A Dynamic Machine Learning Framework for System-Wide Drug Shortages Prediction and Autonomous Supply Chain Rerouting in U.S. Healthcare Infrastructure

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Date; July 21, 2026

Abstract

Drug shortages represent a persistent and escalating crisis within the U.S. healthcare system, threatening patient safety, inflating operational costs, and exposing fundamental vulnerabilities in pharmaceutical supply chains. Despite increasing awareness, current shortage management remains predominantly reactive, relying on manual tracking and static forecasting methods that fail to capture the complex, dynamic nature of supply disruptions. This study addresses this critical gap by developing and validating a dynamic machine learning framework that integrates predictive analytics with autonomous supply chain rerouting capabilities. The proposed framework employs a hybrid architecture combining Gradient Boosting, Random Forest, and a Dueling Double Deep Q-Network (D3QN) to forecast shortage probabilities up to 90 days in advance, coupled with a reinforcement learning-based rerouting agent that dynamically adjusts procurement pathways upon shortage confirmation. Retrospective analysis of FDA Drug Shortages Database records (2018-2026) and CMS Medicare Part D utilization data demonstrates that the framework achieves 89.4% prediction accuracy (AUC-ROC = 0.92), outperforming baseline static models by 22.3%. The autonomous rerouting mechanism reduces estimated shortage impact duration by an average of 18.6 days compared to manual intervention benchmarks. This research provides a validated, replicable framework for transitioning healthcare supply chain management from reactive crisis response to proactive, data-driven resilience.

Keywords: Drug Shortages, Machine Learning, Supply Chain Resilience, Reinforcement Learning, Healthcare Infrastructure

1. Introduction

1.1 Background

Drug shortages have emerged as one of the most intractable challenges confronting the U.S. healthcare system, affecting patient care, escalating costs, and placing unsustainable burdens on clinicians and pharmacists. The American Society of Health-System Pharmacists (ASHP) has tracked active drug shortages continuously since 2001, with the number of new shortages identified annually remaining persistently high over the past decade (Ventola, 2018). These shortages span a wide range of therapeutic categories, including life-saving oncology agents, antibiotics, and emergency medications, creating clinical scenarios where alternative therapies are suboptimal or unavailable.

The etiology of drug shortages is multifactorial, stemming from interconnected vulnerabilities within the pharmaceutical supply chain. Manufacturing quality issues, raw material unavailability, regulatory actions, sole-source supplier dependencies, and sudden demand surges during public health emergencies all contribute to disruption risk (Fox et al., 2019). The COVID-19 pandemic starkly illuminated these vulnerabilities, as supply chains strained under unprecedented demand for critical drugs while manufacturing facilities faced shutdowns and logistics networks fractured. In the U.S., supply chain inefficiencies account for approximately 25% of hospital operating costs, highlighting the systemic economic burden (Ahmed, Hossain, & Hasan, 2026).

The operational consequences of drug shortages are staggering. U.S. hospitals allocate over $900 million annually and expend more than 20 million labor hours addressing medication shortages, with 43% of institutions reporting medication errors directly associated with these shortages (Socal et al., 2025). A recent survey of 437 hospital pharmacy professionals found that 78.3% cited drug shortages as their top challenge for the seventh consecutive year, with 60% managing more than 10 active shortages simultaneously (Managed Healthcare Executive, 2026). Despite this persistent burden, the predominant approach to shortage management remains reactive, with 69.7% of pharmacy professionals relying on spreadsheets and manual tracking tools (Managed Healthcare Executive, 2026).

1.2 Problem Statement

The limitations of existing approaches to drug shortage prediction and management are well-documented but inadequately addressed. Traditional forecasting methods, including time-series analysis and simple regression models, treat shortage prediction as a static classification task, failing to capture the dynamic, sequential nature of supply disruptions (Ala et al., 2026). These models typically ignore the asymmetric consequences of prediction errors: missed shortages (false negatives) can result in treatment delays and adverse patient outcomes, while false alarms (false positives) may trigger unnecessary emergency procurement costs and supplier switching.

Conventional supply chain management practices compound this problem through several critical gaps. First, the reliance on manual tracking and spreadsheet-based workflows introduces significant delays between shortage detection and response, with pharmacy professionals spending between 3 and 20 hours weekly managing shortages (Managed Healthcare Executive, 2026). Second, the fragmented nature of healthcare supply chains—involving multiple manufacturers, distributors, group purchasing organizations, and individual healthcare facilities—prevents the system-wide visibility necessary for proactive coordination. Third, existing tools provide predictions without actionable decision support, leaving procurement managers to manually interpret forecasts and determine appropriate responses without systematic guidance on optimal rerouting strategies.

Recent advances in machine learning have demonstrated promise in addressing these limitations. Studies have applied Random Forest, Gradient Boosting, and deep learning models to drug shortage prediction, achieving improved accuracy over traditional approaches (Ala et al., 2026; Gali, Molavi, & Alavi, 2025; Dharavath, 2025). However, these efforts have focused predominantly on prediction accuracy rather than building integrated frameworks that translate forecasts into autonomous, optimal supply chain actions. Furthermore, existing models rarely incorporate the asymmetric cost structure of shortage management or embed prediction within a sequential decision-making framework that reflects how supply chain actors respond to evolving risks (Ala et al., 2026).

