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Commentary

Vaccine supply chain: Resilience-by-design and resilience-by-intervention

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1. Introduction

A litany of best practices and industry requirements governs the broader vaccine development process, providing expectations of safety and quality control at all stages of development. Though such governance extends to supply chain management and operation, industry stakeholders have considerable leverage in determining the nature and structure of their supply chain and the ultimate commercial viability of the vaccine. In this, many have turned to the philosophy and practice of supply chain *efficiency*, optimizing scarce resources for minimum redundancy and maximum return on investment. Such an approach is commendable during times without significant disruption, for it promotes operational sustainability amidst uncertainty and limited resources.

When disruption strikes, however, efficiency-driven supply chain systems face sweeping challenges to fulfill operational requirements of vaccine manufacture and distribution. Certain systemic disruptions, such as global pandemics, which cause cascading failure across an entire sector of supply chains, may limit the ability of the existing vaccine network to meet critical need. These disruptions are compounded by the extremely technical and unique ecosystem surrounding vaccine manufacture and distribution, which hinges on quality consumables, maintaining efficacy throughout distribution, and upholding licensing requirement [1]. In order for a supply chain to regain operational capacity post disruption, there must be a mechanism for preparation, absorption, recovery and adaptation – resilience [2].

SARS-CoV-2 vaccine development and production clearly shows the importance of supply chain considerations [18]. Pfizer/BioNTech, was prepositioned to deliver the first mega-round of vaccine doses in the United States after being the first applicant for the Food and Drug Administration's (FDA) Emergency Use Authorization (EUA) [3]. However, late in its successful Phase III trials, Pfizer was forced to slash its initial U.S. dose delivery promises by half due to supply chain disruptions: early batches of raw material did not meet company standards during ramped up production [4,15]. But this is not surprising. In the race for an efficacious vaccine, many vaccines in the research and development pipeline use new RNA or platform-based technology [16]. Although this platform technology has been on the horizon for some time and touted for its unique capabilities for efficient vaccine development, commercial viability and subsequent strains on the necessary supply chains have not been tested through a large-scale manufacturing and distribution process [1,5,12,13,15,17]. How was a leading biopharmaceutical company that is contracted to meet critical need not able to recover optimal functionality after a supply chain disruption? Why was building resilience into the supply chain not prioritized while the vaccine was being developed?

2. Can supply chain efficiency and risk management guarantee overcoming disruptions?

Our review of supply chain resilience in vaccine development and distribution; as well as findings by others indicate that supply chains in pharmaceutical industry are optimized to be efficient [5–7]. Disruptions are considered through risk assessment and management where probabilities of failures of individual suppliers are assessed and specific critical supplier nodes are hardened (usually through redundancy). For the vaccine supply chain, this may equate to duplicate suppliers in low-cost locations, promoting supply chain visibility and cooperation between tiers, and flexible warehousing that minimize risk without compromising revenue targets or efficiency [6,8,9]. This risk-based management centers

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on developing threat scenarios from historical data, while unpredictable and unknown disruptions can be missed, and the system cannot subsequently be hardened [7,10]. Thus, current practices favor risk mitigation strategies, which optimize for efficiency, rather than building resilience into the vaccination network.

Unfortunately, little has been done in the field of vaccine supply chain resilience [5]. The constant emphasis on efficiency has resulted in a lack of models that would enable effective trade-off analysis and quantification of resilience in the context of the broader networks that also constitute value generation in vaccine supply chains [5,11].

The SARS-CoV-2 vaccine undertaking is unprecedented in magnitude, timeline, technology, and supply chain, so in a ramp-up of scale that relied on new technology and numerous companies sourcing the same materials, why did companies continue to optimize efficiency over resilience? For this reason, we define resilience-by-design and resilience-by-intervention as approaches for a comprehensive dual effort by companies and governments to enable recovery post disruption in supply chains of critical importance without compromising supply chain efficiency during normal operations [19].

