Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Resilience and efficiency for the nanotechnology supply chains underpinning COVID-19 vaccine development
Maureen S Golan, Emerson Mahoney, Benjamin Trump and Igor Linkov

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.

Address
U.S. Army Engineer Research and Development Center, Vicksburg, MS, United States

Corresponding author: Linkov, Igor (igor.linkov@usace.army.mil)

Current Opinion in Chemical Engineering 2021, 34:100759
This review comes from a themed issue on Nanotechnology: nanomaterials for energy and environmental applications
Edited by Dionysios D Dionysiou, Suresh Pillai, and Sami Rtimi
For a complete overview see the Issue
Available online 27th October 2021
https://doi.org/10.1016/j.coche.2021.100759
2211-3398/Published by Elsevier Ltd.

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 become 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 chain will give the global 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*]. 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].
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

### Table 1

| 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. |
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.

**Acknowledgement**
This study was funded in parts by the US Army Corp of Engineers Military Funding Programs. The views and opinions expressed in this paper are those of the individual authors and not those of the US Army or other sponsor organizations.

**References and recommended reading**
Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Sampat BN, Shaden KC: The COVID-19 innovation system. Health Aff 2021, 40:400-409 http://dx.doi.org/10.1377/hlthaff.2020.02097.
2. Bown CP, Bollyky TJ: How COVID-19 vaccine supply chains emerged in the midst of a pandemic. World Econ 2021 http://dx.doi.org/10.1111/twec.13183. Accessed Oct 10, 2021.
3. Runde DF, Savoy CM, Staghn J: Global COVID-19 Vaccine Distribution Handbook. Center for Strategic & International Studies: 2021 https://www.csis.org/analysis/global-covid-19-vaccine-distribution-handbook.
4. NPR: A Pharmacist Who Deliberately Ruined COVID Vaccine Doses Is Going To Prison. 2021 https://www.npr.org/2021/06/08/1004585024/the-pharmacist-who-deliberately-ruined-covid-vaccine-doses-is-going-to-prison.
5. Stolberg S: Johnson & Johnson Put in Charge of Plant That Ruined Millions of Vaccine Doses. The New York Times; 2021. 26 April 2021.
6. Paris C: Supply-chain Obstacles Led to Last Month’s Cut to Pfizer’s Covid-19 Vaccine-Rollout Target. 3 December 2020. The Wall Street Journal, Dow Jones & Company; 2020www.wsj.com/articles/pfizer-slasheds-its-c19-vaccine-rollout-target-after-facing-supply-chain-obstacles-11607027787.
7. Hynes W, Trump BD, Love P, Linkov I: Bouncing forward: a resilience approach to dealing with COVID-19 and future systemic shocks. Environ Syst Decis 2020, 40:174-184 http://dx.doi.org/10.1007/s10669-020-09776-x
Hynes et al. discount 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.
8. Crommelin DJA, Anchordoquy TJ, Volkin DB, Jisook W, Mastrobattista E: Addressing the cold reality of mRNA vaccine stability, J Pharm Sci 2021, 110:997-1001 http://dx.doi.org/10.1016/j.xphs.2020.12.006.
9. Piotkin S, Robinson JM, Cunningham G, Iqbal R, Larsen S: The complexity and cost of vaccine manufacturing – an overview. Vaccine 2017, 35:4064-4071 http://dx.doi.org/10.1016/j.vaccine.2017.06.003.
10. Wouters OJ, Shadlen KC, Salcher-Konrad M, Pollard AJ, Larson HJ, Teerawattananon Y, Jit M: Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment. Lancet 2021, 397:1023-1034 http://dx.doi.org/10.1016/S0140-6736(21)00306-8.
11. U.S. Food and Drug Administration (FDA): COVID-19 Vaccines. Coronavirus Disease 2019 (COVID-19), 2021 https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19-covid-vaccines.
12. Buschmann MD, Carrasco MJ, Alishetty S, Paige M, Alamh MG, Weissman D: Nanomaterial delivery systems for mRNA vaccines. Vaccines 2021, 9:65 http://dx.doi.org/10.3390/vaccines9010065.
13. Rele S: COVID-19 vaccine development during pandemic: gap analysis, opportunities, and impact on future emerging infectious disease development strategies. Hum Vaccin Immunother 2021, 17:1122-1127 http://dx.doi.org/10.1080/21645515.2020.1822136.
14. Shen Y, Hao T, Ou S, Hu C, Chen L: Applications and perspectives of nanomaterials in novel vaccine development. MedChemComm 2018, 9:226-238 http://dx.doi.org/10.1039/C7MD00158D.
15. Bhaskar S, Tan J, Bogers MLAM, Minussen T, Badaruddin H, Israeli-Korn S, Cheshbrough H: At the epicenter of COVID-19 – the tragic failure of the global supply chain for medical supplies. Front Public Health 2020, 8:562882 http://dx.doi.org/10.3389/fpubh.2020.562882
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.
which were regionalized because of the virus, and these problems were exacerbated by a lack of trust among stakeholders.

