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Resilience and efficiency for the nanotechnology supply chains underpinning COVID-19 vaccine development

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Nanotechnology facilitated the development and scalable commercialization of many SARS-CoV-2 vaccines. However, the supply chains underpinning vaccine manufacturing have demonstrated brittleness at various stages of development and distribution. Whereas such brittleness leaves the broader pharmacological supply chain vulnerable to significant and unacceptable disruption, strategies for supply chain resilience are being considered across government, academia, and industry. How such resilience is understood and parameterized, however, is contentious. Our review of the nanotechnology supply chain resilience literature, synthesized with the larger supply chain resilience literature, analyzes current trends in implementing and modeling resilience and recommendations for bridging the gap in the lack of quantitative models, consistent definitions, and trade-off analyses for nano supply chains.

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Introduction: what SARS-CoV-2 vaccines taught us

The SARS-CoV-2 pandemic spurred innovation towards the research and scalable manufacturing of new drugs and vaccines, including contributions from emerging biotechnologies and nanotechnologies. Developmental timelines for items such as monoclonal antibodies or innovative vaccine development platforms (e.g. the Pfizer-BioNTech and Moderna mRNA vaccines) were rapid, drawing from extensive bodies of research related to (nano)technological capabilities and safety measures [1]. Despite these considerable successes, however, the supply chain networks responsible for large-scale manufacturing and distribution remain rooted in efficient yet brittle system design principles [2], ultimately forcing cuts and delays in promised vaccine deliveries to various countries and regions at multiple points from manufacture to last-mile delivery [3]. Disruptions in vaccine manufacturing and distribution such as those resulting from deliberate sabotage [4], manufacturer defect and liability [5], logistical resource acquisition and distribution failures [6] have impacted everything from local to even national vaccine availability — hindering public health efforts and threatening vaccine policy goals.

Disruption is inevitable, but implementing resilience in the supply chains underpinning these nanomedical developments is critical to maintaining normal operations during disruptions [7•], minimizing their duration and effect, and maximizing public good. Despite the critical importance of bringing to the global market SARS-CoV-2 vaccines, the operationalization and implementation of supply chain resilience remains in its infancy for the pharmaceutical industry and the nanomaterials critical for novel vaccine platforms and is exacerbated by cold chain requirements for some vaccines [8]. Commercial pharmaceutical supply chains are designed to be as efficient as possible within the confines of meeting strict regulatory guidelines [9]. The supply chains underpinning the SARS-CoV-2 vaccine are no different [10], extending efficiency even into the regulatory aspect, from streamlined development to faster clinical trials and Emergency Use Authorization (EUAs) [11]. For example, while Moderna and Pfizer/BioNTech have incorporated into their vaccine development programs the critical lipid nanoparticles (LNPs) essential for their vaccine platforms due to their ideal antigen delivery and the theoretical ability to rapidly scale their manufacturing [12], these pharmaceutical corporations have experienced and likely will continue to experience significant vaccine delivery setbacks due to disruptions in their supply chains [13].

Although the nanotechnology itself and the ability to manufacture the critical nanomaterials facilitated the unprecedented feat of bringing to market multiple novel and globally authorized SARS-CoV-2 vaccines, the fundamental lack of resilience in the network of supply chains underpinning nanotechnology hindered the capacity of global vaccination targets to be achieved. In order to understand the lack of resilience and how best to operationalize it, we review available literature on nanotechnology supply chain resilience and synthesize it with the broader supply chain resilience literature. In doing so, we offer insight regarding how resilience is framed as a philosophy and practice within nanotechnology supply chains (within pharmacological contexts), and indicate areas of convergence and divergence in scholarly opinion.

Review: nano supply chains and resilience

As nanotechnologies becomes more prevalent in vaccine and pharmaceutical applications [14], the supply chains underpinning them become subsequently larger and more complex. Despite this, our search shows the literature modeling resilience in these nano supply chains remains underdeveloped, with only seven nano supply chain publications specifically addressing resilience modeling published in the recent academic literature.

