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Commentary

Working towards a sustainable, healthy market for vaccines: A framework to support evidence-based policymaking

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1. Introduction

The COVID-19 pandemic underscores the pivotal role vaccines play in disease prevention across the globe. It also brings to light the complexity of developing, manufacturing, and deploying vaccines. A well-functioning (i.e., healthy) global vaccines market is essential to enable sustained vaccine innovation to meet current and emerging public health threats and requires a balance across supply- and demand-side factors. Upstream, this necessitates a policy environment that enables resource-intensive research, development, and manufacturing efforts required to create a reliable supply of high-quality, innovative vaccines. Downstream, reliable systems and infrastructure are required to identify priorities, establish predictable demand, and supports continuous delivery. This ensures that national immunization programs reach large population cohorts and that relevant vaccines can reach their full potential.

The multitude of efforts to facilitate the rapid development, manufacturing, and deployment of COVID-19 vaccines reveals the need for a common framework that can help stakeholders understand supply- and demand-side complexities and make informed decisions that support the global vaccines market. This commentary presents a conceptual Healthy Vaccines Market Framework (HVMF) that is intended to facilitate such understanding, dialogue, and decision-making across stakeholders. The HVMF helps to define key characteristics of a healthy market and examine intended and unintended consequences of market-shaping interventions in the short- and long-term. It also considers the interdependencies of markets at the national, regional, and global levels.

2. Healthy vaccines market framework

We performed a literature review to identify existing vaccines market frameworks and inform the development of the HVMF. [1,2] We refined and validated the framework through expert interviews. Using a case study approach to illustrate the framework's utility, we selected for efforts to accelerate and scale-up COVID-19 vaccines development and manufacturing.

We define the goal of a healthy vaccines market as one that supports sustainable innovation in order to address public health needs. The HVMF (Fig. 1) is comprised of three parts that represent dependencies within a vaccines market: (i) five essential characteristics of markets at the national, regional, and global level; (ii) supply- and demand-side activities and corresponding policies that drive these characteristics; and (iii) key stakeholders that shape markets. We describe the five characteristics of a market and illustrate their centrality to the HVMF in Table 1. The concentric circles at the center of the framework illustrate that national, regional, and global vaccines markets are interconnected and do not operate in isolation.

Key supply- and demand-side activities that influence the health of the market are listed on the left- and right-hand side of the HVMF respectively and are not intended to be exhaustive. On the demand-side, introduction of new vaccines requires assessment frameworks and corresponding evidence (e.g., disease surveillance data) that evaluates the full societal value of vaccination.[3] Investment in vaccination programs, infrastructure, and human resources contributes to equitable access to and uptake of vaccination services. Streamlined, efficient processes based on accurate data and long-term planning support timely procurement, forecasting, and stock management.[4] A demand-side that functions effectively, is well-resourced, and recognizes the far-reaching value of vaccination, continues to signal the need for ongoing investment in vaccine innovation.

On the supply-side, vaccine development and manufacturing are global endeavors that are intricately linked to policies, systems, and infrastructure spanning across countries and stakeholders. Risks (i.e., upfront investment and opportunity costs) associated with research and development (R&D) for companies necessitates policies, investors, and investment models that enable and reward innovation.[5,6] The nature of the global vaccine supply chain warrants supply-side stakeholders to create supply chain resiliency to secure manufacturing and delivery of their products.[7] Lastly, global vaccine supply and access strategies are informed by demand

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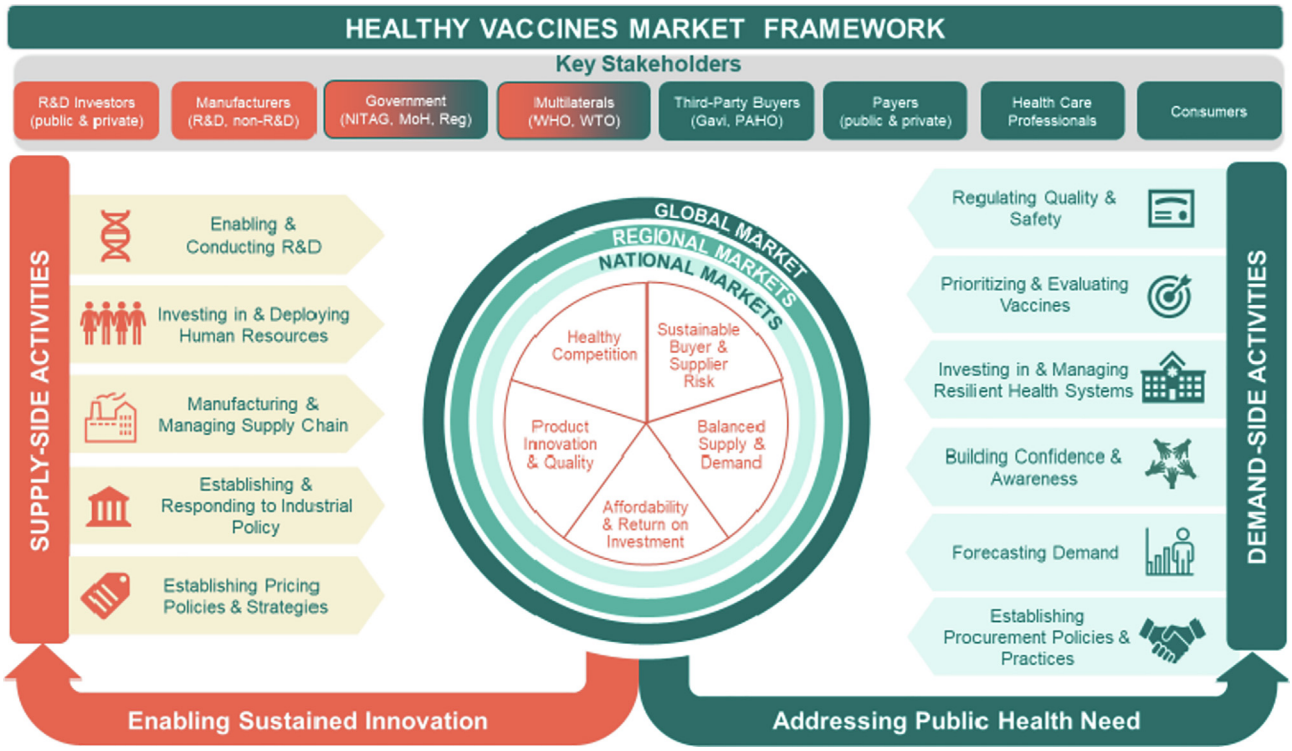