16. Diaz-Elsayed N, Charkhgard H, Wang MC: Sustainable and resilient manufacturing for the post-COVID-19 era. Smart Sustain Manuf Syst 2020, 4:264-268 http://dx.doi.org/10.1520/SSMS20200053.

17. Goel S, Hawi S, Goel G, Thakur VK, Agrawal A, Hoskins C, Pearce O, Hussain T, Upadhyay HM, Cross G, Barber AH: Resilient and agile engineering solutions to address societal challenges such as coronavirus pandemic. Mater Today Chem 2020, 17:100300 http://dx.doi.org/10.1016/j.mtchem.2020.100300.

18. McClements DJ, Barrangou R, Hill C, Kokini JI, Lila MA, Meyer AS, Yu L: Building a resilient, sustainable, and healthier food supply through innovation and technology. Annu Rev Food Sci Technol 2021, 12:1-28 http://dx.doi.org/10.1146/annurev-food-092220-030824.

19. Sarkis M, Bernardi A, Shah N, Pathanapathnas M: Decision support tools for next-generation vaccines and advanced therapy medicinal products: present and future. Curr Opin Chem Eng 2021, 32:100689 http://dx.doi.org/10.1016/j.coche.2021.100689.

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 just one-fifth of the time of traditional vaccine facilities and only 1/36th 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.

20. Alam ST, Ahmed S, Ali SM, Sarker S, Kabir G, ul-Islam A: Challenges to COVID-19 vaccine supply chain: implications for sustainable development goals. Int J Prod Econ 2021, 239:108193 http://dx.doi.org/10.1016/j.ijpe.2021.108193.

This is an extremely pertinent and novel study that prioritizes certain issues that were experienced in the vaccine supply chains from the beginning stages of their development. The authors analyze the interconnectedness of different challenges, identifying which were related and which caused which. These challenges were chosen as identified within the current literature at the time and with help from vaccine supply chain experts. This is an important source mentioning further research in the right direction to support both policy and industry leaders in vaccine supply chains. They obtained qualitative information from all of the industry leading COVID vaccine manufacturers to make their case.

21. Uddin M, Majumder B, Rose GS: Robustness analysis of a memristive crossbar PUF against modeling attacks. IEEE Trans Nanotechnol 2017, 16:396-405 http://dx.doi.org/10.1109/TNANO.2017.2677882.

22. Wall A, Kundu S, Arnold AJ, Zhao G, Basu K, Das S: Satisfiability attack-resistant camouflaged two-dimensional heterostructure devices. ACS Nano 2021, 15:3453-3467 http://dx.doi.org/10.1021/acsnano.0c10651.

23. Simchi-Levi D, Simchi-Levi E: We Need a Stress Test for Critical Supply Chains. Harvard Business Review; 2020 https://hbr.org/2020/04/we-need-a-stress-test-for-critical-supply-chains.

24. Ivanov D: Supply chain viability and the COVID-19 pandemic: a conceptual and formal generalisation of four major adaptation strategies. Int J Prod Res 2021, 59:3535-3552 http://dx.doi.org/10.1080/00207543.2021.1890852.