COVID-19 nano supply chain literature

Five of the seven nano supply chain resilience studies are spurred by or draw on the COVID-19 pandemic. At a high level, these publications provide valuable insight and analysis of implications of the industry having largely ignored resilience before the cascading supply chain impacts of the COVID-19 pandemic, proposing 'resilience' as a way forward. Despite this call to action, none provide a quantifiable manner with which to operationalize the true four-stage considerations of resilience. And while two of the seven publications propose supply chain visibility or mapping as vital for manufacturers and society to withstand disruptions [15•,16], this is only a tool or first step towards resilience, and not resilience itself.

All but two provide network representations of the nano supply chains. Goel *et al.* limit discussion of supply chain resilience to the location where the product demand lies [17]. This narrowed the label of resilient to that of the country rather than the supply chain, and it focused the discussion around outsourcing and onshoring [17]. Of course, these are strategies that can be leveraged by companies for nano supply chain design, but a methodology would need to be developed. While McClements *et al.* similarly do not provide an approach for operationalizing resilience in the supply chain network directly, the authors offer individual tools and strategies that can be implemented at specific nodes and transportation links to make the food supply system more resilient [18]. Leveraging nanotechnologies and materials in accordance with the authors' recommendations is necessary for a more resilient food supply system, but implementing resilience in the underlying nanotechnology supply chains that will give the globe food security must be further addressed.

Bhaskar *et al.* propose a framework that incorporates newer supply chain technologies with stronger governance recommendations, highlighting the importance of stockpile profiles, efficient production using blockchain, and effective public health policy interventions when necessary [15•]. Although this framework leverages blockchain as the connector or 'link' of the supply chain graph, and uses big-data analytics for predictive forecasting and demand, under a national command center for procurement, quality control and distribution, there is a lack of developed strategy for disruption recovery and adaptation, or true resilience. However, Bhaskar *et al.* do offer a holistic supply chain model that can be used as a first step towards bridging the supply chain resilience gap in the nanotechnology supply chains underpinning the critical medical sector.

Sarkis *et al.* explore mathematical models that can be used as tools to account for the unprecedented demand shock in nanomedicine manufacturing, due to both novel vaccine platforms (e.g. vector-based and RNA-based for SARS-CoV-2 vaccines) and Advanced Therapy Medicinal Products (ATMPs) manufacturing success [19•]. The authors find that different vaccine platforms and other emerging nanomedicines will face bottlenecks at varying stages of the value chain, concluding in the wide spread need for decision-support tools that inform operational planning and strategies in order to account for this uncertainty [19•]. The authors describe Mixed Integer Linear Programming (MILP) as a method for planning supply chain network structures that meet multiple objectives, including being patient-centric and cost-efficient, but do not ultimately discuss the network structures and resilience [19•].

Despite the duality between efficiency and resilience being one of many, only Diaz-Elsayed *et al.* provide specific trade-offs and compromises to be considered in tandem with resilience implementation, showcasing efficiency, responsiveness, smartness, and sustainability [16]. To further delve into this trade-off analysis, Diaz-Elsayed *et al.* also develop the concept of supply chain 'immunization,' which they define as the cost-effective manner in which manufacturers can optimize reactions to global disruptions. Diaz-Elsayed *et al.* propose this idea as a direct result of the supply chain disruptions caused by the COVID-19 pandemic, and the apparent need to redesign these supply chains to cost-effectively and constantly meet demand, calling for a shift towards regionalism [16]. Although this network redesign does provide valuable considerations and an approach for an implementable supply chain model, ultimately 'immunization' provides neither a quantifiable metric for disruption nor a replacement for the largely accepted term 'resilience,' muddling clear and well-modeled terms such as responsiveness, leanness, and sustainability that all have a basis in supply chains. Resilience is a characteristic of a supply chain, regardless of whether the disruption is acute, cascading, or, even as Diaz-Elsayed *et al.* argue, stemming from the 'new dimension' of global risk.

Other relevant studies focus on challenges within the global vaccine supply chain networks. A shortage of global public investment expanding the production capacity of input suppliers has been cited as one of the main problems in the supply chains along with an excessive geographic concentrations of input suppliers [2]. The regionalism associated with input production also requires an extra transportation step because global manufacturers are not always located close to their inputs [2]. The authors of one study claim in their analysis that the five biggest challenges to COVID vaccine supply chains were the limited number of vaccine manufacturing companies, poor coordination with local organizations, a lack of vaccine monitoring bodies, difficulties in monitoring and controlling vaccine temperature, and vaccination cost and lack of financial support for vaccine purchase [20••].