The specific unsolved problem, therefore, is the absence of a validated, integrated framework that combines dynamic shortage prediction with autonomous, cost-sensitive supply chain rerouting capabilities in the U.S. healthcare context. This gap prevents healthcare organizations from transitioning from reactive shortage management to a proactive, resilience-oriented operational model.

1.3 Objectives of the Study

General objective:
To develop and validate a dynamic machine learning framework that integrates system-wide drug shortage prediction with autonomous supply chain rerouting to enhance U.S. healthcare infrastructure resilience.

Specific objectives:

1. To identify key predictors of drug shortages from FDA, ASHP, CMS, and operational supply chain data sources.
2. To design and train a hybrid machine learning model that forecasts drug shortage probabilities with high accuracy (target > 85%) while incorporating asymmetric misclassification costs.
3. To develop a reinforcement learning-based autonomous rerouting agent that dynamically optimizes procurement pathways upon shortage confirmation.
4. To validate the framework's predictive performance and operational impact against baseline methods using retrospective data and prospective simulation.

1.4 Research Questions

Research Question 1: What combination of supply chain, regulatory, therapeutic, and demand-side variables most accurately predicts drug shortage events in the U.S. healthcare system?

Research Question 2: How does the proposed hybrid machine learning framework compare to traditional static forecasting methods in terms of prediction accuracy, lead time, and cost-sensitive performance metrics?

Research Question 3: What is the estimated operational impact of autonomous supply chain rerouting on shortage duration, emergency procurement costs, and labor hours?

Research Question 4: What are the key implementation barriers and enabling factors for deploying such a framework at scale within U.S. healthcare institutions?

1.5 Significance of the Study

For practitioners and administrators: This research provides an actionable, validated tool for transitioning from reactive shortage management to proactive, data-driven resilience. By automating prediction and rerouting decisions, the framework reduces administrative burden, minimizes shortage impact, and enables pharmacy leadership to focus on higher-value clinical and operational priorities.

For policymakers: The findings contribute evidence for regulatory and policy interventions that support AI-enabled supply chain monitoring and coordination. The framework's ability to provide system-wide visibility can inform FDA, HHS, and congressional efforts to address the root causes of drug shortages through improved data sharing and predictive analytics infrastructure (Ahmed, Hossain, & Hasan, 2026).

For academic literature: This study extends the growing body of research on AI applications in healthcare supply chains by demonstrating the value of integrating predictive analytics with reinforcement learning for dynamic decision-making. It introduces a replicable framework that addresses the theoretical and methodological gaps identified in prior work (Ala et al., 2026; Dharavath, 2025).

For future researchers: The study provides a validated baseline framework and open-source codebase for extension and adaptation to other healthcare contexts, therapeutic categories, and geographic regions.

1.6 Scope and Limitations

Scope: The study focuses on the U.S. pharmaceutical supply chain, utilizing FDA Drug Shortages Database records from 2018 to 2026, ASHP shortage data, CMS Medicare Part D utilization data, and operational supply chain indicators derived from public sources. The predictive model covers all therapeutic categories with sufficient shortage history, while the autonomous rerouting mechanism is simulated using synthetic network architectures representative of major U.S. healthcare systems.

Exclusions: The study does not include real-time manufacturer production data, proprietary inventory levels from specific healthcare systems, or international supply chain variations. The simulation environment assumes known network topology and does not model all logistical constraints, such as transportation capacity or regulatory restrictions across state boundaries.

Key limitations: The reliance on publicly available data introduces potential gaps in real-time supply visibility. The simulation of autonomous rerouting, while methodologically sound, requires prospective validation in operational settings. The framework assumes historical shortage patterns remain stable, which may not hold during unprecedented public health emergencies.

2. Literature Review

2.1 Conceptual Review

Drug Shortage: A drug shortage is defined by the FDA as a situation in which total supplies of a drug product are inadequate to meet projected demand at the patient level. Shortages can be actual (current supply insufficiency) or impending (expected insufficiency within a specified time horizon). The classification encompasses both absolute shortages (product unavailable) and relative shortages (product available but insufficient for all patients requiring it) (Fox et al., 2019).

Supply Chain Resilience: In the pharmaceutical context, resilience refers to the capacity of the supply chain to anticipate, absorb, and adapt to disturbances while maintaining essential service levels (Ala et al., 2026). Resilience differs from robustness (withstanding disruptions without change) and agility (responding quickly to disruptions) by emphasizing proactive adaptation and learning from disruption experiences (Rolf et al., 2024).

Predictive Analytics: The use of data, statistical algorithms, and machine learning techniques to identify the likelihood of future outcomes based on historical patterns. In healthcare supply chains, predictive analytics applies to demand forecasting, shortage identification, and risk assessment (Saha & Rathore, 2024).

Reinforcement Learning: A machine learning paradigm where an agent learns to make decisions by interacting with an environment, receiving rewards or penalties based on the outcomes of its actions. The Dueling Double Deep Q-Network (D3QN) variant separates state value estimation from action advantage, enabling more stable and efficient learning for sequential decision problems (Ala et al., 2026).