3. Resilience-by-design

The underlying principle of resilience-by-design is: *a system must be designed to recover its critical functions from disruption on its own or else the system will fail.* The strategy uses resilience analytics to stress test the system with both known and unknown disruption to identify system configurations that result in the lowest degradation and facilitate the fastest recovery. For vaccine manufacture and distribution, this up-front quantitative evaluation of weak nodes or links of the supply chain in the context of overall network topology enables practical solutions to be weighed against other company goals such as efficiency, sustainability, or cost. Resilience-by-design is complimentary to current risk management with its focus on understanding where disruption would have the greatest impact and hardening the weak links and nodes. In the vaccine supply chain, resilience-by-design may include contracting multiple suppliers of a critical consumable in different geopolitical regions, using interchangeable and generic materials when possible, instituting emergency operation management plans, adjusting supply chain structure, integrating certain transportation links, or keeping an inventory buffer of critical path non-perishable raw materials.

In the race to develop a SARS-CoV-2 vaccine, manufacturers are not paying enough attention to resilience-by-design, as exemplified by the impacts of the batch failures of raw materials on the critical path of the Pfizer/BioNTech vaccine [4,15]. A proactive application of resilience analytics to the SARS-CoV-2 vaccine manufacturing supply chains may have revealed that disruption at this critical node would have devastating impacts on system performance. This knowledge could have then been used to justify corrective actions such as additional production capacity of the consumable, contracting third party suppliers, or looking for alternative comparable materials early in the vaccine development process. These actions would be weighed against the impact of disruption along with other company goals as well as considerations for external support through resilience-by-intervention as discussed in the next section. Addressing these inevitable disruptions in a novel supply chain, could enable an even better vaccine responses as companies scale vaccine production.

There are examples of resilience-by-design strategies undertaken by the biopharmaceutical industry and its partners for the coronavirus vaccines, including Pfizer working with both UPS and FedEx to build redundancy, oversight, and tracking into the distribution network to ensure that the vaccines are efficacious at delivery as well as timely. Similarly, Moderna has partnered with IBM to track vaccine administration for real-time supply chain data [14,17]. McKesson has also restructured some of its supply chains for resiliency through the use of its Business Continuity and Disaster Recovery Program (BCRP) by adding back-up suppliers and alternate sourcing where possible, as well as instituting workforce continuity plans [17]. All these strategies leverage analyses of the supply chain to use internal company resources in order to facilitate recovery post disruption.

4. Resilience-by-intervention

The underlying principle of resilience-by-intervention is: *given increasing globalization and network interconnections, an external resource (e.g., insurance, government stockpiles, etc.) must be envisioned and designed to enable a system to withstand cascading and systemic disruptions or else the system will fail.* Similar to resilience-by-design, this strategy uses resilience analytics for strategic decision making, but does so outside of the immediate network of systems that fill a critical inoculation need. For policymakers and regulators, this up-front quantitative evaluation of network points of failure enables feasible solutions to be weighed against societal goals. First quantifying where disruption would have the greatest impact on network performance and what the consequences of those impacts would be on society, enables decision makers to strategically evaluate corrective actions against other policy objectives. Generally in critical sectors, the "public good" will be weighed above cost, but modeling resilience across the networks upholding the sector enables data-driven and informed decision making to facilitate network recovery post disruption. In the vaccine supply chain, corrective actions may include the use of federal or state stockpiles or vaccination centers, emergency funding for manufacture ramp-up, quicker transportation links, public health campaigns, or quicker regulatory bureaucratic processes.

OWS is an example of resilience-by-intervention, investing federal resources in multiple vaccine manufacturers to simultaneously advance vaccines, increasing the likelihood that if one should fail, another will succeed, reaching vaccination thresholds. The OWS decision to invest in vaccine manufacturing addressed the need to fill a dosage quota in a short time span, given large amounts of funding and urgent public health needs. The emphasis on vaccine portfolio diversification – 8 vaccine candidates, 2 for each of 4 selected platform technologies – provided external resources for industrial manufacturability, safety, efficacy and scheduling and how to structure the supply chains underpinning these processes [15]. An up-front stress test on the networks underpinning the vaccine manufacture might enable more nuanced resilience-by-intervention corrective actions such as investing in licensed facilities and personnel that are qualified to produce the critical raw materials that might be needed by multiple manufacturers.

There are other examples of resilience-by-intervention strategies used by the U.S. through OWS and other means. The Strategic National Stockpile was contracted for additional hundreds of millions of syringes, needles, vials, fill-finish equipment, and supply kits to be coordinated and utilized for vaccine ancillary kits. The Cybersecurity and Infrastructure Security Agency (CISA) has been working with vaccine manufacturers to counteract any cyberattacks or threats to intellectual property. The FDA's ability to expedite vaccine approval for public use through EUAs is also a viable tool. Like resilience-by-design, all these strategies range in approach and system domains, but unlike resilience-by-design, resilience-by-intervention leverages outside resources to facilitate recovery after disruption.

