC) are complex systems facing hybrid problems stemming from both the demand and supply sides while dealing with human life, with no room for error and trial to solve them [2]. In 2019, the World Health Organisation reported 5.7 – 8.4 million annual deaths worldwide from poor-quality care, with nearly two billion people globally having no access to required medicines [3]. Many existing studies on improving healthcare service delivery are qualitative [4,5], recommending innovative technology like electronic systems coming at the cost of implementation, management and maintenance. The innovations, however, are continuously reported as insufficient to solve the problems in the supply chain, as they are short-lived [6,7]. Given the persistent problems in the medicine supply chain, coupled with a constrained budget, researchers are continuously implementing operations tools like simulation modelling to improve performance and improve service delivery [8–10].

For decades, modelling has been employed in the pharmaceutical supply chain (PSC) [11–13], with the main focus on the blood system [14–17], vaccines [18–20] and medical oxygen SC [21–23]. Like any other SC in the healthcare sector, the medicine supply chain is vital, considered the blood life of the industry [24,25], having drugs flowing through the entire system. The reminder is that the quality of healthcare delivery depends on the availability of medicines at the right place, on time, in the right quantities, and on the quality to meet demand [26,27]. With the continuous demand for universal health coverage and achievement of the United Nations sustainable development goal (SDG) 3.8, it is essential to identify innovative approaches that can be used to ensure a well-functioning supply chain, best captured using simulation modelling. Simulation has the strength to evaluate the performance of medicine supply chains and experiment with different interventions to inform data-driven decisions [28].

We systematically review existing studies using simulation focusing on the different simulation techniques applied in the medicine

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supply chain, namely, discrete event simulation (DES), system dynamics (SD), and agent-based simulation modelling (ABM). The choice of simulation methods was made based on the review of simulation techniques used generally in supply chain management (SCM) across different industries and backed up by Kammoun, Loukil and Hachicha, who recommend reviewing the three simulation techniques [29,30]. By understanding the limitations and challenges faced by previous studies, we shape our study to address the gaps and contribute to the advancement in the field. We acknowledge that other modelling approaches have widely been used in the healthcare system and have proved helpful in decision-making [31–33]. [29,30] used mathematical modelling approaches, [34,35] combined simulation and optimisation to exploit each method's strength. Campuzano recommends reviewing studies combining mathematical and simulation modelling approaches to manage supply chains [30]. However, simulation offers comparative ease in incorporating complicated features of the entire system, which mathematical modelling-based methods fail to capture [36–38]. On the contrary, supply chain decision-makers in the healthcare sector consider simulation an alternative approach [39] while experimenting with solutions to support decision-making processes associated with various SCM problems [40,41].

Our study aims to contribute to the existing body of knowledge and ultimately enhance the efficiency and effectiveness of the medicine supply chain, leading to improved healthcare service delivery. Synthesising studies that applied simulation approaches provides valuable knowledge about the current and emerging trends of approaches in the medicine supply chain domain. Also, the study identifies gaps, the implication of simulation and their practical implementation in the real world. To the best of our knowledge, this is the first study systematically reviewing the application of simulation modelling tools on the medicine supply chain as a decision tool for improved service delivery. The study answers the following questions.

**RQ1.** How have discrete event, agent-based, and system-dynamics simulation modelling approaches been applied to medicine SCM?

**RQ2.** What is the impact of simulation modelling on supporting decision-making in the context of medicine SCM, and what gaps have been identified in the literature?

The paper is organised as follows: firstly, we present a conceptual framework while extracting variables of the study; we then discuss the current state of the art in research and breakthroughs in the field through a systematic literature review, identifying the different approaches applied to the medicine supply chain under distinct contexts; we recognise the impact simulation has played on medicine supply chain management and finally, propose gaps in studies that have used identified approaches.

## 2. Framework and variable extraction

### 2.1. Conceptual framework

In this section, we develop a conceptual framework identifying the variables to be captured in our study. Variables were extracted relying on research question 1: "How the different simulation approaches of discrete event simulation, Agent-based modelling and system dynamics have been applied to manage the medicine supply chains". The variables were selected based on the argument that the model development process is an iteration between the real and model world involving three properties of mapping, reduction and pragmatism [42] (Fig. 1). Mapping identifies the real-world medicine supply chain problem that needs a solution. This involves collecting data on the system and identifying the key performance indicators to be measured. The reduction formulates the problem in the real world into a model world through conceptualisation by determining key elements to be captured [42]. The third property of pragmatism defines guidelines followed in determining a simulation approach relating to implementing the solutions [42].

However, while defining the variables, we noticed that studies used the word approach [43–45] interchangeably to mean a simulation method [46–48] or a simulation methodology [49], contributing to the confusion. Also, verification and validation was found to be conducted throughout model development. To mitigate the confusion during analysis, we aimed to identify studies reporting verification and validation at the framework's conceptual and model-building stages.

#### 2.1.1. Step 1. Problem-identification

We included empirical papers that addressed a real-world problem. The first step involves a clear definition of the system and supply chain problems to be studied, the research question to be answered by the simulation, and the objectives and scope of the study. For every supply chain problem, we identify the country of the study, year of publication, and publication source. The year relates to the year of publication, as it was challenging to identify the year the study was conducted. The publication source refers to the journal or conference name disseminating the research; the supply chain problem refers to the issue or problem that requires an understanding. The country refers to the name of the country where the study was conducted; to mitigate any confusion, we refer to the country as "case study country". Supply chains have different decision points, with individual agents' rules affecting the system's entire performance; therefore, we include the decision level variable to understand the level at which the problem was investigated. The variables are added to understand the research's current and future trends, the different medical supply chain levels at which the issues were addressed, and the study's dissemination source. We also include the country of the study to understand whether the problems discriminated against the setting, are specific to a given country, or are similar across countries.

