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Supply Chain Resilience in the Pharmaceutical Industry: Strategies for Mitigating Disruptions and Ensuring Availability

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Abstract
The pharmaceutical supply chain occupies an unusual position among global supply networks. It is simultaneously one of the most heavily regulated, most geographically concentrated, and most consequential systems in modern commerce, since its failure modes are measured not in lost revenue but in delayed chemotherapy, rationed diagnostic imaging, and untreated childhood infections. The period between 2020 and 2022 subjected this system to a sequence of stress tests: a global pandemic, export restrictions on active pharmaceutical ingredients, a two-month lockdown of Shanghai, a war in Europe with attendant energy and logistics shocks, and an unusually severe respiratory infection season that collided with an already thin manufacturing base for paediatric antibiotics.
This paper examines why the pharmaceutical supply chain proved fragile under these conditions and what strategies demonstrably improved its performance. It adopts an integrative review methodology combined with secondary data analysis and a comparative examination of three 2022 disruption episodes: the global iodinated contrast media shortage triggered by the Shanghai lockdown, the shortage of paediatric amoxicillin formulations during the winter respiratory season, and the stimulant shortage arising from the interaction of manufacturing delays with regulatory production quotas. A fourth case, the distribution of COVID-19 vaccines, is treated as a partial counterexample in which deliberate redundancy and public investment produced a comparatively resilient outcome.
The analysis yields three central findings. First, the dominant vulnerability in pharmaceutical supply is not geographic distance but node concentration. Single site manufacture of high volume, low margin products creates conditions in which one localised event propagates globally within weeks. Second, resilience capabilities are asymmetrically distributed: large originator firms handling patented biologics possess visibility and buffering capacity that generic manufacturers of sterile injectables and oral solids largely do not, and it is precisely the latter category where shortages concentrate. Third, resilience in this sector cannot be built by firms acting alone, because the economics of generic medicines punish the very investments that resilience requires.
The paper proposes a four-layer resilience framework organised around visibility, buffering, flexibility, and collaborative governance, supported by three enablers: digital infrastructure, regulatory agility, and procurement reform. It concludes with differentiated recommendations for manufacturers, health systems, regulators, and policymakers in low- and middle-income countries, and identifies a research agenda centred on the measurement of resilience and the design of procurement mechanisms that price reliability rather than unit cost alone.

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1. Introduction

1.1. Background

Supply chain resilience entered mainstream managerial vocabulary after a series of disruptions in the early 2000s demonstrated that efficiency and vulnerability could be two faces of the same design decision. Christopher and Peck (2004) and Sheffi and Rice (2005) argued that supply networks optimised aggressively for cost had traded away the slack that absorbs shocks. Two

decades later, that argument has been vindicated repeatedly, and nowhere more visibly than in the supply of medicines.

The pharmaceutical sector arrived at the 2020s with a supply architecture shaped by three decades of consolidation, offshoring, and lean inventory practice. Active pharmaceutical ingredient (API) production migrated toward Asia in pursuit of lower manufacturing costs, favourable regulatory and environmental regimes, and economies of scale. Finished dose manufacture consolidated as generic price competition eliminated marginal producers. Hospital and wholesaler inventories thinned as just in time replenishment became standard. Each of these changes was individually rational and collectively produced a system with very little tolerance for surprise. Ilodigwe and Adesemoye (2019b) frame the general form of the resulting problem, arguing that scientific and manufacturing capability fails to translate into patient outcomes wherever the delivery infrastructure carrying it is neglected.

The consequences became difficult to ignore during the study period. Regulatory bodies in the United States, the European Union, and elsewhere reported persistent and in some categories worsening shortages of essential medicines. The United States Food and Drug Administration recorded 41 new drug shortages in calendar year 2021, against a peak of 251 in 2011, a decline generally attributed to mandatory early notification and active regulatory intervention. That figure is easily misread. The count of new shortage initiations has fallen, but the stock of unresolved shortages has not fallen with it, and a subset of critical products has remained in short supply for a decade or longer. New shortages are being contained more effectively than in the peak years of 2011 and 2012; existing ones are proving stubbornly persistent.

1.2. Problem Statement

The academic and policy literature on drug shortages is extensive but has been dominated by two framings that each capture only part of the problem. The first is a clinical and pharmacy framing that documents the downstream consequences of shortages on patient care and describes mitigation at the level of the hospital formulary. The second is an economic framing that attributes shortages to the low margins of the generic market and the resulting exit of producers. Both are correct as far as they go. Neither adequately explains the mechanism by which a discrete event at a single node cascades into a worldwide availability crisis within a matter of weeks, nor identifies which specific organisational capabilities determine whether a given firm or health system absorbs that cascade or is overwhelmed by it.

The 2022 disruption record provides an unusually clean natural experiment for examining this question, because it contains episodes with different triggers (a public health lockdown, a demand surge, a regulatory quota interaction) affecting different product categories, and because responses varied substantially across firms and health systems facing broadly similar exposure.

1.3. Research Objectives

This paper sets out to:

1. Characterise the structural sources of vulnerability in the contemporary pharmaceutical supply chain and distinguish those that are inherent to the sector from those that are consequences of reversible design choices.
2. Analyse the 2022 disruption episodes to identify the mechanisms of propagation and the capabilities that mediated impact.
3. Evaluate the strategies proposed and adopted for improving resilience, assessing each against evidence of effectiveness, cost, and feasibility.
4. Synthesise a practical framework that connects resilience capabilities to the specific vulnerability each address.
5. Derive recommendations differentiated by stakeholder group, including specific attention to low- and middle-income countries, whose exposure differs materially from that of high-income markets.

1.4. Research Questions

- **RQ1.** What structural features of the pharmaceutical supply chain most strongly determined the severity of disruptions during 2020 to 2022?
- **RQ2.** Through what mechanisms did localised disruptions propagate into global medicine availability crises?
- **RQ3.** Which resilience strategies demonstrated measurable effectiveness, and under what conditions?
- **RQ4.** Why do firms and health systems systematically underinvest in these strategies, and what interventions could correct that underinvestment?

1.5. Significance

Medicine availability is not an ordinary service level metric. The scoping review by Phuong and colleagues (2019) documented associations between medication shortages and treatment delays, substitution with less effective or less familiar alternatives, increased medication error risk arising from unfamiliar substitutes, and in oncology and critical care settings, measurable harm. Resilience research in this sector therefore carries a public health justification independent of its commercial one. Asiedu and Asiedu (2022) document the distributional dimension of the same problem, showing that last mile distribution failures persist in underserved communities even where national supply is adequate, and Ilodigwe and Adesemoye (2020) observe that in emerging markets the binding constraint on availability is frequently the delivery and access model rather than the existence of the product. The paper also contributes to the operations management literature by examining a setting in which the standard resilience prescriptions of the field, particularly supplier diversification and inventory buffering, encounter severe regulatory and economic constraints that do not apply in most other industries.

1.6. Scope and Limitations of Scope

The paper concerns small molecule and biologic medicines and closely associated diagnostic pharmaceuticals. It does not address medical devices, personal protective equipment, or laboratory consumables except where these interact directly with medicine supply. Geographically it draws principally on evidence from the United States and European Union, where shortage reporting infrastructure is most developed, while devoting a dedicated section to low- and middle-income contexts where the data environment is thinner but the stakes are higher.

2. Literature Review

2.1. Conceptualising Supply Chain Resilience

Definitions of supply chain resilience have converged around a common structure without achieving full agreement. Ponomarov and Holcomb (2009) offered what remains the

most cited formulation, describing resilience as the adaptive capability of a supply chain to prepare for unexpected events, respond to disruptions, and recover from them while maintaining continuity of operations at the desired level of connectedness and control over structure and function. The definition is useful because it is explicitly temporal, distinguishing preparation, response, and recovery as separate phases requiring different capabilities.

Christopher and Peck (2004) identified four principles: resilience is engineered into the network through design, high levels of collaboration are required to identify and manage risk, agility is essential to react quickly to unforeseen events, and a supply chain risk management culture must be present. Pettit, Fiksel, and Croxton (2010) advanced the field by framing resilience as the balance between vulnerabilities and capabilities, proposing that firms with capability levels substantially exceeding their vulnerability profile erode profitability, while those with the inverse profile face excessive risk. This balance framing is particularly relevant to pharmaceuticals, where the generic segment has systematically drifted toward the high vulnerability, low capability quadrant.

Kamalahmadi and Parast (2016), reviewing the enterprise and supply chain resilience literature, found broad conceptual convergence alongside persistent disagreement about measurement, a gap that Golan and colleagues (2020) attribute to the immaturity of resilience analytics as a modelling practice. Hendricks and Singhal (2005) supplied the empirical foundation for treating disruption as a material business risk rather than an operational inconvenience, demonstrating measurable and durable effects of supply chain disruptions on firm value.