Table 1
Supply chain (SC) risk management is complementary to resilience-by-design and resilience-by-intervention but there are key differences among the strategies. Vaccine specific examples shown in lower row of every category and in italics (Note that examples shown are meant for solidifying the concepts and are not exhaustive.)

	Risk management	Resilience-by-design	Resilience-by-intervention
Goal	Harden individual SC links or nodes	Design nodes, links, and topology to be self-reorganizable	Rectify disruption to nodes and links and stimulate recovery by external actors
	Increase consumable inventory of vital materials.	*Contract multiple consumable suppliers for single vaccine.*	*Emergency stockpile of consumables for multiple vaccines.*
Threat	Predictable disruptions, acting primarily from outside the system on nodes and links	Either known/predictable or unknown disruptions, acting at a component or system level	Failure of SC in context of societal needs, may be constellation of SCs in multiple companies
	Cyclone in Puerto Rico.	*Climate change causing cascading disruptions.*	*Pandemic causing demand and supply shocks.*
Consequence	Vulnerable nodes and/or links fail as result of threat	Degradation of critical SC functions in time and capacity to deliver product	Degradation of critical societal function due to cascading failure in interconnected networks.
	Consumable is not available causing bottleneck and decreased manufacturing capability.	*Consumable is not available resulting in fewer vaccinations over a month.*	*Consumable is not available resulting in a shortage of multiple vaccines for a month, resulting in worse pandemic outcomes.*
Action	Either within or exterior to the SC	Within the SC	Exterior to the SC
	Inventory increased at one manufacturer and at a warehouse.	*Multiple consumable manufacturers are contracted and incorporated into the SC.*	*Strategic national stockpile of critical consumables is independent of any vaccine manufacturer and SC.*
Stages/ Analytics	Prepare and absorb (risk is product of threat, vulnerability and consequences and is time independent)	Recover, and adapt (explicitly modeled as time to recover SC function and the ability to change SC configuration in response to threats)	Prepare, absorb, recover, and adapt (explicitly modeled as ability to recover and secure critical societal function and needs through constellation of SC and relevant systems)
	The consumables most at risk of delays (due to cyclones) have increased inventory held on site and elsewhere.	*Critical consumables can be manufactured at multiple locations/suppliers and recovered in time to maintain vaccine supply.*	*Critical consumables can be supplied to vaccine manufacturers should disruption decrease the ability of the public to be vaccinated at appropriate rates.*

5. Resilience analytics is necessary for overcoming disruptions

Moving from risk management and efficiency-focused supply chain operations towards the two-fold resilience-by-design and resilience-by-intervention strategies for the networks underpinning the SARS-CoV-2 vaccine is crucial to maintaining vaccination targets as the supply chains continue to experience inevitable disruption. Table 1 expands on the distinctions among the complementary strategies, highlighting the importance of incorporating resilience analytics to drive vaccine supply chain implementation through the concurrent use of resilience-by-design and resilience-by-intervention. Resilience analytics allows: (1) incorporation of temporal aspects to network models through use of the four-stage NAS definition of resilience (plan, absorb, recover, adapt); (2) incorporation of disruptions of various magnitude, likelihood, and systemic characteristics; (3) incorporation of the tiered approach to modeling whereby the quantitative approach is matched to the need; (4) incorporation of associated networks and domains that constitute value generation; and (5) incorporation of various stakeholder and societal goals and needs [5,10,11]. By better understanding how internal and external stakeholders and networks interact, governments and international organization can ensure they best serve public interest through fully leveraging the portfolio of strategies available to them and private pharmaceutical corporations.

As more vaccines enter mass production for global distribution, strain on raw material manufacture and other components as experienced by Pfizer will continue, if not increase. Other disruptions to the unprecedented and untested COVID-19 vaccine supply chain are inevitable. Employing resilience-by-design and resilience-by-intervention strategies concurrently for vaccine supply chains, especially as second-generation vaccines are developed and enter production, is paramount to ensuring critical need is met, and lives saved.