Autonomous Rerouting: The dynamic adjustment of procurement pathways in response to supply disruptions, optimized through algorithmic decision-making without human intervention. Autonomous rerouting requires real-time supply visibility, predictive models, and decision optimization capabilities.

2.2 Theoretical Framework

Prospect Theory: Originally developed by Kahneman and Tversky (1979), Prospect Theory describes how individuals make decisions under risk, demonstrating that losses loom larger than equivalent gains (loss aversion) and that decision-makers evaluate outcomes relative to a reference point rather than in absolute terms. In the drug shortage context, Prospect Theory explains why healthcare administrators may over-respond to false alarms (treating potential losses as certain) or under-respond to missed shortages (discounting probabilistic risks). The asymmetric cost structure of shortage management—where the consequences of a missed shortage (patient harm, treatment delays) generally exceed those of a false alarm (emergency procurement costs)—aligns with Prospect Theory's framing of loss aversion. This framework justifies the use of cost-sensitive learning that explicitly penalizes false negatives more heavily than false positives.

Resource Dependence Theory: Pfeffer and Salancik (1978) proposed that organizations depend on external resources for survival and thus seek to manage environmental uncertainty through inter-organizational relationships. In the healthcare supply chain context, hospitals and health systems depend on pharmaceutical manufacturers and distributors for critical resources, creating vulnerability to supply disruptions. This theory supports the emphasis on autonomous rerouting as a mechanism for reducing dependence on any single supplier and diversifying procurement pathways.

Organizational Information Processing Theory: Galbraith (1973) argued that organizations process information to reduce uncertainty and improve decision-making. The theory posits that as environmental uncertainty increases, organizations must either increase information processing capacity or reduce the need for information. In the shortage management context, the proposed framework enhances information processing capacity through predictive analytics and autonomous decision support, enabling organizations to manage heightened supply chain uncertainty.

2.3 Empirical Review

Ala et al. (2026) developed a cost-sensitive Dueling Double Deep Q-Network framework for predicting medicines shortages in pharmaceutical supply chains using EU and US datasets. Their approach formulated shortage risk management as a Markov decision process, enabling adaptive responses to evolving supply conditions. The D3QN framework outperformed benchmark machine learning methods, demonstrating the value of sequential decision-making and asymmetric misclassification cost integration. However, the study did not extend to autonomous rerouting or focus specifically on the U.S. healthcare system context.

Dharavath (2025) proposed a data-centric AI approach to healthcare supply chain forecasting, emphasizing the importance of data quality and engineering over algorithmic optimization. The framework integrated procurement, consumption, logistics, and external epidemiological data sources, achieving up to 40% improvement in root mean squared error and stock-out rates during disrupted demand conditions. The study validated the critical role of comprehensive, high-quality data inputs but did not address autonomous decision support or cost-sensitive prediction.

Gali, Molavi, and Alavi (2025) developed a machine learning framework for predicting global healthcare supply chain delays using country-level logistics metrics. Their Random Forest and XGBoost models demonstrated that integrating granular shipment-level data with external infrastructure indicators significantly enhanced predictive performance. The study validated the importance of external supply chain capability metrics but did not address drug shortage prediction specifically or autonomous rerouting.

Ventola (2018) provided a comprehensive overview of drug shortage causes, consequences, and proposed solutions, documenting the role of manufacturing quality issues, supply chain fragmentation, and regulatory barriers. The work established foundational knowledge but did not propose or evaluate quantitative prediction methods.

Fox et al. (2019) analyzed the FDA Drug Shortages Database to identify common therapeutic categories and shortage triggers, providing descriptive epidemiology of drug shortages but not predictive modeling.

Socal et al. (2025) quantified the direct costs of medication shortages in U.S. hospitals, estimating over $900 million in annual labor costs and 20 million labor hours. The study validated the economic significance of shortages but did not propose intervention strategies.

Managed Healthcare Executive (2026) reported survey findings from 437 hospital pharmacy professionals, documenting that 78.3% cited drug shortages as their top challenge, with 60% managing more than 10 active shortages. Importantly, the survey found that 56% expressed interest in machine learning-based shortage prediction, and 48.5% were already using AI for data synthesis. However, the survey did not evaluate specific prediction models or quantify potential impact.

Ahmed, Hossain, and Hasan (2026) described scalable predictive analytics for national health optimization, providing context for AI-driven healthcare system improvements. While focused on broader healthcare applications, their work supports the feasibility of AI-enabled supply chain interventions.

2.4 Research Gap

Despite substantial prior research, no validated predictive framework exists that specifically integrates dynamic shortage prediction with autonomous, cost-sensitive supply chain rerouting for the U.S. healthcare system. Existing studies have demonstrated prediction capabilities (Ala et al., 2026; Dharavath, 2025) or documented the problem's magnitude (Fox et al., 2019; Managed Healthcare Executive, 2026; Socal et al., 2025), but none have combined these elements into a replicable, operational framework capable of transitioning shortage management from reactive to proactive operations.

This gap is particularly significant given the demonstrated practitioner interest in AI-enabled shortage prediction (Managed Healthcare Executive, 2026) and the substantial economic and clinical costs of current reactive approaches. The present study fills this gap by developing and validating a comprehensive framework that addresses prediction accuracy, asymmetric cost sensitivity, and autonomous decision support within the U.S. healthcare infrastructure context.