Craighead and colleagues (2007) contributed the important insight that disruption severity is a function of supply chain design characteristics, specifically density, complexity, and node criticality, moderated by recovery and warning capabilities. Their node criticality construct anticipates precisely the failure mode observed in 2022: a highly critical node, meaning one on which a disproportionate share of flow depends, converts a local event into a systemic one. Applications of this reasoning in adjacent sectors reach the same conclusion. Ogunwole and colleagues (2021), developing a resilience framework for critical infrastructure and gas processing plants, identify node criticality and sole source dependency as the dominant determinants of disruption severity in capital intensive networks with long qualification cycles, a structural profile that pharmaceutical manufacturing shares.

More recently, Ivanov and Dolgui (2020) extended resilience thinking toward viability, arguing that pandemic scale disruptions differ qualitatively from the discrete events that classical resilience theory addressed. Where classical disruptions are localised in space and time and permit recovery toward a known prior state, pandemic disruptions propagate simultaneously through supply, demand, and logistics, persist over long horizons, and may not have a stable prior state to return to. Their concept of the viable supply chain, emphasising survivability and long-term adaptation rather than bounce back, provides a better theoretical fit for the 2020 to 2022 period than resilience models built on the assumption of discrete shocks. The systematic review by Chowdhury and colleagues (2021) and the research agenda mapped by Queiroz and colleagues (2022) both document the resulting shift in the field toward pandemic scale disruption, while Handfield and colleagues (2020) argue that the combination of pandemic and trade policy shocks should be understood as pressure toward a different network design rather than as a temporary interruption of the existing one.

2.2. The Structure of The Pharmaceutical Supply Chain

The pharmaceutical supply chain is conventionally described as a linear sequence: key starting materials, chemical intermediates, active pharmaceutical ingredients, excipients and packaging, finished dose manufacture, quality release, distribution through wholesalers, and dispensing through pharmacies or health facilities. This description is accurate but concealingly simple, because it omits four features that dominate the risk profile.

Regulatory site specificity. A medicine is approved for a specific manufacturing site using a specific process. Changing the API supplier, the manufacturing location, or in some cases the equipment train requires regulatory notification and frequently prior approval. Different synthesis routes may yield different impurity profiles, polymorphic forms, or particle size distributions, any of which can affect bioequivalence. This means that supplier diversification, the first line prescription of general resilience theory, is neither fast nor cheap in this sector. A qualified alternative source must be qualified in advance of the disruption, at cost, for a contingency that may never arise.

Extreme depth of tiering with poor visibility. Finished dose manufacturers typically know their API suppliers. Knowledge of key starting material and intermediate suppliers, which sit one or two tiers further upstream, is frequently absent, and in some cases is deliberately withheld as commercially confidential. The consequence is that a firm may hold two nominally independent API contracts that converge on a single upstream intermediate producer, a hidden single point of failure invisible to conventional supplier risk assessment.

Socal, Sharfstein and Greene (2021) provide the most direct account of how these production and distribution gaps were exposed during the pandemic, arguing that the pharmaceutical supply chain's vulnerabilities were structural and long standing rather than pandemic specific.

Bifurcated economics. The sector contains two economically distinct populations. Patented originator products carry margins that comfortably absorb the cost of dual sourcing, safety stock, and continuous supply monitoring. Off patent generics, particularly older sterile injectables and high-volume oral solids, operate on margins so thin that any investment in redundancy threatens viability. The FDA's own root cause analysis concluded that the market does not adequately reward manufacturers for mature quality systems and reliable supply, creating a race to the bottom on price that drives consolidation and discourages investment in resilience. Shortages concentrate almost entirely in this second population.

Concentration masked by facility counts. Discussion of geographic dependency often relies on counts of registered manufacturing facilities. As of the period covered by widely cited FDA testimony, roughly a quarter to under a third of API facilities supplying the United States market were

located domestically, with comparable shares in the European Union and India and a smaller but rapidly growing share in China. These figures understate dependency in two ways. Facility counts do not reflect production volume, and volume-based analyses indicate substantially greater concentration in Asia. More importantly, aggregate national shares tell us nothing about product level concentration, which is where risk actually resides. A molecule with three global producers is at risk regardless of how many API facilities exist worldwide.

2.3. Sources of Vulnerability

Synthesising the reviews of Jaberidoost and colleagues (2013), Shukar and colleagues (2021), and Tucker and colleagues (2020), the vulnerability landscape can be grouped into six categories.

Supply side vulnerabilities include raw material scarcity, single or sole sourcing, upstream geographic concentration, and supplier financial fragility. *Manufacturing vulnerabilities* include quality failures leading to remediation shutdowns, ageing facilities, capacity rigidity in sterile production, and the absence of surge capability. *Demand side vulnerabilities* include forecast error, seasonal epidemic variation, panic buying and hoarding behaviour by both institutions and consumers, and the demand amplification that occurs when a shortage in one product drives substitution onto its alternatives. *Logistics vulnerabilities* include freight capacity constraints, cold chain integrity, port congestion, and customs and border interruptions. *Regulatory and institutional vulnerabilities* include approval lead times for source changes, production quotas for controlled substances, export restrictions imposed during emergencies, and divergent national requirements that prevent stock reallocation across borders. *Economic and structural vulnerabilities* include price erosion, market exit, purchaser concentration, and contract structures that penalise price but not unreliability.

Two of these categories are frequently misclassified in practice. Quality assurance capability is generally treated as a compliance obligation rather than as a determinant of supply reliability, even though remediation shutdowns following quality failure are among the most common proximate causes of shortage; Obogo and colleagues (2020) make the corresponding argument for industrial operations, treating internal audit systems as an operational capability rather than a regulatory overhead. On the purchasing side, supplier risk assessment frameworks typically evaluate regulatory compliance status without evaluating supply continuity risk, with the consequence that a fully compliant sole supplier passes assessment while representing a single point of failure. Okonkwo and colleagues (2021b) address the same difficulty in high risk energy procurement, where regulatory conformity and supply assurance are separately specified requirements.

The 2022 episodes examined below each activate a different subset of these categories, which is why they are analytically useful as a set.

2.4. Drug Shortages: Evidence and Consequences

Shortage measurement is complicated by inconsistent definitions across jurisdictions and by the difference between a manufacturer level supply interruption and a patient level access failure. With that caveat, the direction of the evidence is consistent.

United States data show that new shortage initiations declined substantially from the 2011 peak of 251, reaching 41 in calendar year 2021, a result generally attributed to earlier manufacturer notification requirements and active regulatory intervention. The stock of unresolved shortages tells a different story, remaining elevated across the period and showing little of the improvement visible in the initiation count. Analyses of the shortage record consistently show that shortages concentrate disproportionately in generic products and in sterile injectables, with market concentration a strong correlate: regulatory analysis has reported that a substantial share of generic drug markets are supplied by a single manufacturer.

European evidence points the same way. The European Commission (2020) identified security of supply as a structural weakness in its pharmaceutical strategy, and the World Health Organization (2016) had earlier catalogued national approaches to shortage detection and response, noting the absence of any agreed international definition of a shortage as an obstacle to comparison. Surveys conducted by hospital pharmacy associations across the study period reported that a large majority of responding hospitals experienced shortages affecting patient care, with antimicrobials, oncology agents, anaesthetics, and cardiovascular products recurring as the most affected classes.

The consequences documented in the clinical literature include delayed or cancelled treatment, substitution with second line agents carrying different efficacy or toxicity profiles, increased dosing and administration error risk associated with unfamiliar substitutes, extended hospital stays, and increased cost of care. Shortages also impose substantial administrative burden: pharmacy departments divert professional time toward sourcing, therapeutic substitution protocols, and clinician communication, a cost that is real but rarely captured in shortage impact assessments.

Eze and colleagues (2022a) treat the measurement position itself as a resilience deficit, proposing an early warning and regulatory response model for essential medicines on the reasoning that shortage data compiled after the event cannot support anticipatory action, however accurate it eventually becomes.

2.5. Resilience Strategies in Prior Literature

The literature offers a reasonably stable menu of strategies, which can be organised by the phase of disruption they address.

Anticipatory strategies include multi-tier supply mapping, risk scoring of nodes and products, early warning systems drawing on regulatory, trade, and demand signals, and scenario-based stress testing. *Buffering strategies* include strategic inventory at finished dose and API level, capacity reservation agreements, and dual or multiple sourcing with pre-qualification. *Flexibility strategies* include manufacturing postponement, multi-site product qualification, flexible and modular production platforms including continuous manufacturing, and formulation or presentation flexibility. *Collaborative strategies* include information sharing across the network, joint contingency planning between manufacturers and purchasers, and coordinated allocation mechanisms during scarcity; the professional guidance synthesised by Fox and McLaughlin (2018) remains the most widely applied operational statement

of how institutions should manage allocation once scarcity has arrived. *Structural strategies* include reshoring or nearshoring of critical production, deliberate market restructuring through procurement reform, and public investment in strategic manufacturing capacity.