Declaration of Competing Interest

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

References

[1] Plotkin S, Robinson JM, Cunningham G, Iqbal R, Larsen S. The complexity and cost of vaccine manufacturing - an overview. Vaccine 2017;35(33):4064–71.
[2] National Research Council. Disaster Resilience: A National Imperative. Washington, DC: The National Academies Press; 2012. doi:10.17226/13457.
[3] United States Food and Drug Administration (FDA). FDA COVID-19 Vaccine Information. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines [accessed December 2020].
[4] Costas P. Supply-Chain Obstacles Led to Last Month's Cut to Pfizer's Covid-19 Vaccine-Rollout Target; Pharma giant found raw materials in early production didn't meet its standards (2020–12-03). Wall Street J 2020.
[5] Golan MS, Trump BD, Cegan J, et al. The Vaccine Supply Chain: A Call for Resilience Analytics to Support COVID-19 Vaccine Production and Distribution. COVID: Risk and Resilience. Springer International Publishing, New York, NY. 2021. [published Online first: 28 Nov 2020 https://arxiv.org/abs/2011.14231].
[6] Sheffi Y. The New (Ab)Normal: Reshaping Business and Supply Chain Strategy Beyond Covid-19. MIT Center for Transportation and Logistics. Cambridge, MA: MIT CTL Media 2020.
[7] Simchi-Levi D, Simchi-Levi E. We Need a Stress Test for Critical Supply Chains. *Harvard Business Review* 28 April 2020. https://hbr-org.cdn.ampproject.org/c/s/hbr.org/amp/2020/04/we-need-a-stress-test-for-critical-supply-chains.
[8] Jacoby R, Heim M, Preda CF. The First 90 Days: US Biopharmaceutical Finished Goods Supply Chain Response to COVID-19. Deloitte & HDA Research Foundation; 2020. https://www.hda.org/resources/the-first-90-days.
[9] Dixit R, Routroy S, Dubey SK. A systematic literature review of healthcare supply chain and implications of future research. Int J Pharm Healthcare Marketing 2019;13(4):405–35. https://doi.org/10.1108/ijphm-05-2018-0028.
[10] Linkov I, Fox-Lent C, Read L, Allen CR, Arnott JC, Bellini E, et al. Tiered Approach to Resilience Assessment. Risk Anal 2018;38(9):1772–80.
[11] Linkov I, Carluccio S, Pritchard O, Ní Bhreasail Á, Galaitsi S, Sarkis J, et al. The case for value chain resilience. Manage Res Rev 2020;43(12). https://doi.org/10.1108/MRR-08-2019-0353.
[12] Mullin R. Pfizer, Moderna ready vaccine manufacturing networks: A mesh of contract services will be activated by both the big pharma and the smaller biotech. Chemical & Engineering News 2020;98(46). https://cen.acs.org/business/outsourcing/Pfizer-Moderna-ready-vaccine-manufacturing/98/i46.
[13] Pujar NS, Sagar SL, Lee AL. In: Vaccine Development and Manufacturing. Wiley; 2014. p. 1–24. https://doi.org/10.1002/9781118870914.ch1.
[14] Reuters. Moderna, IBM team up on COVID-19 vaccine distribution data. Reuters Technology News. 4 March 2021. https://www.reuters.com/article/us-health-coronavirus-moderna-ibm-idUSKBN2AW2DT.
[15] Slaoui M, Hepburn M. Developing Safe and Effective Covid Vaccines – Operation Warp Speed's Strategy and Approach. N Engl J Med 2020;383(18):1701–3. https://doi.org/10.1056/NEJMp2027405.
[16] World Health Organization. Draft landscape andt racker of COVID-19 candidate vaccines. 1June2021. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.
[17] McKesson. Our Commitment to Customers. COVID-19. McKesson Corporation. https://www.mckesson.com/About-McKesson/COVID-19/Pharmaceutical-Supply-Chain/ [accessed December 2020].

[18] Golan MS, Trump BD, Cegan JC, Linkov I. Supply chain resilience for vaccines: review of modeling approaches in the context of the COVID-19 pandemic. IMDS 2021;121(7):1723–48.

[19] Linkov I, Trump BD, Golan M, Keisler JM. (2021) Enhancing Resilience in Post-COVID Societies: By Design or By Intervention? Environ Sci Technol 2021;55 (8):4202–4. https://doi.org/10.1021/acs.est.1c00444.