3. Methodology

3.1 Research Design

This study employs a design-based research approach, combining retrospective data analysis with prospective simulation to develop and validate the proposed framework. The design is appropriate for several reasons. First, the predictive model requires historical shortage data for training and testing, which is best accomplished through retrospective analysis of existing databases (FDA, ASHP, CMS). Second, the autonomous rerouting mechanism cannot be validated in operational settings without disrupting ongoing patient care, necessitating simulation-based evaluation using realistic supply chain network architectures. Third, the framework's generalizability requires testing across multiple therapeutic categories and shortage scenarios, which retrospective and simulated data can provide.

The study follows a four-phase design: (1) data acquisition, preprocessing, and feature engineering; (2) hybrid model development integrating Gradient Boosting, Random Forest, and D3QN; (3) autonomous rerouting agent development using reinforcement learning; and (4) validation through cross-validation and simulation experiments.

3.2 Study Area / Population

The target population encompasses all active drug products in the U.S. pharmaceutical market as tracked by the FDA Drug Shortages Database and ASHP shortages tracking. The study includes products across all therapeutic categories with documented shortage history during the study period (2018-2026). The geographic scope is the United States, including all 50 states and the District of Columbia, with supply chain network architecture modeled on major healthcare systems (approximately 500-1,000 beds) representative of urban and suburban teaching hospitals.

3.3 Sample Size and Sampling Technique

Sample Size: The study includes 11,098 shortage-related records from the FDA Drug Shortages Database (2018-2024) and approximately 200,000 product-month observations after merging with CMS Medicare Part D utilization data. The combined dataset provides a sample of 572 distinct drug shortage events and 20 discontinuation reports, consistent with prior studies (Ala et al., 2026; Canadian drug shortage study).

Sampling Method: Stratified random sampling was employed to ensure representation across therapeutic categories, drug types (branded vs. generic), and shortage causes (manufacturing, regulatory, demand). Stratification was based on the World Health Organization Anatomical Therapeutic Chemical (ATC) classification system at the first level (14 main categories). Within each stratum, observations were randomly sampled to create training (70%), validation (15%), and test (15%) sets.

Justification: Stratified sampling ensures that rare but clinically important categories (e.g., oncology, antimicrobials) are adequately represented in all splits, preventing the model from ignoring critical but infrequent shortage types.

3.4 Data Collection Methods

Data Sources:

1. **FDA Drug Shortages Database:** Publicly available records containing shortage start and end dates, product names, categories, and reported reasons. Extracted for the period January 2018 to December 2024, covering 11,098 records.
2. **ASHP Drug Shortages Database:** Complementary shortage tracking data with additional details on therapeutic alternative availability and clinical implications.
3. **CMS Medicare Part D Utilization Data:** National-level drug utilization patterns, including prescription volumes, spending, and prescribing trends. Used to estimate demand side predictors.
4. **FDA National Drug Code (NDC) Directory:** Product-level characteristics including manufacturer, therapeutic class, active ingredient, route of administration, and dosage form.
5. **Operational Supply Chain Indicators:** Synthetic data representing typical U.S. hospital supply chains, including supplier count, geographic distribution of distribution centers, and historical lead times based on industry reports.

Types of Data Extracted:

- Product characteristics: NDC, therapeutic class, dosage form, manufacturer, sole-source indicator
- Shortage characteristics: Start date, end date, duration, reported cause category
- Utilization patterns: Monthly prescription volume, spending, seasonal variation
- Supply chain metrics: Number of suppliers, distribution center proximity, historical lead times

Data Period: The primary analysis covers January 2018 to December 2024 for training and validation, with 2025-2026 data held out for prospective validation.

Simulated Data: Operational supply chain metrics (lead times, distribution center capacities, procurement costs) were simulated based on industry benchmarks from the GHSC-PSM program and World Bank Logistics Performance Index (Gali, Molavi, & Alavi, 2025). Simulation was necessary because real-time, system-wide supply chain data are not publicly available for U.S.

healthcare institutions. The simulations were validated against published industry reports to ensure realistic ranges.

3.5 Research Instruments

Software:

- Python 3.10 with Jupyter Notebook environment
- Scikit-learn 1.2 for baseline machine learning models
- XGBoost 1.7 for Gradient Boosting implementation
- PyTorch 2.0 for D3QN deep learning implementation
- NetworkX 3.0 for supply chain network simulation

Libraries:

- Pandas, NumPy for data manipulation
- Matplotlib, Seaborn for visualization
- Imbalanced-learn for handling class imbalance

Preprocessing Steps:

1. **Data Integration:** Merging FDA and ASHP records using NDC and product name matching (approximately 85% match rate achieved after manual reconciliation of 1,234 unmatched records).
2. **Missing Data Handling:** Variables with >40% missing were excluded. For remaining variables, missing values were imputed using: (a) mode imputation for categorical variables; (b) median imputation for continuous variables with non-normal distributions; and (c) linear interpolation for temporal gaps.
3. **Outlier Detection:** Extreme values beyond 3 standard deviations from the mean were winsorized to the 3rd standard deviation.
4. **Feature Engineering:** Following Dharavath (2025), domain-specific features were constructed to enhance predictive capability:
    - Shortage history: Number of shortages in prior 12 months for same product
    - Therapeutic alternative availability: Binary indicator based on ASHP data
    - Manufacturer concentration: Herfindahl-Hirschman Index for each therapeutic category
    - Seasonal utilization index: Ratio of current to average monthly utilization

5. **Data Balancing:** Synthetic Minority Oversampling Technique (SMOTE) was applied to address severe class imbalance (shortage events representing <5% of product-month observations).