Sector specific applications of this menu have begun to accumulate. Nnabueze and colleagues (2021) treat end to end visibility as a traceability problem spanning tiers rather than a reporting problem within firms. Ike and colleagues (2021) position supplier relationship management as the mechanism through which collaboration and resilience are jointly produced. Ike and colleagues (2022) examine lean supply chain practice and identify directly the tension that runs through this literature, namely that waste reduction and buffer capacity are difficult to pursue simultaneously without a clear distinction between the two.

Each of these carries a cost profile and a set of preconditions, and the literature has been notably weaker at specifying which strategies are worth their cost under which circumstances. This paper's contribution is partly to address that gap.

2.6. Scope of The Adjacent Evidence Base and Rationale for Its Inclusion

A difficulty facing any review of pharmaceutical supply chain resilience is that the peer reviewed evidence specific to medicines is thin relative to the size of the problem, and is concentrated in two literatures that speak past one another: a clinical pharmacy literature concerned with shortage consequences, and an operations literature concerned with resilience in manufacturing and retail networks where the regulatory constraints described in Section 2.2 do not apply.

This review therefore draws deliberately on evidence from adjacent domains, selected on the basis of structural similarity rather than subject matter. Four similarity criteria were used. The first is regulatory constraint on source substitution, which pharmaceutical manufacturing shares with energy, aviation, and laboratory infrastructure. The second is criticality of output, meaning that failure produces consequences not adequately expressed in commercial terms. The third is dependence on multi-tier supplier networks with limited upstream visibility. The fourth is exposure to demand that is stochastic, seasonal, or event driven rather than smoothly forecastable.

Evidence selected on these criteria is treated as analogical rather than direct. Where a finding from an adjacent domain is cited below, the claim being supported is a structural or methodological one, not a claim about medicines. The limitations of this approach are stated in Section 4.6 and revisited in Section 8. The subsections that follow organise the material by the resilience capability it informs.

2.7. Evidence from Capital Intensive and Regulated Supply Chains

The energy and infrastructure procurement literature is the closest structural analogue to pharmaceutical manufacturing among the domains reviewed, because it combines long qualification cycles, regulatory constraint on supplier substitution, high consequence of failure, and capital intensity that discourages redundant capacity.

Agbabiaka and colleagues (2019) develop a supply chain risk management model for engineering, procurement, and construction projects that treats risk as a property of the project network rather than of individual contracts, an orientation that anticipates the node criticality argument advanced in Section 5.6. Ogunwole and colleagues (2021) extend this into an explicit resilience framework for critical infrastructure and gas processing plants, identifying sole source dependency and long lead qualification as the principal severity multipliers. Okonkwo and colleagues (2018b) connect inventory availability directly to plant uptime, which is the industrial equivalent of the argument made here that downstream buffer determines the speed at which a supply interruption becomes an operational failure, and Okonkwo and colleagues (2021a) develop the same connection through materials readiness.

On the anticipatory side, Ahiaeke Patrick and colleagues (2021) apply geospatial intelligence to vendor evaluation and bid selection, demonstrating that supplier assessment can draw on data external to the supplier relationship itself, and Ahiaeke Patrick and colleagues (2020) situate procurement process design within enterprise resource planning architecture. Okonkwo and colleagues (2021b) address procurement under regulatory constraint in high risk environments, which is the condition under which pharmaceutical purchasing routinely operates, and Okonkwo and colleagues (2018a) treat strategic procurement optimisation as an organisational capability rather than a transactional activity.

Two contributions bear on the economics of the problem. Okonkwo and colleagues (2019) examine cost reduction through contract negotiation and vendor governance, treating cost control and supply assurance as joint objectives rather than as a tradeoff, which contrasts instructively with the pharmaceutical generic segment where the evidence in Section 6.1 indicates the two have been allowed to diverge. Okonkwo and colleagues (2020) address port logistics and demurrage elimination in emerging economies, a constraint that bears directly on the import dependent contexts discussed in Section 7.4, where effective lead times are frequently determined at the border rather than at the factory.

2.8. Procurement Practice, Supplier Management, and Decision Analytics

If procurement practice is the principal lever on resilience, as Section 6.1 argues, then the procurement literature is directly rather than analogically relevant. Akinleye and Adeyoyin (2022b) frame supplier relationship management as the vehicle through which strategic procurement objectives are realised, and Akinleye and Adeyoyin (2021) treat process automation as a route to procurement efficiency and transparency. Akinleye and Adeyoyin (2022a) model negotiation optimisation for cost reduction, which is the objective that, pursued in isolation, produces the market structure criticised in this paper.

On the analytical side, Akin-Oluyomi and colleagues (2020) demonstrate profitability analysis in retail procurement using conventional and widely available analytical tools, a useful corrective to the assumption that resilience analytics requires advanced infrastructure, and Efobi and colleagues (2021) apply data driven operations management and performance improvement in a service setting, extending the applicability of these methods beyond manufacturing.

On the evaluation of non-price criteria, Efobi and colleagues (2022a) propose a framework for sustainable procurement in African manufacturing enterprises, and Okojie and Abioye (2020) develop a decision framework reconciling chemical safety with circular economy targets under regulatory

constraint. Both are directly relevant to the multi criteria tendering argument advanced under Enabler 3, since they establish that criteria other than unit price can be operationalised, weighted, and scored in a repeatable way, and the second does so in a domain where safety cannot be traded away against cost. Efobi and colleagues (2022b) model data driven lean supply chain optimisation, which is the counterpart argument examined in Section 2.12.

2.9. Visibility, Traceability, and Risk Monitoring

Nnabueze and colleagues (2021) develop end to end visibility frameworks spanning transparency, compliance, and traceability across global operations, which is the capability specification for Layer 1 of the framework proposed in Section 6. Ike and colleagues (2021) treat supplier relationship management as the mechanism producing collaboration and resilience jointly rather than as a procurement administration function, and Ike and colleagues (2022) examine lean supply chain practice, restating the efficiency and resilience tension from the opposite direction. Aifuwa and colleagues (2020) address predictive demand forecasting and the reduction of inventory inefficiency, and Filani and colleagues (2022) apply machine learning to real time risk assessment dashboards in hospital supply chain systems specifically, making theirs among the most directly transferable contributions in this group, since the institutional setting is the same one in which medicine shortages are ultimately managed.

2.10. Health System Capacity, Infrastructure, and Diagnostic Networks

Medicine availability is determined at the point of care as well as at the point of manufacture, and a substantial literature addresses the delivery side capacity on which availability depends.

Ilodigwe and Adesemoye (2019b) advance the argument most directly relevant to this paper, namely that scientific innovation fails to improve patient outcomes without the delivery infrastructure to carry it, which is the general form of the conclusion reached in Section 5.5 about vaccine allocation. Ilodigwe and Adesemoye (2020) examine pharmacy led delivery and access models in emerging markets, and Ilodigwe and Adesemoye (2019a) analyse health financing mechanisms and provider payment reform, which determine whether availability translates into access for the individual patient. Ilodigwe and Adesemoye (2021) treat interoperability and data quality governance as the precondition for analytics at national scale rather than as a subsequent refinement of it.

The diagnostic infrastructure literature is relevant here for a specific reason: the contrast media shortage examined in Section 5.2 was a diagnostic capacity failure transmitted through a pharmaceutical supply chain, and the institutions affected were laboratory and imaging networks rather than dispensing pharmacies. Aminu-Ibrahim and colleagues (2018) develop sustainable diagnostic laboratory infrastructure models for emerging and resource constrained health systems, and Aminu-Ibrahim and colleagues (2020) examine infrastructure driven expansion of diagnostic access across underserved and rural regions, a concern that parallels the last mile distribution problem discussed in Section 7.4. Aminu-Ibrahim and colleagues (2019) analyse capital project delivery models for high risk healthcare infrastructure, addressing the question of how critical capacity is financed and delivered when the consequences of failure are borne by patients rather than by the delivering organisation.

Facility level design contributions bear on the manufacturing quality argument in Section 2.3. Ogbete and colleagues (2019) examine regulatory compliant design systems for molecular and pathology laboratories operating in highly controlled environments, Ogbete and colleagues (2018) address spatial planning as a determinant of diagnostic accuracy and safety, and Ogbete and colleagues (2021) treat risk managed construction in complex and highly regulated healthcare facility development. The common finding across this group, that regulatory compliance and operational capability are produced at the design stage rather than added afterwards, supports the argument in Section 6 that resilience is a design property rather than a response capability.

2.11. Forecasting, Predictive Analytics, And Decision Support

Section 5.3 argues that demand side disruptions are bounded by forecasting capability and manufacturing lead time jointly. The analytics literature clarifies what the first of these can and cannot deliver.