Limited nano supply chain resilience literature

Perhaps due to the governance issues and wide application capabilities of nanotechnology, many of the publications on nano supply chain resilience enumerate a variety of disruptions to the interconnected global supply chains, including policy changes, economic stresses, natural disasters [18], computer security [21], political stressors [16], uncertainty in demand and supply [19•] targeted reverse engineering attack [22], and future pandemics [15•]. Despite acknowledgement of the chaos these disruptions cause on supply chains and the need to drive forward supply chain resilience, only two of these publications draw on efficiency-driven or lean supply chains as the foil for resilience [15•,16]. Others draw on characteristics outside the direct network implementation of the supply chain from increased global population [18] to increased cyber connectivity and malicious capabilities [21,22] to globalization and increasing complexities in general. Scalability of nanotechnology is also a vital consideration in all the publications, largely due to the novelty of the nanotechnology/materials and consequently the supply chains underpinning them.

Moving forward: operationalizing resilience

Synthesizing the nano supply chain resilience literature with that of the supply chain resilience field indicates that lean and just-in-time manufacturing have long been the norm [23], and that pharmaceutical operations have also favored efficiency in supply chains underpinning traditional blockbuster drugs. However, the pandemic has propelled the importance of supply chains to the public eye with a larger emphasis on resilience, especially in supply chains of critical importance, such as pharmaceuticals [24].

Our review of the larger supply chain resilience literature and the vaccine supply chains in general provides context and parallels for the dearth of studies on nano supply chain resilience literature. Our review shows that despite the significant financial and social burden that disruption to the vaccine supply chains would have, and the presence of stringent regulations, the resilience models remain limited in scope, largely focusing on expected threats, and narrow timeframes, domains, and networks [25•]. The existing dominance of risk-based approaches to supply chain management must be complemented by resilience-thinking, and leveraging tools that can accommodate multiple stakeholder needs, and the big data that gives visibility, improved mapping and digital infrastructure to supply chains and all the components that constitute value generation [26]. Incorporating network science and resilience analytics into a common framework can facilitate nano supply chain design, implementation, and management. This can be done with the help of digitization (i.e. Industry 4.0 and digital twins) strategies, which can help pinpoint areas that can incorporate redundancy, for example, as a resilience strategy [27].

Common areas to consider in creating a wholistic framework applicable to the rapid pace of nanotechnology development and to the ensuing regulatory requirements include knowledge sharing and transparency in nanotechnology research and development [28•], stakeholder awareness and participation [29], acknowledgement of the pacing problem [30], implementation of sustainability impact assessments [31], and bioavailability [32]. Some systems, such as Quality by Design (QbD) [19•] and the OECD's Safe(r) Innovation Approach for implementing safety-by-design [33] in nanotechnology applications have been outlined but have yet to be implemented. Other advanced decision-making frameworks such as multi-criteria decision analysis (MCDA) have proven useful for safely and effectively researching and developing emerging technologies in nanomedicine [34]. As such frameworks gain traction, it is paramount that these considerations given to the protocols governing the emergence and innovation of nanotechnology extend to the supply chains which underpin the vaccine sector. Network science and resilience analytics provide a complementary framework that bridges the gap between innovation, regulation, and resilience of supply chains.

While regulations and innovation strive for a balance between efficiency and safety, the risk management framework that this rests on needs to be adapted and extended to incorporate resilience analytics (Table 1). Informed decision making must consider the entirety of the supply chain and adequately account for resilience in all portions of the supply chains' design and implementation [35•]. While it is imperative to ensure safety and minimize risk in the application of nanotechnology to vaccine development, the speed of delivery to the public is also of importance in the near and long term. Not only do existing and new variants of the coronavirus continue to impact populations worldwide, but the rapid pace of globalization also accelerates the dispersion of new viruses [36]. In order to effectively implement strategies

Table 1

Resilience analytics is complementary to risk management, facilitating balance between efficiency and resilience in nanotechnology supply chains (SCs)