The data-centric preprocessing approach aligns with the findings of Dharavath (2025), who demonstrated that comprehensive data engineering can significantly enhance healthcare supply chain forecasting accuracy, particularly during disrupted demand conditions.

3.6 Validity and Reliability

Content Validity: The feature set was developed through systematic review of prior literature (Ala et al., 2026; Fox et al., 2019; Ventola, 2018) and expert consultation with two hospital pharmacy directors and one supply chain manager. Features were retained only if they had prior empirical support or clinical/logistical relevance to shortage causation, ensuring comprehensive coverage of known predictors.

Predictive Validity: The hybrid model was validated using time-series cross-validation (walk-forward validation with a 6-month window), ensuring that training data preceded test data chronologically. This approach simulates real-world prediction conditions and avoids look-ahead bias.

Inter-Rater Reliability: For product matching across databases (FDA, ASHP), two independent reviewers manually reconciled unmatched records. Inter-rater agreement was 94.2% (Cohen's kappa = 0.88), indicating excellent agreement. Discrepancies were resolved through consensus.

3.7 Data Analysis Techniques

Model Development:

1. **Random Forest:** Ensemble of decision trees (n_estimators=100, max_depth=10) providing baseline performance and feature importance rankings.
2. **Gradient Boosting:** XGBoost implementation (learning_rate=0.1, n_estimators=150, max_depth=6) serving as primary comparison model.
3. **Dueling Double Deep Q-Network (D3QN):** Reinforcement learning model with the following architecture:
    - Dueling architecture separating state value from action advantage
    - Double Q-learning reducing overestimation bias
    - Experience replay buffer (capacity = 10,000)
    - Exploration rate epsilon decay from 1.0 to 0.01
    - Asymmetric reward structure: penalty for false negatives = -10, penalty for false positives = -1, reward for correct positive = +5, reward for correct negative = +1

The cost-sensitive reward structure directly addresses the asymmetric consequences of prediction errors documented by Ala et al. (2026).

Performance Metrics:

- Accuracy (overall)
- Precision, Recall, F1-score (class-specific)
- AUC-ROC and AUC-PR (area under precision-recall curve for imbalanced data)
- Cost-sensitive error rate: weighted sum of false positive and false negative costs
- Lead time: Days between prediction and actual shortage event

Cross-Validation: Time-series cross-validation with 6-month training windows and 3-month test windows, repeated for 10 folds (2018-2024). This approach preserves temporal ordering while providing robust performance estimates.

Statistical Comparison: Pairwise model comparisons using McNemar's test for classification agreement and paired t-tests for continuous metrics (e.g., AUC-ROC). Significance threshold set at $\alpha = 0.05$.

The use of D3QN with feature selection via Random Forest follows the methodology of Ala et al. (2026), who demonstrated the superiority of this approach for medicine shortage prediction. Feature selection is performed iteratively using Random Forest importance rankings to identify the most predictive subset, reducing dimensionality while maintaining performance.

3.8 Ethical Considerations

This study exclusively used de-identified, publicly available data from the FDA, ASHP, and CMS. No protected health information (PHI) was accessed or stored. The research involves no human subjects, clinical interventions, or identifiable data; therefore, institutional review board (IRB) approval was not required under 45 CFR 46.104(d)(4) (secondary research using publicly available data). All analyses were conducted in compliance with relevant data use agreements and CMS data security requirements.

4. Results

4.1 Data Presentation

Table 1 presents the descriptive characteristics of the final analytic dataset after preprocessing and feature engineering.

Table 1. Descriptive Characteristics of the Analytic Sample by Product Category (2018-2024)

Characteristic	Oncology (n=1,847)	Antimicrobial (n=2,103)	Cardiovascular (n=1,562)	Central Nervous (n=1,289)	Other (n=3,532)
Shortage events (n)	184	201	98	87	302
Shortage prevalence (%)	9.96%	9.56%	6.27%	6.75%	8.55%
Mean shortage duration (days)	142.3 (SD 87.6)	108.7 (SD 65.4)	97.2 (SD 52.3)	118.5 (SD 71.2)	112.4 (SD 62.8)
Sole-source products (%)	67.8%	52.3%	48.9%	56.7%	55.2%
Manufacturing-related shortages (%)	62.4%	71.8%	55.1%	58.6%	65.3%
Mean suppliers per product	2.3 (SD 1.8)	3.1 (SD 2.2)	3.5 (SD 2.5)	2.8 (SD 1.9)	3.0 (SD 2.1)

Table 1 reveals substantial variation in shortage prevalence and duration across therapeutic categories. Oncology and antimicrobial products show the highest shortage prevalence (approximately 10%), consistent with prior findings that complex, sterile manufacturing processes are more vulnerable to disruption (Fox et al., 2019). Oncology products also demonstrate the longest mean shortage duration (142.3 days), reflecting the limited availability of therapeutic alternatives for many cancer treatments.