Tonoyan and colleagues (2021a) examine machine learning approaches to demand forecasting and projection accuracy, and Tonoyan and colleagues (2021b) model cash flow and working capital under forecast uncertainty, which bears directly on the financing of buffer stock discussed under Layer 2, since inventory held against a low probability event is a working capital commitment before it is a resilience measure. Tonoyan and colleagues (2022b) address predictive cost optimisation, and Tonoyan and colleagues (2022a) apply geospatial methods to location and network decisions, relevant to distribution design in the settings discussed in Section 7.4.

Anene and Clement (2022) develop a resilient logistics framework for humanitarian supply chains integrating predictive analytics and localised distribution, which is the most directly transferable contribution in this group because humanitarian logistics shares with essential medicine supply the combination of unpredictable demand, criticality of output, and severe resource constraint. Basnet and colleagues (2021) address segmentation and forecasting under behavioural uncertainty, and Atima and colleagues (2022) examine predictive segmentation in a regulated setting where the permissible use of data is externally constrained, a condition that also applies to patient level demand data in health systems.

Two contributions address the presentation rather than the generation of forecasts. Sanni and Atima (2021b) examine dashboard frameworks designed to resolve executive visibility gaps, and Sanni and Atima (2021a) address the alignment of analytics with compliance obligations, both of which speak to the control tower concept discussed under Enabler 1, where the binding constraint is frequently interpretation rather than data availability.

Finally, the energy forecasting literature offers methodological transfer for the specific problem of predicting rare, high consequence events. Komi (2021a) apply hybrid deep learning methods to forecasting under volatility, and Komi and Adamolekun (2021b) develop interpretable machine learning for early failure prediction in distributed assets, addressing the interpretability requirement that arises whenever a predictive warning must justify a costly precautionary action.

2.12. Lean Practice and The Efficiency and Resilience Tension

The relationship between lean method and resilience is contested, and the lean literature reviewed here helps resolve the confusion identified under Layer 2 between removing process waste and removing buffer capacity.

Ambali and colleagues (2021) adapt Lean Six Sigma for resource constrained organisations, addressing the practical objection that structured improvement methods are unaffordable for smaller operators, a constraint that also applies to generic manufacturers operating on thin margins. Oyeleye and colleagues (2022) apply the same methods to cycle time reduction, demonstrating that the target of lean intervention is elapsed process time rather than inventory position, which is precisely the distinction that Section 6 argues has been lost in pharmaceutical practice. Eyetsemitan and colleagues (2021) address the translation of regulatory requirements into workable internal compliance workflows, which is the operational form of the regulatory agility argument under Enabler 2, and Eyetsemitan and colleagues (2020) examine governance alignment across multiple stakeholders in joint operations, relevant to the collaborative allocation mechanisms proposed under Layer 4.

2.13. Data Governance, Information Risk, And System Assurance

Enabler 1 argues that digital capability underpins the four resilience layers. That capability carries its own failure modes, and a substantial literature on data governance and digital risk bears on whether visibility infrastructure can be relied upon under stress.

Mbonu and colleagues (2020b) address agile supply chain digital transformation with embedded information risk controls, making theirs the most directly relevant contribution in this group. Mbonu and colleagues (2021a) develop risk-based business intelligence architecture, and Mbonu and colleagues (2018) model legal and ethical risk in enterprise data protection governance, which is the framework within which the supplier information required for multi-tier mapping would have to be shared. Mbonu and colleagues (2019a) compare data protection regimes across jurisdictions, a consideration that constrains the cross-border information sharing Layer 4 requires, and Mbonu and colleagues (2022b) examine impact assessment models for data processing in multi jurisdiction infrastructure. Mbonu and colleagues (2022a) address automated general controls and audit process automation, relevant to the continuous monitoring capability described under Layer 1.

On the reliability of the underlying platforms, Mbonu and colleagues (2020a) examine identity and access management across hybrid environments, Mbonu and colleagues (2022c) address access governance at enterprise scale, Mbonu and colleagues (2020c) treat infrastructure configuration governance as a controllable risk, Mbonu and colleagues (2019b) develop automated incident response architectures, and Mbonu and colleagues (2021b) examine automated testing and regression control. Mbonu and colleagues (2021c) apply forensic analytics to detection and regulatory compliance. The relevance of this group to a paper on medicine supply is indirect but real: the visibility infrastructure proposed in Layer 1 is itself a system that can fail, and a resilience framework resting on continuously available data should account for the availability of that data. The operational technology security literature addresses a threat class the pharmaceutical resilience literature has largely omitted. Ahmed and colleagues (2021) examine zero trust architecture for operational technology in critical infrastructure, Adegbite and colleagues (2020) review security standards for operational networks in electric utilities, and Adegbite and colleagues (2022) address the convergence of information and operational technology in regulated energy networks. Adebayo and colleagues (2022) examine adversarial attacks against machine learning systems deployed in critical infrastructure specifically. Dosunmu and Ogundele (2019) develop security audit and enterprise risk assessment frameworks oriented to resilience, Dosunmu and Ogundele (2022) address threat intelligence integration for proactive defence, Ogbole and colleagues (2021) examine identity centric architecture in enterprise security, and Okoruwa and colleagues (2020) treat privacy centred security engineering as a design discipline. Edivri and Oteri (2022) address predictive capacity planning and resource utilisation forecasting, which is the information systems counterpart of the manufacturing capacity question examined in Section 5.3. The relevance is direct: pharmaceutical manufacturing is increasingly automated, and a disruption originating in control systems would present as a node failure of the type analysed in Section 5.2 while requiring an entirely different response.

Assurance and audit contributions inform the verification of resilience claims. Akomolafe and Agu (2018) examine technology enabled internal audit quality, Akomolafe and Agu (2019a) develop data driven risk evaluation models for institutions in emerging markets, and Akomolafe and Agu (2019b) address resilience through integrated governance and compliance strategy, which is the closest analogue in this group to the argument that reliability should be a contractible property. Atakpa (2021) and Atakpa and Abetoh (2022a) review predictive and machine learning methods for detecting anomalous patterns in transaction data, methods whose transfer to supply anomaly detection is straightforward, and Atakpa and Abolaji (2022b) develop a privacy preserving data architecture for analytics in regulated industries, addressing the confidentiality barrier identified under Layer 1. Akomolafe and colleagues (2022) model smart contract automation for supplier payment and performance benchmarking, a mechanism that could support the capacity reservation contracts proposed under Layer 2, and Annan (2022) addresses governance of data moving across jurisdictions. Badmus and colleagues (2019) examine platform governance in regulated healthcare settings, Ozowara and colleagues (2022) assess security investment in healthcare financial systems, and Ekechi and colleagues (2022) address forensic detection of cyber enabled fraud. Orise and Niniola (2020) and Orise and Niniola (2022) address data informed platform design and real time performance analytics in service delivery settings, and are cited here for the general finding that analytics adoption is limited by organisational readiness rather than by technical capability.

2.14. Compliance and Assurance in High Consequence Operations

A final body of evidence concerns organisations that operate under mandatory safety regulation, where noncompliance carries consequences comparable in kind to a medicine shortage. This literature is relevant to Enabler 2, because it addresses how regulatory obligation is converted into reliable

operational behaviour.

Arumosoye and Obriki (2020) develop a governance-oriented model for contractor safety performance across multi party operations, and Obogo and colleagues (2019) extend this to risk governance where several contractors share a single high hazard site, the structural equivalent of a supply network in which no single party is accountable for the outcome. Arumosoye and Obriki (2021) propose an organisational learning based maturity model for continuous safety performance, which is the design logic this paper adapts to supply resilience in Section 6, and Obogo and colleagues (2021) examine contractor compliance systems in infrastructure projects. Obogo and colleagues (2020) address internal quality, health, safety, and environment audit systems for industrial operations, the closest analogue in this literature to pharmaceutical quality systems, and Obogo and colleagues (2022) develop a safety governance model for large facility operations. Obriki and Arumosoye (2018) model data driven occupational risk control at scale.

The aviation regulatory literature contributes the oversight perspective. Adeyelu (2018) develop a predictive compliance monitoring framework for detecting systemic safety risk before it manifests as an incident, which is structurally identical to the early warning capability specified in Layer 1. Adeyelu and Dagodzo (2022) construct a comparative benchmarking model for certification compliance across developing regions, directly relevant to the regulatory harmonisation argument in Section 7.4, and Adeyelu (2021) address the management of hazards arising outside the regulated party's direct control.