#### 2.1.2. Step 2. Conceptual modelling

The real-world system or problem is too complex and requires simplification. Simplification requires introducing the model input parameters and distribution assumptions to understand better and communicate the problem [50,51]. At this modelling stage, the modeller can use graphical tools to abstract the system, describing the problem in detail and the level of complexity needed, allowing easy problem communication with the owners. We include the variable to understand if there is one way in which the modellers communicate the problem to the owner. We include verification and validation at this stage to understand how existing studies checked for the accuracy of the conceptual description, including the defined underlying structural and logical simplifications in representing the system. We include the simulation approach variable to understand whether there is a relationship in the approach applied in addressing specific medicine supply chain problems. Also, we are interested in the relationship between the conceptual model and the simulation approach.

#### 2.1.3. Step 3. Model building

We are interested in the software package or programming language the modeller uses to translate the conceptual model into the computer. Model verification checks for model accuracy in representing the conceptual description, ensuring no errors, bugs or oversight [52,53]. Model validation checks for the correctness, reproducibility, robustness and reliability of the developed model in representing the real-world system, increasing the confidence in the model output against the real world [54–56]. We include the variable to understand whether and how medicine supply chain models have been verified and validated. During validation, we extract variables of simulation impact to comprehend whether the modeller's chosen approach impacts the medicine supply chain in a given setting.

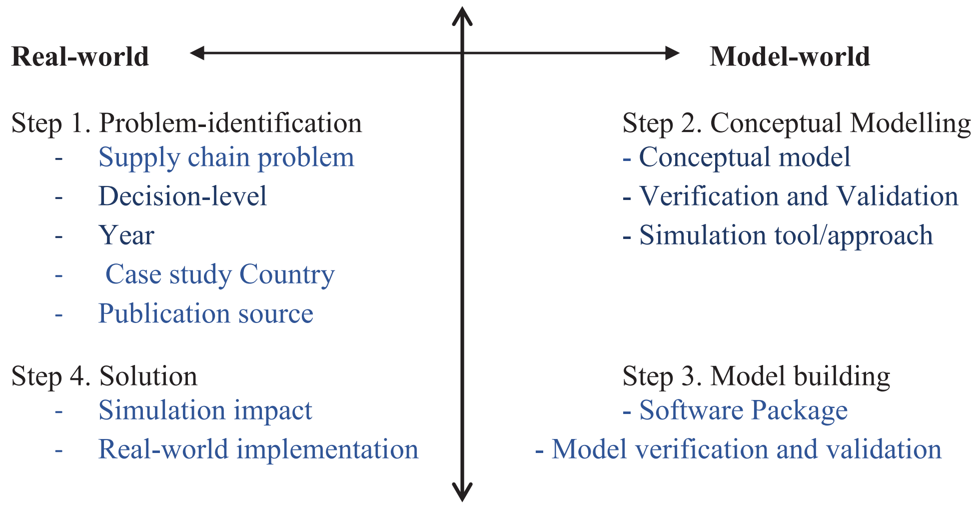


**Fig. 1.** Conceptual framework and study variables.

#### *2.1.4. Step 4. Solution*

To ensure improvement in any investigated system, the modeller communicates the model findings, insights and suggestions to the problem owner [42]. We are interested in studies whose models were implemented into real-world practice to understand whether policy-makers and decision-makers have confidence in the simulation models. Real-world implementation of the programmed model implies a useful model.

## 3. Literature review methodology

Our systematic review maps and assesses the existing intellectual territory on studies modelling the medicine supply chain using simulation. Our study builds on the current knowledge while identifying gaps in the literature on simulation tools used to inform decision-making while managing medicine supply chains. Decision-making tools refer to techniques, tools, methods, frameworks, approaches, and methodologies organisations use to support decision-making within strategic management [57]. Our review follows the criteria and methods with 4 steps described in Booth's search, Appraisal, Synthesis and Analysis (SALSA) guideline approach [58].

### *3.1. Search process*

Our search aimed to identify high-quality publications with high-impact factors. We searched three databases, Scopus, Web of Science (WoS), and PubMed, to develop an understanding of the application of simulation in the medicine supply chain state of the art and provide recommendations for improvement. The search involved keywords on "medicine supply* chain" OR "pharmaceutical supply chain" AND "simulation" AND NOT "vaccines*". We use the Boolean combination "AND" to include all terms that may be far apart; "OR" to have documents that contain any pharmaceutical supply chain, "AND NOT" to exclude a specific word of vaccines an asterisk "*" broadens the search results so we do not miss out on any relevant document.

#### *3.1.1. Study selection and eligibility*

To understand the current state of the art on simulation application, we include empirical studies from articles and conference papers to represent real-life findings [59]. Reviews were excluded from the study as they provide a summary of practical work with a contribution of identifying gaps. Journals and conference proceedings document types are considered for the search as information in these documents is either under study, or completed, or peer-reviewed, increasing the finding credibility and accuracy. Open-access paper documents in English, published between 2000–2023, were considered for the study. Initially, in the search, we included different healthcare products of blood and vaccine supply chains generating a large scope of results – these were excluded later as their management differed. Although all health-related supply chains are sensitive in dealing with perishable items, involving planning, making, sourcing, delivering and returning [60], some differences are unique to these three supply chains. For example, blood supply chains deal with donor banks [15,61] not present in the medicine supply chain, and vaccine supply chains require cold chains [62], which is not the case for medicines as they can be managed at any temperature level. We were interested in having an in-depth understanding and analysis of the application of simulation models in the medicine supply chain, which appeared to have fewer studies among the other supply chains; we included the search term "pharmaceutical supply chain" as some researchers use the terms interchangeably. During the search, we found that the word "medicine supply chain" is used interchangeably across fields of healthcare and agriculture, as both humans and animals use medicines. To mitigate any confusion that may arise in our results, we limit our search results to the keyword "human species", excluding keywords of "food supply, animals, cell culture, bone, bird disease, biochemicals, food chains, drinking water, agriculture disease management.