25. Golan MS, Trump BD, Cagan JC, Linkov I: Supply chain resilience for vaccines: review of modeling approaches in the context of the COVID-19 pandemic. Ind Manage Data Syst 2021, 121:723-741 http://dx.doi.org/10.1108/IMDS-11-2020-1022.

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 vaccine, adaptation and recovery, while adhering to the National Academy of Science definition that we refer to in our review.

26. Resilinc Corporation: A New Metric for Measuring Supply Chain Resiliency: an Introduction to Resilinc R ScoreTM and Its Application to the High-tech Industry Supply Chain. Resilinc and Global Supply Chain Resiliency Council; 2017 https://www.resilinc.com/white-papers-reports/.

27. Pujawar IN, Bah AH: Supply chains under COVID-19 disruptions: literature review and research agenda. Supply Chain Forum Int J 2021 http://dx.doi.org/10.1080/16258312.2019.1392568. Accessed Oct 10, 2021.

28. Soeteman-Hernández LG, Sutcliffe HR, Sluijters T, van Geuns J, Noordermeer CW, Sips AJAM: Modernizing innovation governance to meet policy ambitions through trusted environments. Nanolismap 2021, 21:1-7 http://dx.doi.org/10.1016/j.ipact.2021.100301.

Soeteman-Hernández et al. shed light on the caution necessary in the early stage development of nanotechnology. They propose a nano-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.

29. Soeteman-Hernández LG, Blab GA, Carattino A, Dekker F, Dekkers S, van der Linde M, van Sichoutou C: A methodology of implementing nano-specific safety and safety by design principles in academia. Nanolismap 2020, 19:100243 http://dx.doi.org/10.1016/j.ipact.2020.100243.

30. Trump BD, Keisler JM, Galaitis SE, Palma-Oliveira JM, Linkov I: Safety-by-design as a governance problem. Nano Today 2020, 55 http://dx.doi.org/10.1016/j.nantod.2020.100989.

31. Sánchez Jiménez A, Puelles R, Pérez-Fernández M, Gómez-Fernández P, Barruetabea L, Jacobsen NR, Suarez-Merino B, Micheletti C, Manier N, Trouiller B et al.: Safe(r) by design implementation in the nanotechnology industry. Nano Today 2020, 20 http://dx.doi.org/10.1016/j.nantod.2020.100267.

32. Schmutz M, Borges O, Jesus S, Borchard G, Perale G, Zinn M, Sips AJAM, Soeteman-Hernández LG, Wick P, Som C: A methodological safe-by-design approach for the development of nanomedicines. Front Bioeng Biotechnol 2020, 8:258 http://dx.doi.org/10.3389/fbioe.2020.00258.

33. Organisation for Eco nomic Co-operation and Development (OECD): Moving Towards a Safe(r) Innovation Approach (SIA) for More Sustainable Nanomaterials and Nano-enabled Products. 2020:96 https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=en+j/m/mono2020/36/REV1&doclanguage=en.

34. Rycroft T, Trump B, Poinset-Jones K, Linkov I: Nanotoxicology and nanomedicine: making development decisions in an evolving governance environment. J Nanopart Res 2018, 20 http://dx.doi.org/10.1007/s11051-018-1460-3.

35. Golan MS, Jeremeg LH, Linkov I: Trends and applications of resilience analytics in supply chain modeling: systematic literature review in the context of the COVID-19 pandemic. Environ Syst Decis 2020, 40:222-243 http://dx.doi.org/10.1017/ s10689-020-09777-w.

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 authors 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. They highlight 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.

36. Shin MD, Shukla S, Chung YH, Beiss V, Chan SK, Ortega-rivera OA, Wirth DM, Chen A, Sack M, Pokorski JK: COVID-19 vaccine development and a potential nanomaterial path forward. Nat Nanotechnol 2020, 15:646-655 http://dx.doi.org/10.1038/s41565-020-0737-y.

37. National Academies of Science (NAS): Disaster Resilience: A National Imperative. The National Academies Press; 2012 http://dx.doi.org/10.17226/13457.

38. Di Sia P: Nanotechnology among innovation, health and risks. Procedia Soc Behav Sci 2017, 237:1076-1080 http://dx.doi.org/10.1016/j.sbspro.2017.02.158.