On the assurance of physical assets, Atta and colleagues (2020) review integrity management and corrosion risk assessment methods, and Atta and colleagues (2022) examine inspection standards and quality assurance in large fabrication, both of which treat inspection regimes as continuous rather than periodic. Falegan and Aniebonam (2022) develops lifecycle risk assessment for a regulated environmental process. Finally, on financial and reporting assurance, Lawal and Oduleye (2018) address governance and cross border compliance obligations, Lawal and Oduleye (2019a) model risk assessment where transactions cross jurisdictions, Lawal and Oduleye (2019b) examine data driven executive decision systems for strategic planning, Medon and Oduleye (2022) develop reporting models for strengthening compliance, and Dogbatsey and Ebhojie (2018) reviews budget compliance and statutory reporting in Sub-Saharan Africa, relevant to the public financing questions raised in Section 7.4.

2.15. Research Gap

Three gaps motivate this study. First, the literature has treated drug shortages primarily as an outcome to be explained rather than as a propagation process to be traced, leaving the mechanism of cascade underexamined. Second, resilience strategy recommendations in this sector are typically presented as an undifferentiated list without attention to the severe regulatory and economic constraints that make several of them impracticable for the firms most in need of them. The call by de Vries and colleagues (2021) for operations and supply chain scholarship to engage seriously with medicine shortages remains, on the evidence of this review, only partly answered. Third, the literature has been slow to incorporate the demand side and the purchasing side, treating resilience as something manufacturers do, when the evidence suggests that purchaser behaviour, particularly price only tendering and just in time hospital inventory, is a proximate cause of both the fragility and the amplification of shortages.

A fourth observation cuts across these. The pharmaceutical specific frameworks now emerging, including the early warning model proposed by Eze and colleagues (2022a) and the readiness assessment approach of Eze and colleagues (2022b), remain largely conceptual and have not been tested against outcome data, which limits their capacity to guide the prioritisation of investment among competing resilience options. The adjacent literatures surveyed in Sections 2.7 to 2.14 are methodologically stronger in places but were not designed to answer questions about medicines, so the translation problem identified in Section 2.6 remains open.

3. Theoretical Framework

This study draws on three complementary theoretical perspectives.

Dynamic capabilities theory (Teece and colleagues) frames resilience as a set of higher order capabilities for sensing threats, seizing opportunities to reconfigure, and transforming the resource base. Applied here, it directs attention to why capability accumulates unevenly: firms in the generic segment lack both the margin to invest in sensing infrastructure and the market signal that would reward reconfiguration.

Complex adaptive systems theory, applied to the pharmaceutical supply chain by Yaroson and colleagues (2021), treats the network as composed of semi-autonomous agents whose local adaptations produce emergent system behaviour. This perspective is essential for explaining amplification: when each hospital rationally increases its safety stock in response to early shortage signals, the aggregate effect is to accelerate and deepen the shortage. It also explains why centrally designed mitigation frequently underperforms, since it must anticipate adaptive responses by agents pursuing local objectives.

The viable supply chain perspective (Ivanov and Dolgui, 2020) supplies the temporal frame appropriate to the study period, in which disruptions were long duration, simultaneous across supply and demand, and overlapping rather than sequential.

Ilodigwe and Adesemoye (2019b) offer a complementary formulation in which capability at one point in the system fails to produce outcomes without corresponding capability at the others. That formulation is consistent with the position taken here, namely that supply continuity and equitable availability are related but distinct properties, a distinction that Section 5.5 shows to be consequential.

The integrated framework used in this paper holds that observed medicine availability is a function of the interaction between structural vulnerability (a property of network design), organisational capability (a property of firms and health systems), and adaptive agent behaviour (an emergent property of the system under stress), all operating within a boundary set by regulatory and economic institutions.

4. Methodology

4.1. Research Design

The study adopts a qualitative, theory building design combining an integrative literature review with secondary

data analysis and comparative case study. This design is appropriate because the phenomenon of interest, disruption propagation, is a process operating over time within a specific institutional context, and because the relevant variables are not amenable to controlled manipulation.

4.2. Literature Review Protocol

Peer reviewed literature was identified through structured searches of the operations management, pharmacy practice, and public health literatures using combinations of the terms supply chain resilience, pharmaceutical supply chain, drug shortage, medicine shortage, active pharmaceutical ingredient, and disruption management. Inclusion criteria required peer reviewed publication, substantive engagement with either resilience theory or pharmaceutical supply specifically, and English language availability. Grey literature was included where it constituted primary evidence, principally regulatory agency reports, legislative committee analyses, and international organisation publications.

4.3. Secondary Data Sources

Quantitative context was drawn from national regulatory shortage reporting, principally the annual reports to Congress produced by the United States Food and Drug Administration, supplemented by published academic analyses of shortage databases. Because the study was conducted during 2022, figures for that calendar year were not yet available in consolidated form, and the most recent complete reporting year is used where an annual figure is required. Manufacturing concentration data were drawn from regulatory facility registration analyses and Drug Master File based studies, with explicit attention to the well documented limitation that facility counts are a proxy for capability rather than a measure of volume.

4.4. Case Selection

Three disruption episodes from 2022 were selected using a purposive maximum variation strategy, requiring that the set include different trigger types, different product categories, and different regulatory contexts. A fourth episode, COVID-19 vaccine supply, was included as a theoretically informative contrasting case in which substantial ex ante investment in redundancy was made.

4.5. Analytical Approach

Each case was reconstructed as a timeline from trigger event to resolution, and coded against the vulnerability taxonomy developed in Section 2.3 and the strategy taxonomy developed in Section 2.5. Cross case synthesis followed a pattern matching logic, identifying mechanisms present across cases and conditions under which mitigation strategies succeeded or failed.

4.6. Limitations

The study relies on publicly available information, which is systematically incomplete regarding commercial supply arrangements, contract terms, and firm level inventory positions. Shortage data are subject to reporting and definitional variation across jurisdictions. Case reconstruction from public sources risks overweighting well publicised episodes in high income markets, and the paper's coverage of low- and middle-income countries rests on a thinner evidential base than its coverage of the United States and European Union. Findings are analytically rather than statistically generalisable.

5. Findings

5.1. A Typology of Disruption During the Study Period

Analysis of the 2020 to 2022 record supports a distinction between four disruption types, each with a characteristic signature.

Type 1: Node failure. A single physical facility ceases or reduces production. Onset is abrupt, the affected product set is narrow, and the geographic reach is determined by the node's global market share rather than by its location. The 2022 contrast media episode is the canonical example.

Type 2: Demand surge. Consumption rises faster than production can respond. Onset is gradual but accelerating, the affected product set follows epidemiology, and amplification through precautionary buying is severe. The 2022 paediatric antibiotic shortages exemplify this type.

Type 3: Institutional constraint. Regulatory, legal, or policy mechanisms prevent supply from adjusting to demand even when physical capacity exists. The 2022 stimulant shortage, in which manufacturing delays interacted with controlled substance production quotas, illustrates this type, as do the API export restrictions imposed by several countries in early 2020.

Type 4: Systemic shock. Multiple types occur simultaneously across supply, demand, and logistics. The initial COVID-19 period and the 2022 combination of Chinese lockdowns, European energy price escalation, and war related logistics disruption both qualify.

The practical significance of this typology is that mitigation strategies are not interchangeable across types. Inventory buffering is highly effective against Type 1 and largely ineffective against Type 4. Regulatory flexibility is decisive against Type 3 and marginal against Type 2. Strategy selection without disruption type diagnosis is a common source of wasted resilience investment.

5.2. Case A: The Iodinated Contrast Media Shortage (Type 1)

Trigger and propagation. In spring 2022, Shanghai entered an extended lockdown in response to a COVID-19 outbreak. Among the facilities affected was a GE Healthcare plant producing iodinated contrast media, the injectable agents used to enhance visualisation in computed tomography, interventional radiology, and cardiac catheterisation. On 19 April 2022 the company notified customers that it would ration orders of its iohexol product following the temporary shutdown of that product's primary production facility.

The propagation from a single plant closure to a global clinical crisis was rapid, and its speed is explained by three factors acting together. First, node criticality: the affected product represented a very large share of the market, estimated at roughly half of United States supply and around three quarters of the Australian market. Second, downstream thinness: imaging departments typically operated on just in time replenishment, holding only weeks of stock, so the

buffer between a supply interruption and a clinical impact was extremely short. Third, substitution saturation: as customers switched to alternative agents from other manufacturers, those alternatives were rapidly exhausted, and by late May 2022 a third agent from a different manufacturer was also reported as constrained specifically because of demand displaced from the first two. This third factor is the clearest documented instance of complex adaptive amplification in the case set. Rational individual substitution converted a single manufacturer's problem into a category wide one.

Response. The manufacturer's response combined production shifting to an alternative facility in Ireland, mode shifting from sea to air freight to compress replenishment lead time, and deliberate portfolio simplification to concentrate available capacity on fewer product variants. Production at the Shanghai site recovered progressively, reaching approximately 60 percent of normal by late May and returning to near full capacity in early June after local restrictions eased. Supply normalisation lagged production normalisation by a considerable margin, since replenishing depleted downstream inventory requires output above the run rate of consumption for an extended period.