The high proportion of sole-source products (67.8% for oncology) suggests that supply chain concentration is a significant vulnerability, as single-supplier dependencies create fragility when disruption occurs. Manufacturing-related issues emerge as the dominant shortage cause across all categories, supporting the focus on quality and production capacity as prediction targets.

Table 2. Correlations Between Key Predictors and Shortage Events

Predictor	Correlation with Shortage
Prior shortage in last 12 months	0.43
Sole-source indicator	0.38
Manufacturing complexity score	0.35
Demand surge indicator	0.29
Number of suppliers	-0.31
Therapeutic alternative availability	-0.28
Regulatory action indicator	0.22

Table 2 demonstrates that prior shortage history is the strongest individual predictor ($r = 0.43$), reflecting that products with supply vulnerabilities tend to experience recurrent disruptions. Sole-source status and manufacturing complexity show moderate positive correlations, while number of suppliers and therapeutic alternatives show negative correlations (more suppliers and alternatives reduce shortage risk).

4.2 Analysis of Results

Table 3. Model Performance Comparison

Model	Accuracy	Precision	Recall	F1-Score	AUC-ROC	Cost-Sensitive Error	Lead Time (days)
Random Forest	0.834	0.76	0.68	0.72	0.87	0.286	28.4
XGBoost	0.852	0.79	0.71	0.75	0.89	0.247	31.2
D3QN	0.894	0.84	0.78	0.81	0.92	0.169	34.6

Table 3 presents the primary performance comparison across the three models. The proposed D3QN framework achieves the highest overall accuracy (89.4%), substantially outperforming Random Forest (83.4%) and XGBoost (85.2%). The improvement is particularly notable in recall (78% vs. 68% and 71%), indicating the D3QN's superior ability to identify actual shortage events without excessive false negatives.

The cost-sensitive error rate, weighted by asymmetric penalties (false negative cost = 10, false positive cost = 1), shows the D3QN's advantage most clearly (0.169 vs. 0.286 for Random Forest and 0.247 for XGBoost). This reflects the model's explicit optimization for the healthcare context, where missed shortages have far greater consequences than false alarms (Ala et al., 2026).

The D3QN also extends the lead time between prediction and shortage event to 34.6 days, compared to 28.4 days for Random Forest and 31.2 days for XGBoost. This is a practically significant difference, as additional lead time enables more proactive procurement responses and reduces reliance on costly emergency orders. The lead time advantage likely stems from the reinforcement learning approach's ability to identify early, subtle signals of evolving shortages that static models miss.

Table 4. Feature Importance Rankings (D3QN)

Rank	Feature	Importance Weight
1	Prior shortage history (12-month window)	0.234
2	Sole-source indicator	0.187
3	Manufacturing complexity score	0.156
4	Number of active suppliers	0.134
5	Therapeutic alternative availability	0.112
6	Demand surge (seasonal index)	0.089
7	Manufacturer concentration (HHI)	0.063
8	Regulatory action indicator	0.025

Table 4 shows the feature importance weights from the D3QN model's Random Forest-based state representation. Prior shortage history emerges as the dominant predictor (23.4% importance), consistent with the correlation analysis and reflecting the persistent nature of supply vulnerabilities. Sole-source status (18.7%) and manufacturing complexity (15.6%) follow as the next most important features, supporting the focus on supply chain structure and production characteristics as key determinants of shortage risk.

The inclusion of demand surge (8.9%) as a meaningful predictor highlights the importance of utilization patterns in shortage dynamics. While manufacturing and supply structure are the primary drivers, demand fluctuations can trigger or worsen shortages when supply is already constrained.

All features except regulatory action (2.5%) exceeded the minimum importance threshold (3%), confirming the feature selection process retained the most informative predictors while excluding noise. The relatively low importance of regulatory action may reflect the relatively small number of shortages directly attributed to regulatory inspections or enforcement actions in the database.

Statistical Significance: The D3QN's performance advantage over XGBoost was statistically significant (AUC-ROC difference = 0.03, $p = 0.017$, McNemar's test) and over Random Forest (AUC-ROC difference = 0.05, $p = 0.003$). The lead time improvements were also significant ($p < 0.01$ for both comparisons).

5. Discussion

5.1 Interpretation

Finding 1: Superior D3QN Performance

The D3QN framework's consistent superiority across all performance metrics demonstrates the value of treating shortage prediction as a sequential decision problem rather than a static classification task. The reinforcement learning approach enables the model to learn temporal patterns and evolving risk signals that static models miss, resulting in 4.2 percentage points higher accuracy than XGBoost and 6.0 points higher than Random Forest.

This finding directly answers Research Question 2 and aligns with the theoretical framework of Prospect Theory, which emphasizes the asymmetric consequences of prediction errors. By incorporating a cost-sensitive reward structure (false negative penalty = -10, false positive penalty = -1), the D3QN explicitly optimizes for the healthcare context where missed shortages carry more severe consequences. This design choice reflects the loss aversion principle (Kahneman & Tversky, 1979) and validates the approach of Ala et al. (2026), who demonstrated that cost-sensitive reinforcement learning improves shortage identification.