There is a high likelihood of bias during the entire search process, mitigated by leaving the search open to all countries and publisher sources to understand the differences in the problems by setting them and explaining how they are solved. Our search includes all research areas and publication sources to capture an in-depth understanding of the subject matter Emerald, Elsevier, ProQuest, IEEE, Springer, and Wiley. The initial search generated 320 studies across the three databases downloaded into Excel for the screening and filtration phase, including the inclusion-exclusion criteria, as illustrated in Fig. 2. We adopted a PRISMA statement (Fig. 2) in the study to report the systematic steps in conducting the literature search [63].

### *3.2. Screening and filtration*

#### *3.2.1. Inclusion exclusion criteria*

As shown in Fig. 2, 320 studies were considered for filtration and screening done in phases; in the first phase, 46 publications that crossed the three databases were eliminated, and 274 documents were considered for the second screening phase, which involved the application of the inclusion and exclusion criteria. We then read the title of each publication, and 143 documents were excluded. Based on the title, we excluded papers focusing on supply chains of food,

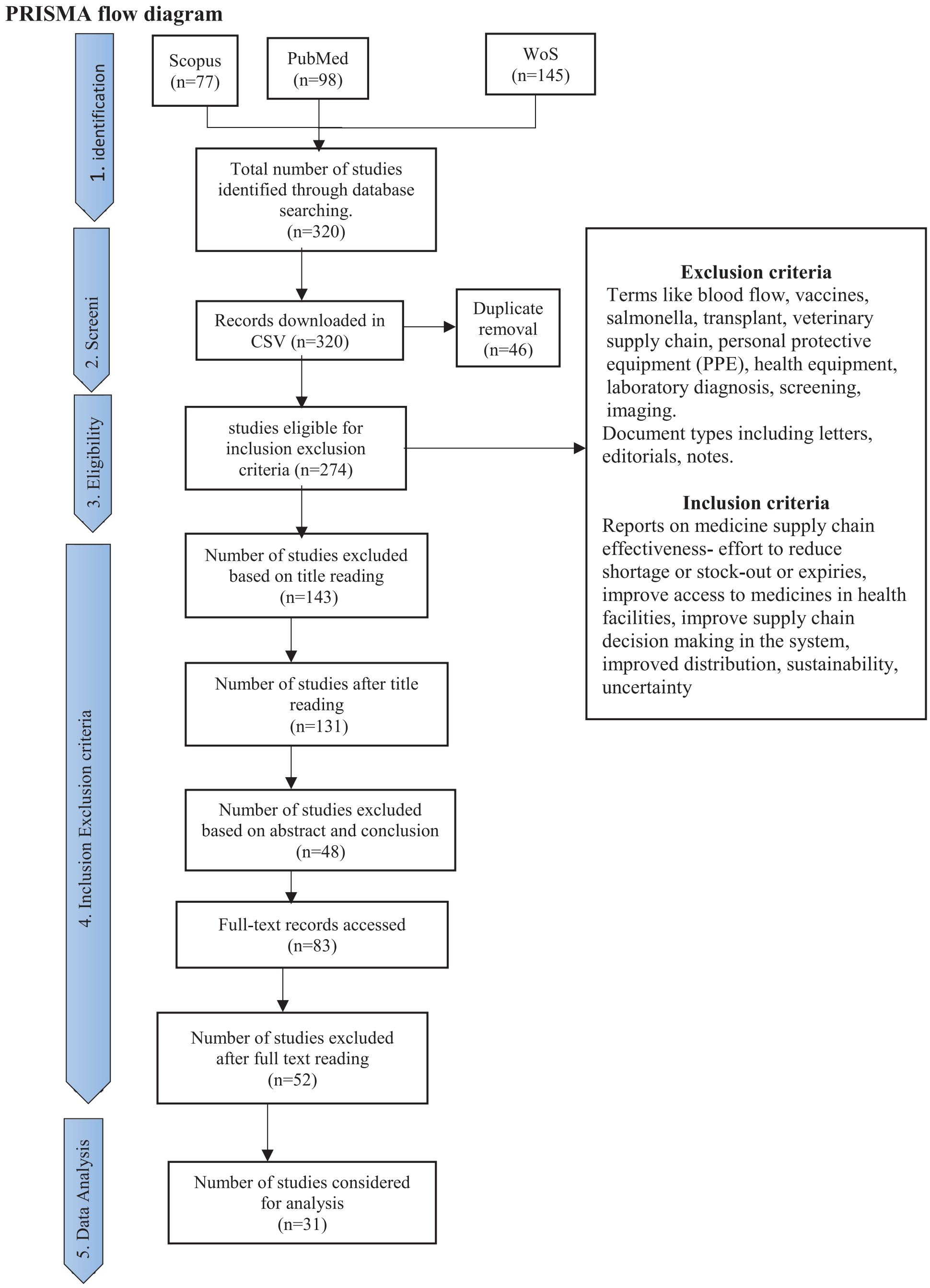


**Fig. 2.** Literature search process.

blood, vaccines and documents that had no relation to the pharmaceutical supply chain, inventory management, planning, uncertainty, and performance in healthcare. 131 papers qualified for the third phase requiring us to read the abstract and conclusion, of which 48 articles were excluded from the study. Documents had to demonstrate a strong relationship with using the simulation or modelling approach concerning the pharmaceutical supply chain to qualify for the next screening phase; the publication should have at least a sentence stating the application of the simulation technique in the management of the pharmaceutical or healthcare supply chain. Studies that used other modelling approaches in sectors of oil and gas, fashion, and agriculture were excluded, with 83 papers qualifying for full-text reading. During the full-text screening phase, we found that using simulation as a term was not straightforward, being referred to while applying optimisation methods, mathematical modelling, developing new tools, and neural networks to solve the problem, attributing to the exclusion of 52 papers. The use of discrete event simulation, system dynamics and agent-based modelling yielded a small number of publications; we, therefore, took a flexible approach by including articles using at least one of the simulation techniques alongside optimisation. 31 publications were analysed in our study as they met the inclusion criteria using one or more simulation tools (ABM, DES, and SD) to manage the medicine or pharmaceutical supply chain.