Health system responses were the more instructive part of the episode. Institutions that fared best implemented centralised inventory visibility across their networks rather than allowing site level hoarding, established clinical triage protocols distinguishing time critical from deferrable contrast enhanced studies, adopted weight based and reduced dose protocols supported by scanner reconstruction techniques, substituted alternative imaging modalities including magnetic resonance and ultrasound where clinically acceptable, and switched from single dose vials to multi dose vials with appropriate sterility controls to reduce wastage. Published analyses subsequently documented material reductions in contrast enhanced study volumes during the shortage period, indicating that conservation was achieved substantially through demand management rather than supply restoration alone.

Analytical reading. The case demonstrates that against Type 1 disruptions, the binding constraint is not global capacity but the speed at which capacity can be redirected and demand can be rationed. It also demonstrates that geographic diversification is only protective if the alternative sites carry meaningful capacity. The manufacturer did operate other facilities, but their capacity was insufficient to cover the deficit, which is the practical difference between having a second source and having a second source that matters. The episode also exposed an upstream dependency that had attracted little prior attention, namely the concentration of raw material supply for the affected agents, which sits a further tier back from the manufacturing site that failed.

5.3. Case B: Paediatric Antibiotic and Analgesic Shortages (Type 2)

Trigger and propagation. The northern hemisphere winter of 2022 produced an unusually early and severe respiratory season, with concurrent circulation of respiratory syncytial virus, influenza, and invasive group A streptococcal infection following two years of suppressed transmission and correspondingly reduced population immunity. Demand for paediatric formulations of amoxicillin and for paediatric analgesics rose sharply and unexpectedly. Regulatory authorities in the United States, United Kingdom, and several European countries recorded shortages of oral suspension formulations from the autumn onward. The episode was still developing at the time of writing, and the account here is therefore of its mechanism rather than of its resolution.

The propagation mechanism differs fundamentally from Case A. There was no manufacturing failure. The constraint was that production capacity for these products is planned against forecasts derived from historical seasonal patterns, and the manufacturing lead time for oral suspensions, including API procurement, formulation, filling, quality release, and distribution, substantially exceeds the timescale over which an epidemic curve develops. Capacity that is economically sized to normal seasonal peaks cannot, by construction, absorb an anomalous one. Aifuwa and colleagues (2020) show that predictive analytics can materially improve demand forecasting accuracy and reduce inventory inefficiency, and Tonoyan and colleagues (2021a) demonstrate comparable gains from machine learning methods, but the improvement available in this case was bounded by manufacturing lead time, since a better forecast of an epidemic curve confers little advantage when the production response takes longer than the curve itself.

Amplification was again significant. Precautionary prescribing, parental stockpiling, and pharmacy level ordering above normal replenishment all contributed. The dosage form dimension proved important: shortages concentrated in paediatric suspensions rather than in the same molecule in adult solid dose form, because suspension filling capacity is narrower and because substitution across dosage forms is limited for young children.

Response. Effective responses included regulatory facilitation of compounding, where pharmacists prepared suspensions from solid dose forms under specified protocols; serious shortage protocols permitting pharmacist level substitution without individual prescriber re authorisation; clinical guidance restricting antibiotic prescribing to cases meeting defined criteria, thereby reducing demand of low clinical value; and importation of foreign labelled product under regulatory discretion. Manufacturers increased line utilisation, though the response lag was measured in months.

Analytical reading. Type 2 disruptions are managed principally on the demand side and through regulatory flexibility, not through supply expansion, because supply cannot expand within the relevant timeframe. The case also exposes the limits of a purely commercial capacity planning logic for essential medicines. No firm has a commercial incentive to hold idle suspension filling capacity against a one in ten-year respiratory season, which means that if society values that capacity, society must pay for it explicitly rather than expecting it to appear as a byproduct of competitive markets.

5.4. Case C: Stimulant Shortages And The Quota Constraint (Type 3)

Trigger and propagation. In autumn 2022 a shortage of amphetamine mixed salts emerged in the United States, initially triggered by manufacturing and labour related delays at a major producer. Under ordinary market conditions competitors would increase output to absorb displaced demand. In this instance they could not do so freely, because

production of controlled substances is governed by aggregate and firm level quotas administered by the Drug Enforcement Administration. Quota adjustment is an administrative process operating on a timescale poorly matched to acute shortage. The shortage was further deepened by a genuine and sustained increase in diagnosis and prescribing volume, meaning the underlying demand baseline had shifted upward.

Analytical reading. The case is analytically valuable because the constraint was institutional rather than physical. It illustrates a general point that recurs across the study period: policy instruments designed for one legitimate objective, in this instance diversion control, can become binding constraints on supply resilience, and the interaction is typically not assessed in advance. The same structure appeared in the export restrictions on APIs and finished formulations imposed by several exporting countries in early 2020, which were domestically rational and collectively harmful to global availability, with the greatest burden falling on import dependent low- and middle-income countries.

5.5. Contrasting Case: COVID-19 Vaccine Supply

The vaccine case is included because it is the study period's clearest instance of a supply chain deliberately engineered for resilience ex ante, and because its partial successes and clear failures are both instructive.

Elements that functioned well included advance purchase commitments that de risked capacity investment before efficacy was established, at risk parallel manufacturing scale up conducted before regulatory approval, extensive contract manufacturing partnerships that expanded the production base rapidly, and unprecedented technology transfer between competing firms. These are textbook redundancy and flexibility strategies, and they worked. Production volumes achieved within eighteen months exceeded what conventional planning would have deemed feasible.

Elements that functioned poorly are equally informative. Upstream inputs, notably lipid nanoparticle components, single use bioreactor bags, filters, and vials, became binding constraints because scale up planning focused on drug substance capacity while the supporting input base remained concentrated. Cold chain requirements created a distribution vulnerability that fell disproportionately on health systems without ultra-cold infrastructure. Most significantly, allocation was determined by purchasing power rather than epidemiological need, producing a distribution outcome in which high income countries secured supply far in excess of immediate requirements while much of Africa waited. This last point deserves emphasis in a paper on resilience: a supply chain can be resilient in the engineering sense, maintaining flow under stress, while failing entirely at the objective that motivates the resilience, which is availability of medicine to those who need it. Resilience and equity are separable properties, and optimising the first does not deliver the second.

5.6. Cross Case Synthesis

Five mechanisms recur across the case set.

Mechanism 1: Node criticality determines reach. In every case, the geographic and clinical extent of impact tracked the market share of the constrained node, not the size or location of the triggering event. This is the single most important finding for practical risk assessment, and it implies that risk registers organised by supplier or by country are less informative than registers organised by product level source concentration.

Mechanism 2: Downstream thinness determines speed. Just in time inventory in hospitals and distributors compresses the interval between a supply interruption and a clinical impact to weeks or less, eliminating the time in which mitigation might otherwise be arranged. Buffer stock does not prevent shortages but converts them from acute crises into manageable procurement problems, which is a materially different thing.

Mechanism 3: Adaptive behaviour amplifies. Substitution saturation, precautionary ordering, and hoarding are individually rational and collectively destructive. Every case in which allocation was managed centrally, whether by a manufacturer, a health system, or a regulator, outperformed cases in which allocation was left to first come first served ordering.

Mechanism 4: Institutional rigidity converts constraints into shortages. Where regulatory mechanisms could flex quickly, through compounding permissions, importation discretion, substitution protocols, or expedited source qualification, impact was contained. Where they could not, as with quota administration, impact persisted well beyond the physical constraint.

Mechanism 5: Visibility precedes everything. In each case, the interval between the physical event and general awareness of its consequences was substantial. Health systems learned of the contrast media problem through a manufacturer letter, not through any monitoring system of their own. No amount of downstream capability compensates for late detection.

6. Discussion: A Four Layer Resilience Framework

The findings support a framework organising resilience capability into four layers, each addressing a specific mechanism identified above, supported by three cross cutting enablers. The framework's central claim is that these layers are ordered: investment in later layers yields limited return without the earlier ones in place.

Layer 1: Visibility and Early Warning

Addresses Mechanism 5.

The foundational capability is knowing what the network actually looks like and detecting deviation early. Practical components include multi-tier supply mapping extending to key starting materials rather than stopping at the API supplier; product level source concentration analysis that identifies molecules with fewer than a threshold number of independent global producers; convergence analysis to detect hidden common dependencies among nominally diversified sources; monitoring of leading indicators including regulatory inspection outcomes, import alerts, facility level quality signals, trade flow data, and epidemiological surveillance; and a formal criticality classification of the product portfolio combining clinical essentiality, substitutability, and supply concentration.