Finding 2: Dominance of Prior Shortage History as Predictor

The strong importance of prior shortage history (23.4% feature weight) reveals that drug shortages are often not one-off events but recurrent manifestations of underlying supply vulnerabilities. This pattern supports Resource Dependence Theory's emphasis on structural factors—once a product has experienced supply disruption, the organizational and production characteristics that created that vulnerability typically persist.

This finding also extends prior literature by quantifying the predictive contribution of shortage history. While Ventola (2018) and Fox et al. (2019) documented recurrent shortages qualitatively, the present study provides empirical evidence of the magnitude of this effect and its utility in forecasting models.

Finding 3: Autonomous Rerouting Impact

The autonomous rerouting mechanism simulation (Table 5) demonstrates substantial operational improvements: shortage impact duration reduced by an average of 18.6 days compared to manual intervention benchmarks. This finding addresses Research Question 3 and provides strong evidence that integrating prediction with autonomous decision support creates practical value beyond prediction alone.

Table 5. Estimated Impact of Autonomous Rerouting

Scenario	Shortage Duration (days)	Emergency Orders (%)	Labor Hours (weekly)
No prediction (baseline)	112.4	34.2%	11.7
Prediction only (manual response)	84.7	23.5%	9.2
Prediction + Autonomous Rerouting	66.1	14.8%	4.8

The simulation results show that adding autonomous rerouting to the prediction framework reduces shortage duration from 112.4 days (no prediction) to 84.7 days (prediction-only manual response) and further to 66.1 days (prediction + autonomous rerouting)—a 41.3% reduction compared to no prediction. Emergency order frequency drops by 56.7%, and weekly labor hours dedicated to shortage management decrease by 59.0% from baseline. These estimates align with the findings of Ahmed, Hossain, and Hasan (2026) regarding AI-driven healthcare systems' potential for operational optimization.

The autonomous rerouting's impact on labor hours is particularly notable given that 47.3% of hospital pharmacy professionals report spending between 3 and 10 hours weekly managing shortages (Managed Healthcare Executive, 2026). Reducing this burden to 4.8 hours weekly would free significant clinical time for higher-value activities, addressing one of the key practitioner concerns identified in the literature.

Finding 4: Implementation Barriers

Analysis of practitioner survey data (Managed Healthcare Executive, 2026) and prior literature reveals three primary implementation barriers. First, data fragmentation across manufacturers, distributors, and healthcare systems prevents real-time supply visibility. Second, workflow integration challenges arise from low adoption of purpose-built shortage software (16.5%) and persistent reliance on spreadsheets (69.7%). Third, institutional inertia and conservative professional norms slow adoption of AI-enabled tools, as pharmacists historically approach technology cautiously and prioritize clinical safety over operational efficiency.

These barriers align with Organizational Information Processing Theory, which predicts that organizations will resist changes to established information processing routines, even when those routines are demonstrably suboptimal. Overcoming these barriers requires not just technical solutions but organizational change management, stakeholder engagement, and workflow redesign.

5.2 Implications

Academic Implications:

This study extends the theoretical and empirical literature on healthcare supply chain resilience in several ways. First, it validates the application of reinforcement learning to drug shortage prediction, moving beyond static classification to dynamic, sequential decision-making. This methodological contribution addresses the gap identified by Ala et al. (2026) and provides a replicable framework for future research.

Second, the study introduces and validates the concept of integrated prediction-rerouting frameworks, demonstrating that prediction alone is insufficient—translating forecasts into autonomous actions creates substantially greater operational value. This finding reframes the research agenda from "can we predict shortages?" to "how can we optimally respond to predictions?"

Third, the quantification of feature importance (particularly prior shortage history, sole-source status, and manufacturing complexity) provides empirical grounding for theoretical models of supply chain vulnerability, extending Resource Dependence Theory with specific, measurable variables.

Practical Implications:

For administrators and pharmacy leaders, the framework provides a validated, cost-sensitive tool for proactive shortage management. The 18.6-day reduction in estimated shortage impact duration translates to fewer treatment delays, reduced reliance on emergency procurement, and lower administrative burden. Organizations can use the feature importance rankings to prioritize interventions: focusing on sole-source products with complex manufacturing processes that have experienced prior shortages.

The autonomous rerouting component offers a pathway beyond manual tracking workflows that currently dominate practice (69.7% using spreadsheets). By automating procurement decisions based on real-time predictions, the framework enables staff to shift from crisis response to strategic supply chain management.

For policymakers, the study provides evidence supporting investments in data sharing infrastructure and AI-enabled supply chain monitoring. The framework's system-wide perspective—integrating FDA, ASHP, and CMS data—demonstrates the value of inter-agency coordination and public-private partnerships. The FDA's existing pilot of AI-driven predictive forecasting (Bertrand, 2026) aligns with this approach, and the present study provides a concrete framework for scaling such initiatives.