## 4. Results

In this study section, we answer research question 1, classifying the simulation application under various techniques and understanding how they were used to solve different medicine supply chain problems. We present findings using the tabulation method to improve readability

**Table 1**
Dissemination of studies.

| Publication source | Count | Percentage |
|---|---|---|
| American Journal of Tropical Medicine and Hygiene | 2 | 6 |
| Annals of Operations Research | 1 | 3 |
| Applied Mathematical Modelling | 1 | 3 |
| BMC Public health | 1 | 3 |
| DARU, Journal of Pharmaceutical Sciences | 1 | 3 |
| First international conference on Advances in system simulation | 1 | 3 |
| Health Policy and Planning | 2 | 6 |
| IEEE | 1 | 3 |
| IEEE International Conference on Industrial Engineering and Management | 1 | 3 |
| IIE Transactions on Healthcare Systems Engineering | 1 | 3 |
| International Journal Health Care Quality Assurance | 1 | 3 |
| International Journal of Industrial Engineering | 1 | 3 |
| International Journal of Production Research | 1 | 3 |
| Iranian Journal of Pharmaceutical Research | 1 | 3 |
| JASS - The Journal of Artificial Societies and Social Simulation | 1 | 3 |
| Journal of Open Innovation | 1 | 3 |
| Journal of quality engineering and production optimisation | 1 | 3 |
| Journal of the Operational Research Society | 2 | 6 |
| Operational Research Society 10th Simulation Workshop - Proceedings | 1 | 3 |
| PloS one | 2 | 6 |
| Procedia Engineering | 1 | 3 |
| Proceedings of the Annual Simulation Symposium | 1 | 3 |
| Proceedings - Winter Simulation Conference | 1 | 3 |
| Proceeding of the Estonian Academy of Sciences | 1 | 3 |
| Processes | 1 | 3 |
| Sustainability (Switzerland) | 1 | 3 |
| System Dynamics Review | 1 | 3 |

and illustrate the aims of studies in applying the modelling approach as a decision tool in the medicine supply chain (Table 3). Although the timeline is limited to 2000, this does not imply that simulation has not been used in healthcare, a lot of studies focused on waiting times, blood supply chains, vaccine supply chains, disease spread, and treatment outcomes. Based on our analysis, the first publication was observed in 2009, simulating the European pharmaceutical supply chain incorporating legal requirements using realistic data to inform the increasing amount of counterfeit pharmaceuticals [64], then in 2010, conducted in the Netherlands, supporting intake and treatment processes in mental health using system dynamics. The outbreak of the COVID-19 pandemic showed a drastic increase in the number of studies (n = 10) between 2019 and 2020, demonstrating the increasing need for resilient supply chains. This relates to the observed multidisciplinary research disseminated across fields, demonstrating collaboration between operations and the health sector (Table 1).

Medicine and supply chain management are two fields relating to the observed work disseminated in health and management science (see Fig. 3). 71% (22 publications) were disseminated in article sources, with 42% (n = 13) from the health sector and 29% (n = 9) from operations management. We found 50% (n = 9) of the dissemination in the operations management to be from a conference proceeding of System Dynamics Review, IEEE, proceedings-winter simulation conference. However, we found the conference work to be work in progress.

**Table 2**
Issues in the medicine supply chain.

| Reference | Medicine supply chain problem | Case study country | Number | Percentage |
|---|---|---|---|---|
| [40,43,67,68] | Medicine availability | USA, India, South Africa, Kuwait | 4 | 13 |
| [41,69,70] | Agent behaviours | Iran, Ghana, Tanzania, USA | 3 | 9 |
| [68,71–75] | Stock-outs/ shortages | China, India, Zambia, South Africa, USA | 6 | 19 |
| [76–80] | Falsified/ Substandard/ counterfeit | Benin, Nigeria, Zambia, Uganda, DRC | 5 | 16 |
| [40,81–83] | Cost | Kuwait, Colombia, Iran | 4 | 13 |
| [79] | Equity | Uganda | 1 | 3 |
| [84] | Medicine intake | Netherlands | 1 | 3 |
| [85] | Low shelf life | India | 1 | 3 |
| [86–89] | Supply | Morrocco, USA | 4 | 13 |
| [43,89,90] | Uncertainty | Tunisia, Norway | 3 | 9 |

Some studies captured more than one medicine supply chain problem.

Papers included in the study are listed in Table 3 in descending order of publication, showing the research effort in the past two decades. Publications analysed in our study are observed cutting across continents, with most of the studies from Asia (n = 10) and Africa (n = 10), followed by America (n = 4), Europe (n = 3), no mention (n = 3), and global (n = 1). The increasing work in low and middle-income countries (Asia and Africa) relates to the medicine supply chain characteristics of poor infrastructures and limited resources, making it difficult to ensure medicines reach everyone in a timely and efficient manner [65,66].

Table 2 shows that medicine supply chain problems are complex, not discriminating among countries with the most investigated issue of shortages or stock-out at 19% (n = 6) in India, the USA, China, Zambia and South Africa. 16% (n = 5) of studies were found to report on falsified or counterfeit medicines in Uganda, Benin, Nigeria, Zambia and the Democratic Republic of Congo (DRC). 13% (n = 4) of studies were found to capture medicine availability, 13% (n = 4) focused on minimising cost and 13% (n = 4) addressed supply-related problems. Equity, medicine intake and shelf-life were the least evaluated issues at 3% (n = 1). The medicine supply chain problems are found to be hybrid, stemming from the downstream and upstream chains. 48% (n = 15) of studies focused on a single decision point, with 60% (n = 9) exploring the downstream echelons of hospitals and patients and 40% (n = 6) assessing the upstream manufacturers, suppliers, and distributors. 19% (n = 6) focused on both the upstream and downstream echelons, whereas 23% (n = 7) did not mention the supply chain level.