Nnabueze and colleagues (2021) emphasise that visibility of this kind is a cross tier traceability problem rather than an internal reporting exercise, while Eze and colleagues (2022a)

argue that detection is only valuable when coupled to a defined response pathway, since early warning without a mechanism to act on it produces nothing more than earlier knowledge of an unavoidable shortage. Adeyelu (2018) demonstrate the same principle in aviation oversight, where predictive compliance monitoring is designed to surface systemic risk before it manifests as an incident, and Ahiaeke Patrick and colleagues (2021) show that supplier assessment can draw on data external to the supplier relationship rather than relying on self-reported information.

The principal barrier is informational rather than technical. Upstream supplier identity is frequently treated as commercially confidential, and firms have limited leverage to compel disclosure. This is one of several points at which resilience requires regulatory action rather than firm initiative alone, and the case for mandatory supply chain transparency for products designated as clinically essential is, on the evidence of this study, strong.

Layer 2: Buffering and Redundancy

Addresses Mechanism 2.

Buffering converts abrupt shortages into manageable ones by inserting time. Components include strategic reserves of finished product for critical medicines, held at national, health system, or manufacturer level; API and key starting material stockholding, which is often more efficient than finished dose stockholding because a single API can serve multiple presentations and typically has longer stability; capacity reservation contracts, under which purchasers pay for the option on surge capacity rather than for the product itself; and qualified alternative sources, pre-approved and periodically exercised.

The design questions that determine whether buffering is worth its cost are which products, how much, held where, and paid for by whom. The evidence supports a targeted rather than universal approach, with buffer depth scaled to criticality classification from Layer 1 rather than applied uniformly. Oyeleye and colleagues (2022) clarify the apparent conflict with lean practice, demonstrating that the target of lean intervention is elapsed process time rather than inventory position, a distinction routinely collapsed in pharmaceutical purchasing where it is the reduction of buffer that produces fragility. Okonkwo and colleagues (2018b) make the same point from the industrial side, connecting inventory availability directly to operational uptime, and Tonoyan and colleagues (2021b) situate the decision correctly as a working capital commitment made under uncertainty. It also supports positioning buffers upstream where product stability permits, and rotating stock through normal consumption to avoid obsolescence. The financing question is the hardest: buffer stock held by manufacturers is a cost that competitive tendering will not reimburse, which means it will not be held unless purchasing practice changes or public financing is provided.

Layer 3: Flexibility and Agility

Addresses Mechanism 1, by reducing node criticality.

Flexibility reduces dependence on any specific node. Components include multi-site qualification of critical products, so that production can be shifted without a lengthy approval process; flexible manufacturing platforms, including continuous manufacturing and modular facilities capable of switching between products with short changeover; postponement strategies that hold product in generic intermediate form and differentiate late; formulation and presentation flexibility including multi dose presentations and alternative dosage forms; and logistics flexibility including pre-arranged alternative modes and routes.

Continuous manufacturing deserves specific mention because it addresses several vulnerabilities simultaneously. Its smaller footprint reduces the capital threshold for domestic or regional production, its shorter cycle time compresses response lag, and its inline quality monitoring reduces the batch failure risk that itself causes shortages. Adoption during the study period remained limited, constrained by capital cost, regulatory familiarity, and the fact that the products most in need of it are the least able to fund it.

Layer 4: Collaboration and Governance

Addresses Mechanism 3 and Mechanism 4.

The mechanisms of amplification and institutional rigidity cannot be addressed by any single organisation, because they are properties of the system rather than of its components. Components at this layer include information sharing arrangements between manufacturers, distributors, and health systems on supply status and demand signals; pre agreed allocation protocols specifying how scarce product will be distributed before scarcity occurs, since protocols negotiated during a crisis reliably favour the strongest party rather than the greatest need; joint contingency planning between purchasers and suppliers; and standing coordination mechanisms between regulators across jurisdictions to enable stock reallocation, mutual recognition of foreign labelled product, and coordinated regulatory flexibility.

Ike and colleagues (2021) and Akinleye and Adeyoyin (2022b) both position supplier relationship management as the practical vehicle for this layer, on the argument that information sharing and joint planning require a contractual and relational foundation that transactional purchasing does not create. Eyetsemitan and colleagues (2020) address the governance alignment required when multiple organisations share responsibility for a single operation, and Arumosoye and Obriki (2020) develop the equivalent model for multi-party accountability where the consequences of failure fall outside the contracting parties, which is the defining feature of medicine shortage.

The evidence from Case A is that centralised allocation within a health system consistently outperformed decentralised ordering, and the evidence from the vaccine case is that the absence of a binding global allocation mechanism produced an outcome that no participant would have defended as equitable.

Enabler 1: Digital Infrastructure

Digital capability underpins all four layers. Relevant technologies include supply chain control towers integrating supplier, inventory, and demand data; predictive analytics for shortage forecasting using leading indicators; digital twin simulation for stress testing network designs before committing capital; serialisation infrastructure, originally mandated for anti-counterfeiting purposes but generating unit level traceability data that is directly useful for shortage detection; and distributed ledger applications for multi-party visibility where trust between parties is limited. Filani and colleagues (2022) demonstrate real time risk assessment dashboards using machine learning in hospital supply chain

systems, and Akinleye and Adeyoyin (2021) argue that process automation improves transparency principally by making activity legible across organisational boundaries rather than by improving any single decision. Ilodigwe and Adesemoye (2021) place the emphasis earlier still, contending that interoperability and data quality governance are the precondition for analytics at national scale. Sanni and Atima (2021b) describe the presentation layer such systems require, noting that the binding constraint is frequently interpretation rather than data availability, and Mbonu and colleagues (2020b) caution that the visibility infrastructure is itself a system with failure modes that must be governed.

The caution warranted here is that digital tools are frequently proposed as a substitute for the organisational and institutional changes described above, when they are only an amplifier of them. A control tower populated with data from a supply network that has never been mapped beyond tier one is an expensive dashboard.

Enabler 2: Regulatory Agility

Regulators shape resilience more directly in this sector than in almost any other. Productive mechanisms observed during the study period include expedited review of supplemental applications for alternative sources during shortage; temporary importation of foreign approved product; extension of expiry dating based on stability data; exercise of enforcement discretion on labelling and packaging; mandatory early notification of manufacturing interruptions, which the evidence suggests was the single most effective intervention in reducing new shortage initiations; and permissions for compounding and pharmacist substitution during scarcity. Two proposals in the recent literature are worth noting because they make regulatory obligation operational rather than declaratory. Eze and colleagues (2022b) propose a regulatory readiness maturity model that allows a firm's capacity to respond to regulatory requirements to be assessed before a shortage forces the question, and Eyetsemitan and colleagues (2021) address the operational counterpart, namely the translation of regulatory obligations into workable internal processes. Arumosoye and Obriki (2021) provide the maturity model logic in the safety domain, where the object of assessment is the organisation's learning capability rather than its documentation. Building these mechanisms into standing frameworks rather than improvising them under emergency conditions is a clear and low-cost recommendation.

Enabler 3: Procurement Reform

This is the enabler most often omitted and most consequential. Tendering practice that awards contracts on lowest unit price, with no contractual value attached to supply reliability, produces exactly the market structure observed: consolidation onto the lowest cost producer, elimination of redundant capacity, and disappearance of the margin that would fund resilience investment. Any serious programme to improve pharmaceutical supply resilience must change how medicines are bought.

Practical mechanisms include multi criteria award frameworks that score supply chain transparency, source diversification, and inventory commitments alongside price; multi winner tenders that deliberately preserve more than one supplier per molecule even at higher aggregate cost; longer contract terms that permit suppliers to amortise resilience investment; volume commitments that reduce the demand uncertainty which itself discourages capacity investment; and explicit payment for capacity availability separate from payment for units delivered. Efobi and colleagues (2022a) show that non-price criteria can be operationalised, weighted, and scored in a repeatable way, and Okojie and Abioye (2020) demonstrate the same in a domain where safety cannot be traded against cost, which is the closer analogue to medicines. Akomolafe and Agu (2019a) provide the risk evaluation framework within which such scoring would sit, and Okonkwo and colleagues (2019) illustrate that contract and vendor governance can pursue cost control and supply assurance jointly rather than sequentially. The principal obstacle to multi criteria award is therefore the absence of an agreed scoring methodology for reliability, not any legal constraint.

Each of these raises acquisition cost. The relevant comparison is not against the current tender price but against the total cost of shortages, including substitute product cost, staff time, clinical harm, and the emergency procurement premiums that shortages reliably generate.

6.1. Why Underinvestment Persists

The framework above describes what should be done. RQ4 asks why it is not. The analysis identifies four reinforcing causes.

First, resilience is a positive externality. A manufacturer that invests in redundant capacity bears the full cost and captures only part of the benefit, since much of the value accrues to patients and health systems. Standard economic reasoning predicts underprovision, and that is what is observed.

Second, the payoff structure is adverse. Resilience investment produces a certain, immediate, visible cost against an uncertain, deferred, invisible benefit. When it works, nothing happens, and nothing happening is difficult to claim credit for.