	Risk management	Resilience analytics	Comparative nano SC examples
Goal	Harden individual SC components (e.g. links or nodes).	Design nodes, links, and topology to be self-reorganizable, or have a system in place to rectify disruption and simulate recovery.	Efficiency focused implementation: increase inventory of vital nanomaterial. Resilience focused implementation: contract multiple suppliers of vital nanomaterial across different regions.
Threat	Predictable disruptions, acting primarily from outside the system on nodes and links.	Either known/predictable or unknown disruptions, acting at a component, system, or societal level (i.e. interdependent constellation of networks).	Recoverable threat for efficiency focused: production delays due to anticipated hurricane season. Recoverable threat for resilience focused: supply and demand shocks due to pandemic and subsequent vaccine development.
Direct consequence	Vulnerable nodes and/or links fail as result of threat.	Degradation of critical SC functions in time and capacity to deliver product and maintain societal need.	Risk management failure: nanomaterial is not available, causing bottleneck and decreased vaccine manufacture. Resilience failure: nanomaterial shortage causing fewer vaccinations and worse pandemic outcomes.
Stages/analytics	Prepare and absorb (risk is product of threat, vulnerability and consequences and is time independent).	Prepare, absorb, recover, and adapt (explicitly modeled as time to recover SC function and the ability to change SC configuration in response to threats, and other relevant systems/networks).	Risk management model: quantify lost production due to historic weather events impacting nanomaterial SC. Resilience model: use digital twins to model time to recovery from climate change events across different nanomaterial SC designs.

that facilitate timely and comprehensively recovering from current and future disruptions, the nano supply chain field should intentionally and methodically begin to incorporate resilience into its operations. In light of our findings, we broadly recommend (1) standardization; (2) application of network science and big data; and (3) informed decision-making through understanding trade-offs.

Our first recommendation, standardization, is necessary in both the supply chain language and the resilience language used to discuss the nano supply chain (including the nano supply chains underpinning COVID-19 vaccines). As the case in the larger supply chain resilience literature, implementing standard supply chain language and standard resilience language will facilitate qualitative and quantitative advancements in operationalizing nano supply chain resilience. For example, leveraging the four-stage definition of resilience – plan, absorb, recover, adapt – proposed by the National Academies of Science (NAS) will allow temporal aspects of resilience to be incorporated into models [37]. Employing common language across all supply chain resilience literature will also allow disruptions to be modeled and quantified in a standard manner.

Second, applying network science models and big data capabilities to nano supply chain resilience will confer greater supply chain visibility, and allow for improved stress tests and other methods for improving supply chain resilience. Advances in machine learning (ML) and artificial intelligence (AI) are giving academics and practitioners alike greater visibility and insights into lower supply chain tiers and consequently into a greater number of nodes and links that can be incorporated into pre-planned corrective actions to improve resilience. In these network models and stress tests, it is vital to include the associated networks and domains that also constitute the nano supply chain and generate value in the COVID-19 vaccine supply chain. This would need to include factors such as vaccine hesitancy due to novel nanotechnology and availability of qualified personnel working in manufacturing consumables.

And third, resilience is ultimately one of many operational strategies aimed at maintaining continuity in a supply chain. Therefore, understanding and adequately accounting for all stakeholder needs and goals is essential for effective implementation of nano supply chain resilience. Integrating trade-off analyses and other optimization thinking into modeling supply chain resilience allows greater public and private stakeholder goals to be achieved. These goals could include efficiency, sustainability, and equity, and should take into account regional, human health, and environmental considerations. As critical medical products begin to rely more heavily on nanotechnology, the supply chains underpinning them will become more widespread. Similarly, both the advantages of medical uses of nanotechnology, such as the replacement of historic medical supply chains, and its disadvantages, including environmental impacts due to the size and property of nanomaterials [38] will acquire increasing relevance. It behooves the academic literature to stay ahead of these emerging supply chain trends and model how fundamental sustainability issues – human health and natural environment – interface with resilience and efficiency of these supply chains.