57% of analysed studies used Causal loop diagrams, and stock flows to conceptualise the problem, followed by flow charts (21%), mapping the business process (14%) and the Supply Chain Operation Reference framework (7%). Results show system dynamics (SD) 42% (n = 13) was the most applied approach spanning from 2010 to 2022, followed by 29% (n = 9) of the studies using DES between 2009 and 2023. 23% (n = 7) of the studies were found to apply ABM, with the first publication in 2018 and a drastic increase from 2019 to 2023. Few studies (6%, n = 2) were found to combine more than one simulation approach (hybrid model); this was not a surprise, as hybrid modelling is reported to be complex.

## 5. Discussion

### 5.1. Research trend

The trend in research is evidence that there is a high likelihood of a gradual rise in research applying simulation in the medicine

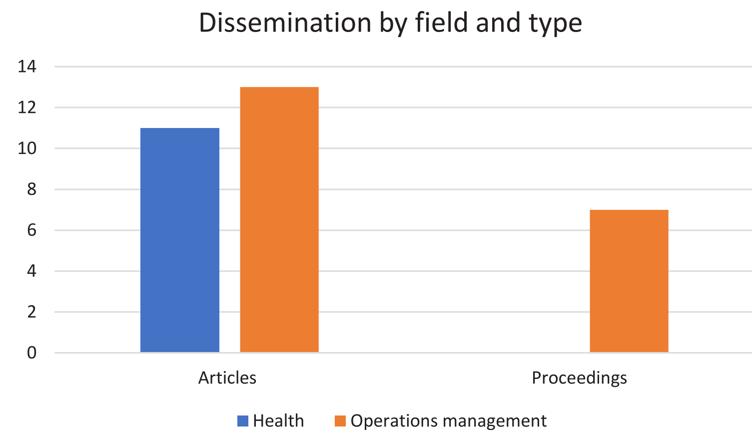


**Fig. 3.** Dissemination categorisation by field and type.

supply chains to inform decision-making worldwide. With most work disseminated from health journals, researchers should be encouraged to seek operations research (OR) journals as they get peer-reviewed feedback on different applied tools and frameworks. With most of the analysed studies in the OR field disseminated in the conference proceeding, more empirical research from the operations articles will generate transparency and evidence for decision-making about the interventions likely to return the best value in the health sector. The dissemination findings in health and OR is evidence that problems in the medicine supply chain are complex, requiring collaboration among disciplines, as each field comes with its core knowledge and expertise. Medicine personnel are experts in treating everyone; management scientists use different operations research tools to promote the effective implementation of various policies worldwide while creating a deeper understanding of the system's possibilities and challenges. The scientific and independent attitude will yield valuable insight and practical advice for strengthening pharmaceutical services.

### *5.2. Application context*

We found that studies addressed medicine supply chain problems of uncertainty, availability, shortages, low-shelf life, quality, cost and behaviour of agents across the continents of Africa, Asia, America, and Europe in countries of Netherlands, USA, Columbia, India, and Norway. The finding is consistent with Pauwels [95], stating that the challenges in the medicine supply chain do not discriminate against the different categories of hospitals but differ across regions, countries, types of drugs, causes, and strategies adopted. Most of the studies focused on stockouts relating to the identified studies on falsified or counterfeit medicines and cost. This suggests that people resort to cheaper generics on the market with the need to minimise the cost of medicines. Also, the falsified studies identified on the African market suggest weak regulations in these areas.

One study focused on manufacturers dispersed across the world [87] relating to the difference in an individual country's policies and guidelines and the purpose of achieving the United Nations Sustainable Development Goal (SDG 3) of Universal Health Coverage (UHC). This suggests that, generalising an intervention across all medicine supply chains may be challenging. However, a study evaluating agent's behaviour in Tanzania and Ghana [69], demonstrated the possibility of generalising a solution across countries with similar medicine supply chain characteristics and problems.

### *5.3. Decision level*

We found that problems in the medicine supply chain are hybrid, stemming from both the demand and supply sides, requiring holistic solutions. Most of the addressed supply chain problems were at a single echelon, creating a gap, as a solution at one level directs towards investigating the preceding stage. This suggests the need for a pragmatic viewpoint while deriving a solution from more than one echelon of the downstream and upstream on the problem under study. However, simulating a multi-echelon supply chain is challenging and complex as it requires many variables and a large amount of data and time.

### *5.4. Conceptual models*

There is no one way to conceptualise a problem, suggesting the decision lies with the modeller. We found that using visual representations in abstracting the model helped communicate the problem. For example, studies used Failure Mode, Effects and Criticality Analysis (FMECA) to identify risks in the supply chain [90], cause and effect diagrams and causal loop diagrams (CLDs) reported describing relationships and feedback between the main problem variables [71,74]. Oruba mapped the antimicrobial supply chain in Bangladesh using the Business Process Map Notation (BPMN) [96]. BPMN is a decision support tool used to understand the organisation's operations and interactions and identify interventions for process improvement [97,98]. The use of different visual representations suggests that modellers understand the problem differently. This relates to Meadows, who reports that conceptual models keep changing with the environment, challenging the supply chain agents to continually align their strategies with current and future states, which look different [50].

However, we found a commonality in studies using CLDs and stock flow diagrams applying the SD approach, and mapping studies using DES. The finding relates to Behdani, Sergeyev, and Lychkina, who state that a simulation approach exists in the system conceptualisation and not in its implementation [99,100]. However, other studies argue that the simulation approach lies in the skills and knowledge of the modeller [30,101,102]. Based on the debate, there is a need to justify what informs the choice of a simulation approach.

### *5.5. Simulation approaches*

The finding is surprising as simulation has widely been applied across industries and healthcare supply chains, especially blood [15,103,104] and vaccines [18–20]. The findings relate to most healthcare studies using qualitative methods to improve the medicine supply chain performance while identifying technologies and innovative strategies [105,106]. We also found that no specific simulation approach is assigned to solving a particular problem in the supply chain. Viana and others [43] used ABM and Kumar in 2014 [67] used SD to simulate the behaviour of the medicine supply chain relating to AbuKhosa, who argue that the choice of the simulation approach should be informed by the problem and built to answer specific questions to represent the problem accurately [107,108].