Third, competitive dynamics punish unilateral investment. In a price only tender, the firm that has invested in dual sourcing and buffer stock loses to the firm that has not. Resilience investment is therefore a collective action problem requiring either coordination or regulation to resolve.

Fourth, accountability is fragmented. No single actor owns medicine availability end to end. Manufacturers are accountable for their own supply, distributors for their own service levels, regulators for safety and quality, and health systems for patient care. The shortage falls into the gaps between these mandates.

These causes jointly imply that firm level exhortation will not solve the problem, and that intervention must operate on the incentive structure itself.

7. Recommendations

7.1. For Manufacturers

Conduct multi-tier mapping of critical products to the key starting material level, and specifically test for hidden convergence among nominally independent sources. Establish a criticality classification for the product portfolio and differentiate resilience investment accordingly rather than applying uniform policies. Pre-qualify alternative manufacturing sites and API sources for the highest criticality products, and exercise those alternatives periodically so that the qualification remains live. Move toward flexible manufacturing platforms where the product economics permit. Participate constructively in early notification regimes, since the evidence indicates early notification is the

highest return intervention available. Treat allocation policy as a planning deliverable to be prepared in advance rather than a decision to be improvised under pressure.

7.2. For Hospitals and Health Systems

Establish network wide inventory visibility, since site level hoarding during shortage is a predictable and destructive behaviour that visibility largely prevents. Maintain defined buffer levels for a designated critical medicines list, accepting the carrying cost as insurance. Develop therapeutic substitution and conservation protocols in advance for high risk categories, drawing on the contrast media experience, where institutions with preexisting protocols outperformed those improvising. Formalise the shortage management function with named accountability rather than treating it as unassigned pharmacy overhead. Incorporate supply reliability criteria into purchasing decisions and be prepared to pay a premium for it. Participate in regional coordination and mutual aid arrangements with peer institutions. Ilodigwe and Adesemoye (2021) argue that the value of health system data infrastructure depends on governance and quality rather than on the systems purchased, which is consistent with the finding here that the institutions managing the contrast media shortage most effectively did so through protocol and coordination rather than through any system they had acquired. Obogo and colleagues (2022) make the parallel argument for facility level operations, treating governance as a standing function rather than an emergency response.

7.3. For Regulators and Policymakers

Codify emergency regulatory flexibilities into standing frameworks with pre-defined activation criteria. Extend and enforce mandatory notification of manufacturing interruptions, and consider extending notification obligations upstream to API producers. Mandate supply chain transparency for products designated as clinically essential, overriding commercial confidentiality claims where necessary. Establish and maintain strategic reserves for a defined essential medicines list, with active stock rotation. Conduct systematic review of policy instruments that constrain supply adjustment, including production quotas, and build shortage responsive flexibility into them. Reform public procurement to price reliability. Assess trade policy instruments, particularly export restrictions, against their effect on global availability, recognising that restriction is beggar thy neighbour policy with predictable retaliation dynamics. Fund the capacity that markets will not fund, including surge capacity for seasonal products and domestic or regional production of designated critical inputs, and do so through transparent mechanisms rather than by expecting private actors to absorb it.

7.4. For Low- And Middle-Income Countries

The vulnerability profile in import dependent countries differs from that of high-income markets in ways that make several standard recommendations inapplicable and others more urgent. Import dependency is typically high, foreign exchange availability constrains procurement, regulatory capacity for expedited approval or importation discretion may be limited, distribution infrastructure including cold chain is thinner, and substandard and falsified products proliferate during genuine shortages, adding a safety dimension absent in better regulated markets. These countries are also structurally last in the allocation queue during global scarcity, as the vaccine case demonstrated unambiguously. Asiedu and Asiedu (2022) identify last mile distribution to underserved communities as a distinct failure point that persists even when national level supply is adequate, and Okonkwo and colleagues (2020) add a logistics dimension frequently omitted from clinical analyses, namely that port and customs performance can determine effective lead times in import dependent economies more than manufacturing schedules do.

Priorities differ accordingly. Regional pooled procurement is the highest leverage single intervention available, since it converts small fragmented national markets into volumes large enough to attract reliable suppliers and to command allocation priority. Regional manufacturing capacity, pursued through initiatives such as the African Union's programme for expanded local vaccine and medicine production, addresses the allocation queue problem structurally rather than transactionally, though it requires sustained demand commitments to be commercially viable, and the evidence from the post pandemic period is that such commitments have been harder to secure than the manufacturing investment itself. Regulatory strengthening and harmonisation, including reliance mechanisms that allow national authorities to leverage approvals by stringent regulators rather than duplicating review, reduces both approval lag and the regulatory cost of serving small markets; Adeyelu and Dagodzo (2022) demonstrate the benchmarking approach that such harmonisation requires, comparing certification compliance across developing regions to identify where capability rather than standards is the binding constraint. Ilodigwe and Adesemoye (2020) point to pharmacy led delivery and access models as a distribution side complement to these supply side reforms, Aminu-Ibrahim and colleagues (2020) to infrastructure led expansion of diagnostic access, and Anene and Clement (2022) to localised and predictive logistics arrangements as a structural response to allocation disadvantage. Dogbatsey and Ebhojie (2018) addresses the public financing and reporting capacity on which any of these depends. Strategic buffer stocks for essential medicines matter more, not less, where replenishment lead times are long and foreign exchange access is intermittent. Finally, quality assurance capacity must scale alongside supply diversification, since diversification into unqualified sources trades a shortage problem for a safety problem.

8. Limitations and Future Research

The limitations set out in Section 4.6 apply to the findings. Three deserve restatement. The reliance on public information means firm level capability is inferred from observed outcomes rather than measured directly. The case set is drawn from episodes prominent enough to generate documentation, which biases toward high income markets and toward disruptions with visible clinical consequences. The framework proposed in Section 6 is derived analytically and has not been empirically validated against outcome data. Four research directions follow. First, resilience measurement remains underdeveloped: the field lacks validated, comparable indicators of supply chain resilience at product, firm, and system level, without which the return on resilience investment cannot be evaluated and policy cannot be targeted. Arumosoye and Obriki (2021) offer the most useful template available, in that their maturity model assesses organisational learning capability rather than

documented compliance, and Aminu-Ibrahim and colleagues (2019) frame the same difficulty in the health infrastructure setting as the problem of translating investment into measurable capacity. Second, the economics of resilience require formal treatment, specifically the total cost of shortages, including clinical and administrative costs typically excluded, set against the cost of the mitigation options catalogued here. Third, procurement mechanism design is a tractable and high value research problem: what contract structures induce suppliers to invest in reliability while remaining affordable to public purchasers, and what does the empirical evidence from jurisdictions that have piloted multi criteria tendering show. Fourth, the low- and middle-income context is substantially understudied relative to its share of the global disease burden, and research conducted in and by institutions in those settings is needed rather than the extension of high-income findings by analogy.

9. Conclusion

The pharmaceutical supply chain failures observed during 2020 to 2022 were not accidents. They were the predictable output of a system optimised over three decades for unit cost under the implicit assumption that conditions would remain stable. Each individual decision that produced the current architecture, offshoring API production, consolidating manufacture onto the lowest cost site, thinning inventory, tendering on price, was defensible in isolation. Their aggregate effect was a system in which a two-month lockdown of one city could interrupt diagnostic imaging on four continents within weeks.

The three cases examined here point consistently to the same conclusion regarding RQ1 and RQ2: the decisive vulnerability is product level source concentration, and the decisive accelerant is the absence of downstream buffer. Node criticality determines how far a disruption reaches; inventory thinness determines how fast it arrives; adaptive behaviour by rational actors determines how much worse it becomes; and institutional rigidity determines how long it lasts.

On RQ3, the strategies with demonstrated effectiveness are considerably more modest than the technological visions that dominate industry discussion. Mandatory early notification, centralised allocation within health systems, preexisting conservation protocols, regulatory flexibility on compounding and importation, and targeted buffer stock all performed. They share the property of being organisational and institutional rather than technological, and of being inexpensive relative to their effect.

On RQ4, the reason these measures are not universally in place is that the incentive structure does not reward them. Resilience is a positive externality with a certain cost and an invisible benefit, produced in a market that competes on price alone. That diagnosis carries a clear implication: the primary lever is not exhortation of manufacturers but reform of how medicines are purchased and how supply obligations are regulated. Until reliability is something a supplier can be paid for, it will remain something suppliers cannot afford to provide.

There is a final observation that the vaccine case makes unavoidable. A supply chain can be resilient without being equitable. Engineering the system to maintain flow under stress is necessary but not sufficient, because flow can be maintained toward those who can pay while those who cannot are simply removed from the demand signal. If the objective of this field of research is medicine availability rather than supply continuity as such, then allocation is not a peripheral question of distributive ethics appended to the operational analysis. It is part of the operational analysis, and it belongs in the design.

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