Fig. 1. Healthy Vaccines Market Framework.

Table 1
Characteristics of a healthy vaccines market.

Supply-Side Activities	Definition and Illustrative Examples
Balanced Supply and Demand	A healthy market should deliver appropriate and timely supply to meet predictable demand, as well as potential fluctuations. Advanced demand forecasting and planning are central to achieving this balance, along with early and open dialogue across all stakeholders. Several factors, including manufacturing cycles that average 2 years or more, changes in policies (e.g., new product regulations), or unanticipated departure of a manufacturer from the marketplace, can result in supply interruptions that can last for extended periods of time.
Affordability and Return on Investment	In a healthy vaccines market, vaccines should be affordable to enable access, while also providing the return on investment needed to sustain innovation. Pricing, procurement Affordability varies per country and is dependent on the willingness to pay given budget allocations. Return on investment (ROI) ensures profitability and a return on the costs of R&D, manufacturing, and related activities., ROI includes the societal benefits of vaccination such as averted health care costs or greater workforce productivity. Pricing, procurement, and financial decisions impact both affordability and ROI.
Product Innovation and Quality	A healthy vaccines market should consist of policies that support continued breakthrough and incremental innovation. Policies that foster, incentivize, and reward innovation and ensure product quality across the biopharmaceutical sector, Innovation is fostered by intellectual property (IP) policies and non-IP policies such as grants, prizes, or tax credits that are set by governments, as well as by non-governmental institutions. Rewards for innovative and quality products can also stimulate healthy competition between existing suppliers and potentially attract new entrants.
Healthy Competition	A healthy market ideally includes multiple suppliers of each vaccine type, engaging in dynamic competition in which innovation is rewarded and product superiority is reinforced by government recommendations and payers. Such market conditions are favorable to new vaccine R&D targets, improved technologies for existing vaccines, and new vaccine categories. Healthy competition also ensures there is enough product to meet market demand at the national, regional, and global market level.
Sustainable Buyer and Supplier Risk	In a healthy market, suppliers and buyers are able to absorb some level of risk, without resulting in market exits. market exit. Thus, sustainable risk allows existing suppliers and buyers to remain active in the market resulting in continued investment in R&D and manufacturing on the supply-side and the delivery of immunization services on the demand-side. Sustainable risk may also encourage new entrants in the market, thus incentivizing competition.

forecasts, pricing policies, and procurement mechanisms across countries. As such, market-shaping activities at the national level cannot be viewed in isolation and can have a broader knock-on effect at the regional or global level. This, subsequently, may enable or hinder innovation, timely development, and stable supply of successful vaccine candidates. Such challenges on both the supply- and demand-side of the global market necessitates greater dialogue and collaboration across the vaccine ecosystem.

3. Case study Analysis: Manufacturing of COVID-19 vaccines

The urgent demand for COVID-19 vaccines across the globe has driven a multi-faceted approach to bolster manufacturing capacity and cut development timelines worldwide. The HVMF can help illustrate the need for, the implications of, and the stakeholders involved in these efforts in fostering innovation to meet public health need. First, a range of strategic partnerships have brought