**Table 3**
Summary of analyses studies in ascending order of publication.

| Reference | Aim | Approach | Case study country |
|---|---|---|---|
| [64] | To incorporate legal requirements using realistic data to inform the increasing number of counterfeit pharmaceuticals | DES | Europe |
| [84] | To support the management of intake and treatment processes in mental health care | SD | Netherlands |
| [90] | To assess the risks in the supply chain of a drugstore | DES | Tunisia |
| [91] | To evaluate the configuration of direct shipping to hospitals from manufacturers | DES | – |
| [67] | To assess the availability of folic acid medicines at three stages of the supply chain | SD | India |
| [71] | To assess the shortage of folic acid | SD | India |
| [72] | To investigate the problems of high drug shortage possibility and rupture of liquidity in the drug supply chain of public hospitals in China | SD | China |
| [73] | To characterise the impact of widespread inventory management policies on stock-outs of essential drugs | DES | Zambia |
| [68] | To evaluate the effect of drug shortage on estimating the infectivity of antiviral-treatable epidemics. | SD | USA |
| [74] | To evaluate the impact of potential changes in SCM and develop solutions to challenges faced in the SC. | SD | South Africa |
| [86] | To analyse an effective inventory control method of the wholesaler in the medicine | DES | – |
| [92] | To show a trade-off between the total inventory cost and the needed service level | SD | – |
| [41] | To simulate the behaviour of the two SC echelons of manufacturing and sales, capturing the behaviour pertinent to receiving and ordering | ABM | Iran |
| [93] | To eliminate Medicine stock-out problems in the supply chain | SD | India |
| [76] | To evaluate the impact of interventions to improve medicinal quality | ABM | DRC |
| [78] | To capture the impact of antimalarial use on children under five | ABM | Nigeria |
| [79] | To assess the health equity impact of substandard antimalarials among children under five years | ABM | Uganda |
| [69] | To demonstrate how buyers can learn about the quality of sellers (and their medicines) based on previous successful and unsuccessful transactions, thereby establishing trust over time | ABM | Ghana & Tanzania |
| [40] | To increase the availability of drugs and minimise the overall costs | DES | Kuwait |
| [81] | To simulate the behaviour of the change in the internal costs of medicines in hospitals. | SD | Columbia |
| [77] | To examine the health and economic impact of poor-quality antimalarials on children under five | ABM | Zambia |
| [70] | To assess the impact of drugged driving per se law on crash fatalities | SD | USA |
| [82] | To predict the price of amoxicillin capsules and volumes of production, taking into consideration the cost of raw materials and the producer's profit | SD | – |
| [80] | To assess the health and economic impact of falsified antimalarials | ABM | Benin |
| [43] | To evaluate the medicine SCs' resilience and disruptions in severity and durations at the different SC echelons. | DES, ABM & SD | Norway |
| [85] | To simulate the low-shelf life of medicines in the supply chain | SD | India |
| [83] | To identify elements influencing the sale of generic products during their life cycle to achieve more comprehensive planning | SD | Iran |
| [89] | To support informed and effective decision-making during uncertainty | ABM & DES | North America |
| [87] | To investigate the logistics levers of pharmaceutical manufacturing firms exposed to significant degrees of uncertainty | DES | Global |
| [88] | To provide a simulation-based approach to guide decision-making in a distribution inventory system | DES | Morrocco |
| [94] | To understand the impact of ripple effect in the pharmaceutical supply chain during the COVID-19 pandemic disruption | DES | India |

On the contrary, different approaches were used to describe the same supply chain problem. For example, in 2015 Kumar used SD to eliminate folic acid tabs stock-outs in India [58]. Paul and Vekateswarna used SD to evaluate the effect of drug shortage on estimating the infectivity of antiviral-treatable disease epidemics [68]. Evans used agent-based modelling (ABM) to investigate the issue of poor-quality antimalarials in Uganda [79]. Ackland used ABM to simulate trust between the buyer and how buyers can learn about the quality of sellers (and their medicines) based on previous successful and unsuccessful transactions, thereby establishing trust over time [69]. Ghatari uses ABM to simulate the agent behaviour [41]. Our findings align with Cope, Campuzano and Sanchez, who argue that the choice of the simulation approach depends on the modeller's more significant level of familiarity and skills [30,101,102]. This relates to the real-world scenario of eating rice; one may choose to use their hands, a spoon, fork, or chopsticks; the aim is the same as "eating the rice".

Although the choice of simulation approach relates to the modeller's power in choosing the paradigm of the problem under study, every approach has its unique underlying assumptions. SD assumes that the world comprises rates, levels and feedback loops [50]. Mancal and North argue that DES assumes the world as a process with a sequence of steps simulating changes in a system over time [109], and ABM is a bottom-up approach, capturing agents by agents and interactions by interactions [110].

#### 5.5.1. System dynamics

In our study, we found that System Dynamics (SD) is the most applied approach to minimise medicine shortages [71,72,75], improving the availability of medicines [74,92], minimising medicine costs [81, 82], medicine intake and treatment processes [70,84], the effect of drug shortages on estimating infectivity [68] and medicine low-shelf life [85]. SD is mostly used because of its ability to evaluate different strategic policies, integrate system feedback and delays, and assess relationships between variables and their impact on behaviours [81]. However, medicines supply chains deal with several global networks each having individual behavioural rules governing their operations. SD is reported insufficient to capture these heterogeneities and numerousness [99], a merit of ABM [41].

#### 5.5.2. Agent-based modelling

Supply chains consist of decision levels with individual agents at each echelon operating towards achieving distinct goals, with the behaviour of one agent in the system affecting everyone else in the system. This is attributed to various studies applying Agent-Based modelling (ABM) to simulate the behaviours of individual agents. Pourghahreman and colleagues evaluate the behaviour of the manufacturing and sales agents in the Iranian pharmaceutical supply chain [41]. A study applying ABM in Ghana and Tanzania found that learning from experience and establishing a trusted network eliminates low-quality drugs from the supply chains [69]. In 2019, Ozawa and colleagues applied ABM to evaluate the health and economic impact on the quality of antimalarials in DRC [76]; the analysis did not distinguish which drugs may have resulted from poor manufacturing versus product degradation or improper cold-chain management. Evans and colleagues used ABM in the Ugandan context to assess the health equity impact of substandard antimalarials among children under five years, comparing the rural and urban areas [79]. Although ABM has merits over SD, ABM is inadequate in representing the operational process of the SC network [46], which SD and DES can do. However, DES best represents the linear processes in a SC happening at a specific time [111], whereas SD operates at a macro level, capturing high-level system behaviours.