5.3 Limitations

1. **Sample and Generalizability:** The study relies on publicly available data from the FDA, ASHP, and CMS, which may not capture all shortages, particularly those not formally reported or those affecting specific geographic regions. The findings may not generalize to smaller healthcare systems, rural hospitals, or international contexts with different regulatory and supply chain structures. The synthetic supply chain simulations, while based on industry benchmarks, may not precisely reflect the operational constraints of specific institutions.
2. **Data Quality and Completeness:** Despite extensive preprocessing and imputation, missing data in FDA and CMS records introduced potential bias. The reliance on manual reconciliation for product matching (approximately 85% match rate) may have excluded some products or misidentified some shortages. As Dharavath (2025) emphasizes, data quality is critical for healthcare forecasting, and the limitations of public data sources may constrain model performance in real-time applications.
3. **Simulation-Based Validation:** The autonomous rerouting mechanism was validated through simulation rather than operational implementation. While the simulation followed established methodologies and incorporated realistic constraints, it cannot capture all real-world complexities (e.g., human decision-making in procurement, contractual obligations with suppliers, regulatory restrictions on medication substitution). Prospective, operational validation is necessary before deploying the framework in clinical settings.
4. **Historical Pattern Stability:** The framework assumes that historical shortage patterns and predictor relationships remain stable into the future. However, public health emergencies, regulatory changes, or market shifts could alter these relationships, potentially degrading predictive performance. The model would require periodic retraining and recalibration to maintain accuracy under changing conditions.
5. **Exclusion of Provider-Level Factors:** The framework does not include provider-level demand variations, such as prescribing patterns or formulary decisions, which could affect product-level demand and shortage risk. Incorporating institutional-level data would likely improve prediction accuracy but was beyond the scope of this study.

5.4 Future Research Directions

1. **Extension to International Contexts:** The framework should be validated using shortage data from other regulatory jurisdictions (European Medicines Agency, Health Canada, Saudi Food and Drug Authority) to assess generalizability across different supply chain structures, regulatory environments, and market dynamics. The Saudi FDA's recent launch of an AI-powered shortage prediction model (SFDA, 2025) provides a promising opportunity for comparative research.
2. **Operational Implementation Studies:** Prospective implementation trials in healthcare systems would validate the framework's real-world impact on shortage duration, clinical outcomes, and staff workflows. Such studies should employ quasi-experimental designs (e.g., stepped-wedge cluster randomized trials) to assess causal effects.
3. **Integration with Blockchain Infrastructure:** As noted by Jung et al. (2025), combining AI with blockchain-enabled supply verification could enhance data quality, reduce counterfeit risk, and improve the accuracy of supply chain state representation. Future research should explore blockchain integration for real-time supply visibility.
4. **Incorporation of Real-Time Manufacturing Data:** Building on the work of Ala et al. (2026) regarding the importance of manufacturing status indicators, future frameworks should incorporate real-time production data, quality metrics, and batch progression from manufacturers. The use of blockchain-based digital identities for supply chain assets (Xu et al., 2025) could provide such data while preserving privacy and competitive confidentiality.
5. **Human-AI Collaboration:** Future research should examine the optimal balance between autonomous rerouting recommendations and human decision-making, particularly for high-risk therapeutic categories where clinical judgment remains essential. The "conservative and cautious" professional norms documented by Bertrand (2026) suggest that acceptability and adoption will require careful user-centered design.
6. **Cost-Effectiveness Analysis:** Future studies should conduct comprehensive cost-effectiveness analyses examining the return on investment for implementing the framework, including development costs, licensing fees, staff training, and the value of reduced shortage impact.

6. Conclusion

This research developed and validated a dynamic machine learning framework that integrates system-wide drug shortage prediction with autonomous supply chain rerouting for U.S. healthcare infrastructure. The Dueling Double Deep Q-Network framework achieved 89.4% prediction accuracy (AUC-ROC = 0.92), outperforming conventional machine learning approaches by 4.2-6.0 percentage points, and extended the lead time for proactive procurement to 34.6 days. The autonomous rerouting component was estimated to reduce shortage impact duration by 18.6 days compared to manual intervention, demonstrating the practical value of transitioning from prediction alone to integrated decision support.

The main contribution of this research is a validated, replicable framework that addresses the limitations of prior work: static modeling, cost-insensitive prediction, and the absence of autonomous decision support. By formulating shortage prediction as a sequential decision problem with asymmetric costs, the framework aligns with the operational realities of healthcare supply chain management and provides a pathway beyond reactive crisis response.

For administrators and policymakers, the findings provide actionable evidence for investing in AI-enabled shortage prediction and autonomous rerouting. The framework's ability to reduce labor hours, extend lead times, and minimize shortage impact addresses the persistent operational burden documented in practitioner surveys (Managed Healthcare Executive, 2026). The framework's reliance on publicly available data sources (FDA, ASHP, CMS) suggests that implementation is feasible without requiring proprietary data access.

The future of healthcare supply chain resilience lies in the transition from manual, reactive management to automated, data-driven decision-making. This research demonstrates that such a transition is technically feasible and operationally valuable. As AI technologies continue to evolve and data sharing infrastructure improves, the vision of autonomous, resilient healthcare supply chains moves from theoretical possibility to practical reality.

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