together necessary expertise and resources to advance the development and manufacturing of COVID-19 vaccine candidates. Industry collaborations with academia or small biotechnology companies have leveraged innovation already underway to accelerate early-stage R&D and facilitate large-scale clinical trials, as well as manufacturing and distribution. These collaborations depend on industry's expertise and assets, and its ability to take on financial risk and make a series of investments as vaccine candidates advance through development. The current approach for COVID-19 vaccines has been to scale-up manufacturing in parallel with clinical development. While necessary to accelerate timelines in the short-run for pandemic response, this approach is not typically pursued due to potential for imbalanced supply and demand in addition to sunk costs from idle manufacturing capacity.[8] To offset some of the risk in developing COVID-19 vaccines, push funding has been provided through ad hoc public–private partnerships with government bodies (e.g., the U.S. Biomedical Advanced Research and Development Authority or European Commission) or global institutions (e.g., Coalition for Epidemic Preparedness Innovations). In this capacity, these institutions operate as investors and must consider not only how they offset risk, but also other market characteristics, such as their role in enabling innovation, return on investment (ROI), and maintaining competition over time. Thus, funding mechanisms that enable industry to continue to invest in product lifecycle management activities and maintain tangible assets for use once the immediate needs for COVID-19 vaccine manufacturing have been met can protect market health in the long-term.[9,10].

While push funding helps address upfront capital investment challenges, pull funding and demand forecasting can provide greater market predictability and supply stability. For COVID-19 vaccines, supply stability has been challenged by the evolving epidemiology of the pandemic, uncertainty of which vaccine candidates will come to market, and availability of the specialized knowledge, equipment, and materials required to ramp up supply to meet global demand.[11] In order to accelerate access pathways, reduce buyer and supplier risk, and secure timely supply, global institutions and governments have been utilizing pull funding – both advance market commitments[1] and advance purchase agreements.[2] The COVAX Facility is the most notable effort to coordinate global allocation and procurement for COVID-19 vaccines.[12] While current pull funding mechanisms seek to provide an immediate solution during the pandemic, the current distribution of vaccine doses around the world and supply chain bottlenecks reveal their limitations in the face of an interdependent global vaccines market. Further, with ad hoc regulatory, financing, and procurement policies for purchasing countries, these mechanisms deviate from traditional commercial models for routine vaccines. Stakeholders must understand how they could shift market characteristics in the long-term, including fostering innovation, enabling ROI, and promoting competition.

Lastly, accelerating production of COVID-19 vaccines has necessitated greater regulatory cooperation and streamlining of processes across vaccine markets to create efficiencies and optimize global supply chains. Manufacturing facilities, equipment, and processes require approval by regulators from each country or jurisdiction in which the vaccine will be administered. Regulatory requirements vary by country, and manufacturers and suppliers of auxiliary supplies (e.g., glass vials) may need to recalibrate manufacturing processes depending on geographic demand. Even the slightest process change (e.g., packaging or labeling) requires regulatory post-approval changes; approval timelines can interrupt the entire supply chain and result in delays in production and delivery. Due to these regulatory differences, reallocation of vaccine doses manufactured for one country to another country is extremely difficult. Further global cooperation by regulators, as well as harmonization and streamlining of pre-approval and post-market regulatory requirements, will continue to be fundamental for facilitating rapid availability and access while maintaining highest levels of safety, quality, and efficacy for COVID-19 vaccines. Unifying bodies, like the World Health Organization and the International Coalition of Medicines Regulatory Authorities, play an important role in issuing guidance and establishing global frameworks that can be applied across markets.

4. Conclusion

As the case study demonstrates, a healthy market necessitates a comprehensive, end-to-end approach including: (i) regulatory harmonization and streamlining to improve timely vaccine availability, supply, and innovation; (ii) policies and practices that incentivize innovation; (iii) demand forecasting systems and procurement models to increase market predictability, reduce risk, and supply stability; and (iv) sustained funding and established financing mechanisms for pandemic preparedness. The HVMF illustrates the need for supply- and demand-side stakeholder communication and coordination as they shape national, regional, and global markets because these activities individually and collectively strengthen or degrade market health over time. By understanding market shortcomings and potential direct and spill-over effects of policy proposals to address them, decision-makers can provide timely interventions that strengthen individual and global market health. With this approach we can ensure the global market promotes future growth and innovation, so vaccines realize their full potential.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [J. Spencer, A. Tantri, R. Mitrovich, are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ USA, who may own stock and/or hold stock options in the Company. B. Rachev, and I. Sharma were employees and shareholders of Merck Sharp & Dohme Corp., a subsidiary of Merch & Co., Inc., Rahway, NJ USA when the study was performed. A. Towse, L. Steuten and M. Rodes-Sanchez report grants to the Office of Health Economics from Merck & Co during the conduct of the study; personal fees from various pharmaceutical companies outside of the submitted work and, for the Office of Health Economics, grants and consulting income from various pharmaceutical companies outside the submitted work. This research was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA].

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J. Spencer, A. Tantri, R. Mitrovich, are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ USA, who may own stock and/or hold stock options in the Company. B.

[1] [1] Advance market commitments are where public or private donors make funding commitments to vaccine manufacturers and, in exchange, companies sign a legally-binding agreement to provide vaccines at an affordable price to low- and middle-income countries.

[2] [2] Advance purchase agreements are bilateral agreements between governments and manufacturers where governments agree to purchase a specific number or percentage of vaccines at a pre-negotiated price.

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Author contributions

All authors contributed to the research, the development of the framework, and the writing of the manuscript. All authors reviewed and approved the final version of the manuscript for publication.

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