#### 5.5.3. Discrete event simulation

Of the 31 studies analysed, only 9 applied discrete event simulation (DES). Our findings are surprising, as DES has widely been applied across supply chains in different sectors since the introduction of simulation in the 1950s, with its first application in healthcare used to hospital admission in 1954 [112]. In 2012, Niziolek used DES to evaluate direct shipping and found that shipping directly to hospitals without a warehouse reduces transportation and drug costs [91]. In 2017, Kim and Lee used DES to analyse the effective inventory control method of the wholesaler in the medicine supply chain [86]. Al-Fandi and colleagues used DES to increase medicine availability while satisfying customer demand and reducing backorder holding and ordering costs [40]. They found a statistically significant improvement in each medicine's price and fill rate. Leung and colleagues apply DES in Zambia to capture the dynamism in an inventory control tool while identifying the relevant time steps of the occurrence of replenishment and demand [73]. Diaz and colleagues use DES to investigate the logistics levers of pharmaceutical manufacturing firms exposed to significant uncertainty [87]. Sbai and Berrado simulate decision-making in a Morrocco distribution inventory system [88].

Although simulation modelling calls for simplicity, which can be obtained from the use of a single method, 94% of the analysed studies applying either SD, ABM, or DES, show the inefficiency of a single approach to capture all aspects of the supply chain [72,74]. Our findings show most studies applying a single approach demonstrate the approach's strengths and weaknesses, with only one technique rarely possible to solve the problem independently [113]. This calls for the need to combine more than one approach to investigate the medicine supply chain problems [114–116].

#### 5.5.4. Hybrid modelling

Combining more than one technique is called hybrid modelling [117], having merit over a single approach [118]. Mustafee, Powell and Brailsford define hybrid simulation as combining at least two DES, SD, and ABM approaches to explore a problem [119,120]; with the benefits observed in the strengths of each approach [121], naturally increasing the confidence in the obtained solutions [122]. Of the 31 analysed studies, two studies applied more than one approach. Silva and colleagues combined ABM and DES to simulate North America's supply chain resiliency and sustainability [89]. ABM was used to model the agent's decisions and interactions based on their rules and behaviours, and DES modelled a sequence of events occurring at discrete points in time [89]. In 2021, Viana, Van Oorschot and Årdal combined SD-DES-ABM to evaluate the time it takes for the medicine SC to recover from disruption. SD-DES is used to satisfy orders, make shipments, transform raw materials into finished inventory, and create active pharmaceutical ingredients [43], where the supplier receives orders via the ABM, added to DES to process the queue [43]. It was, however, reported that hybrid simulation increases model complexity and reduces accuracy, which can be solved by developing the methods separately, as each is suited to solve the problems only in one kind of contextual problem [123].

### 5.6. Software package

We found that the software used to implement the model varied by study. This implies that a choice is based on availability and the modeller coding knowledge and skills. We found Netlogo to be the most used for ABM, Venism software, iThink, and Stella platform used for SD. Arena, Flexism, Extend, and Simul8 were used for Discrete Event Simulation. Anylogic was the least-used software package for developing hybrid models relating to package availability at a cost and the need for advanced programming language knowledge [124]. Although analysed studies highlighted these software packages, other packages exist, like SWARM, MASON, and Simio. The existence of multiple software demonstrates the trend in programming languages from FORTRAN and the computer strength compared to the early 1950s when model input was in the form of punched cards and paper tapes.

### 5.7. Verification and validation

A popular saying goes that all models could be considered 'wrong' (in the sense of not fully reflecting reality), but some are valuable in one way or another [125]. To be considered useful, models must be verified and validated to reflect their accuracy and realism in representing the system under investigation. 32% (n = 10) studies reported verifying and validating either the conceptual or simulation model with 3% (n = 1) validating both the conceptual and simulation. Diaz, Kolachana and Falcão Gomes verified and validated the model conceptually and operationally using structured walkthroughs with the users and tracing [87]. Although one study was identified to report conceptual model verification and validation, this does not imply that other studies did not confirm the correctness of their conceptual abstract. Viana, Van Oorschot and Årdal use extreme value tests, structured walk-throughs, and tracing [43]. Studies compared the model inputs against the model output, identified variables with the most significant impact on the system performance [39,81]; sensitivity analysis was used to determine the effect of lead time on medicine stock-outs [71]. Studies reported the lack of data to inform the model validation process [72,88]; relating to the two studies using real data of the system to build confidence [75, 79].

Musatfee and Powell added that hybrid simulation models' verification and validation challenges can be complex due to the interaction of multiple simulation paradigms across agents, requiring many stakeholders to verify and validate [120]. This relates to our findings on studies applying more than one approach, relying on hypothetical data derived from qualitative interviews and publicly available reports, and identifying and including historical quantitative data for validation [43].

### 5.8. Impact of simulation on decision-making

In the section, we answer RQ2 while identifying the impact simulation modelling has on medicine supply chain management. Simulation application has the strength to capture complexities, emergencies, dynamism, and interconnectedness in the medicine supply chain while identifying areas of improvement in service delivery and performance [8–10].

Simulation has proved to cope well with the complexity of the medicine supply chains, as it identifies bottlenecks in the system [111]. Using SD in South Africa's amikacin supply chain, Bam and others identified inefficiently high shortages and long lead times with suppliers accommodating unexpected changes in demand [74]. Using ABM on Uganda antimalarials, Evans found that rural populations experienced 97.9% of the deaths due to poor-quality antimalarials and paid 10.7 times as much for the medicines annually in out-of-pocket expenses compared to urban people [79], using SD in India, Kumar and Kumar identified several medicines stockouts due to uncertain lead times and demand [75]. Pourghahreman and colleagues found that the manufacturing and sales agents in the Iranian pharmaceutical supply chain were not agile [41]. An SD simulation identified a huge stock-out at the different stages of the supply chain, leaving many patients unserved, with few echelons keeping an excess quantity of medicine [71].