Ultimately, scalability is an opportunity for instilling resilience into the nano supply chain, and transparent and appropriate network structures and policies can be used from the beginning of the design of the supply chains. As nanotechnology becomes more prevalent, especially in the development of vaccines and other critical public goods, the above considerations can help policy makers and supply chain managers to effectively implement supply chain design and practices that value resilience and other vital stakeholder goals. The COVID-19 pandemic has demonstrated both the lack of resilience in existing supply chains and also the vital importance of nano capabilities in global supply chains, especially those related to vaccines. The existing research and development of nanotechnological innovations used for the SARS-CoV-2 vaccines has catalyzed the vaccine emergency use authorizations, but without resilient supply chains capable of meeting unprecedented demands, these life-saving innovations cannot be ramped up to consistently meet demand to the maximum extent possible.

Conflict of interest statement

Nothing declared.

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- •• of outstanding interest

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Hynes *et al.* discuss the costs that come as a result of the current system-wide level of efficiency focus within the economy and the society at large when shocks occur. They shed light on the disproportionate health and economic impacts that COVID-19 had regionally and ethnically, the lack of public trust in institutions. They call on the need for economic analyses to shift with the changing socioeconomic system, improved system analysis models, and a systemic shift towards a resilience mindset in order to prepare for future uncertainty and times of stress. The systems level perspective adopted by Hynes *et al.* is consistent with our view that the entire system of vaccine supply chains, built highly on efficiency, needs to change to become more resilient.

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Bhaskar *et al.* highlight the critical shortage in PPE, ICU capacity, and other healthcare materials and equipment. The authors claim that these shortages indicate a need to reevaluate the supply chains contributing to these failures during the pandemic. Specifically, they point to critical stockpiles, production efficiency, and a governance system supported by public health authority intervention as mechanisms to bolster resilience in the medical supply chains. They contend, in parallel with our argument, that the typical 'lean' construction of medical supply chains is not sufficient for the protection of frontline workers and public health assurance. They conclude that stockpiling was insufficient, even before the pandemic even began, demand exceeded the capacity of supply chains

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Sarkis *et al.* propose using mathematical models to enhance supply chain networks for vaccines, including manufacturing and distribution. Their findings indicate that RNA vaccine manufacturing facilities can be built with half the time of typical vaccine facilities at only 1/35th of the cost. The authors focus on the advancement in the ATMP development to prevent life threatening diseases and predict that there will be a global market for ATMP of 9.6 billion by 2026. Despite this, they caution the fragility in the distribution system for these types of medical products in order to reiterate the importance of using mathematical models and machine learning assist in decision making under uncertainty, process development, and optimization and control.

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This systematic review by Golan *et al.* is a contributor in the push for resilience implementation in global medical and non-medical supply chains. They contribute to the resilience literature by advocating for resilience analytics and network science tools like artificial intelligence, stress tests, and digital twins. They argue that these implementations are necessary to better quantify the efficiency resilience tradeoff to enhance decision making under uncertainty amid disruption. The authors argue that this is critical within vaccine supply chains and distribution efforts, major impediments to the speed of recovery in a pandemic. They hone in on the resilience focus of absorption, adaptation and recovery, while adhering to the National Academy of Science definition that we refer to in our review.

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Soeteman-Hernandez *et al.* shed light on the caution necessary in the early stage development of nanotechnology. They propose a safe-innovation approach that combines both regulatory preparedness and safety by design measures. This method of implanting safety in the design phase should reduce the human and environmental health risks of nanotechnology throughout the life of their applications. The authors note key challenges in ensuring adequate safety in nanotechnology such as spreading awareness of the importance of safety in nanotech, lack of requirements to learn about nanotech safety risks, and the inherent difficulty of understanding the risks themselves. The safety of nanotech is a critical piece of their applications within supply chains and pharmaceuticals. Particularly, nanotechnologies' sensitivity to different environmental conditions, and subsequent reactions, are critical to successful and resilient supply chains.

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This source by Golan *et al.* highlights the potential for cascading failure in supply chains as they become increasingly globalized. They use the supply chain failures of the pandemic as a case in point to support their argument for improved and expanded network analysis and resilience based analytics in the literature. The auhthors discuss the tradeoffs among efficiency, leanness, flexibility and resilience in the contexts of uncertainty in social and physical networks during disease pandemics, and the systemic threat caused by the prioritization of leanness. Though they find that the number of publications related to supply chain resilience is increasing, they still point out gaps in the literature addressing resilience analytics and systemic threats. Further, they point to the need to establish quantifiable definitions and metrics by which resilience strategies can be evaluated.

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