Given the budgetary policy under which healthcare operates, simulation has shown to save money [30]. Simulation modelling was seen to experiment with different interventions before real-world implementation [28,116]. Using SD, Kumar and Kumar experimented with different interventions and recommended redistribution of the additional amount of medicines among various nearest parallel stages before expiry [71]; Bam and others in 2017 recommended changes to SCM in South Africa could improve service delivery, leading to an estimated 19,200 shortages and incurs an estimated cost of $880,000 [74]. Testing different interventions with ABM, Ozawa found that the provision of access to quality-assured ACTs and quality antimalarial treatments could reduce the economic impact of malaria by 35%–43% ($p < 0.01$) and decrease deaths by 33%–43% ($p < 0.01$) [76]. Using ABM, Evans found that educating caregivers in Uganda to reject non-ACT treatment had the most significant effect on health equity, benefiting the rural population, reducing deaths by 4.9% and improving the availability of antimalarials at public health facilities [79]. Using ABM, Beargie and others found that the northern regions of Nigeria had a greater burden of antimalarials, with 9700 deaths of under-fives compared to the other areas, with total economic losses accounting for $698 [78].

Simulation efficiently develops rational implementation plans [108]. In 2014, Kumar suggested that various inventory control models can be applied to maintain the optimum quantity of medicine at each stage [67]; in return, Leung used DES in Zambia to evaluate the max–min inventory policy, offering a relatively predictive accuracy and reproducing critical features of actual stock-outs [73]. In 2015, Kumar suggested that their SD model is a prediction tool that can support policymakers on the procurement and supply of folic acid to the entire state of India [71]; in 2019, Beargie recommended that policymakers and donors need to understand the problem and implement interventions to reduce the impact of falsified antimalarials in Nigeria [78]. Franco recommends that the final cost of medicines is not static as it is affected by different factors [81]. The hybrid SC model suggests its capability to absorb and recover from any examined disruptions when implemented interventions [43]. An SD model by Paul and Venkateswaran informs policymakers that the standalone disease transmission model overestimates infectivity compared to an integrated model [68]. The findings are consistent with studies, noting that simulation assists in better decision-making [40,41,49].

Developing any model requires large amounts of data to sufficiently capture the system behaviour [113]. However, most of the analysed studies failed to capture all aspects of the system due to insufficient data limiting the model outcome and real-world applicability [119]. The SD model in South Africa could not capture population and seasonality variables [74]. ABM model in DRC was unable to examine the heterogenous impact within the population [76]; a gap filled by Evans in 2019 in Uganda while simulating the natural heterogeneity across population characteristics, risk of malaria infection, disease outcomes and associated costs; however, it lacked data on the prevalence of substandard medicines [79].

### 5.9. Real-world implementations

We found no model has been implemented in the real-world relating to a 3% (n = 1) study reporting the involvement of the model users in the conceptual and simulation model verification and validation process. Our finding questions the correctness of the model to inform decision makers on improving the system using developed models. This finding is consistent with Stulens and colleagues, who found a gap between simulation theory and practice, as models developed in low and middle-income countries (LMICs) were never implemented [126]. Of interest is that randomised control trials have been implemented such as an inventory control mechanism in Zambia [127].

## 6. Conclusion and future studies

Publications included in the study hold a high impact based on the searched databases, with most of the studies from low and middle-income countries (Asia and Africa) relating to the World Health Organisation reporting that half of the world population and nearly 2 billion people in low-middle-income countries lack total access [128]. Given the complexity of the medicine supply chain dealing with uncertainty and operating under constrained budgets with a goal of improved service delivery, a practical problem emerging in the SCM theory has great potential for researchers using simulation to contribute to healthcare.

We acknowledge several limitations of our study. First, our analysis is based on three databases, contributing to search bias as some important publications may only exist in the excluded databases. Using specific keywords in the search process and the inclusion-exclusion criteria explains the small number of studies that qualified for analysis. A bias was generated during the screening and eligibility process, as papers not relating to pharmaceutical or medicine supply chain, simulation, and modelling in their title or abstract were excluded; some valuable articles may have been eliminated in due course. Focusing only on the supply chain keywords may have excluded many papers; however, the inclusion of articles from across the world and publication sources mitigated the selection and quality bias. Although we could have generated a larger pool of publications, analysing a more extensive collection is beyond the capability of an in-depth analysis, providing an opportunity for future studies to explore work on medicine supply chain management.

We found that the medicine supply chain deals with complex issues from both the demand and supply sides, requiring rigorous decision-making methods of simulation. The number of studies analysed in our study is evidence that the application of simulation is less in the context of the medicine supply chain, a pivot of the healthcare system. Studies focused on improving service delivery, mainly using SD to ensure the availability of medicines and eliminate shortages or stock-outs. DES is the second most applied approach capturing operation problems of supply, inventory control mechanisms, and risks in the pharmaceutical supply chain; the ABM approach focuses on supply chain agents' behaviours. A reminder is that the supply chain is a complex hybrid system composed of continuous material, agent behaviour, and discrete information flows with a single approach reported insufficient to solve the issues. With only two studies combining more than one approach, more effort is needed to employ hybrid simulation (integrating DES with ABM or SD) examining the medicine supply chain. Also, future studies could consider using the different keywords to systematically identify trends in studies adopting hybrid simulation modelling in medicine supply chain management and their implication on decision-making. Although using more than one modelling approach is considered to capture all aspects of the problem, this requires data availability, a challenge reported by our study. Improved data keeping on real-world problems or systems could benefit model input values and verification and validation, boosting the users' confidence in implementing the models and proposed interventions in practice.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

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