Chapter

Supply Chain Logistics and Business Ecosystems Needed for the Development of Natural Vaccines with Novel, Safer, and Noninvasive Delivery Mechanisms

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Abstract

The success of natural, non-invasive vaccines is dependent not only on their efficacy and safety but also on the logistics and business ecosystems required to develop and distribute them. This chapter discusses the challenges and opportunities associated with developing and implementing a supply chain for such vaccines as well as different scenarios that a similar new business could encounter on its path to the market. We examine options for vertical coordination within the value chain in areas such as product manufacturing, packaging, and distribution. Market and stakeholder analysis is also provided, which focuses on contracting strategies, while keeping in mind the importance of an efficient and equitable distribution of vaccines. Lastly, we will explain our most probable road map, how we arrived at that decision, and how this information can be used by natural vaccine producers to develop supply chains.

Keywords: vaccine supply chain, scenario planning, vertical coordination alternatives, supply chain logistics, business ecosystems, value chains, natural vaccines, non-invasive delivery, infrastructure, cost-effectiveness

1. Introduction

The development and distribution of natural, non-invasive vaccines hold immense potential for revolutionizing immunization [1–3]. These vaccines provide effective and safe immunization without the need for invasive procedures [1]. However, their success depends on efficient supply chain coordination and robust business ecosystems [4]. This chapter explores the challenges and opportunities in developing and implementing supply

chains for novel, non-invasive vaccines, recognizing the critical role of logistics and business strategies in taking these vaccines from research and development to the market.

Immunization is a cornerstone of public health, preventing the spread of infectious diseases and saving millions of lives each year [5]. While the current vaccine market and its traditional supply chain have achieved significant vaccination coverage worldwide, there are limitations within this framework that demand innovative solutions [6]. For instance, the COVID-19 pandemic highlighted the need for better-funded, flexible, and strengthened vaccine supply chains, emphasizing the importance of exploring alternative supply chain models [4, 7]. As the demand for effective vaccines rises, new companies are entering the vaccine market to provide innovative, globally-impactful, and transformative solutions. However, establishing and maintaining a successful vaccine company requires a deep understanding of the current vaccine market and supply chain intricacies (see **Figures 1**-**4**).

This perspective chapter focuses on natural vaccines, outlining the essential steps in creating a robust supply chain for these vaccines. It also provides guidance on market analysis, helping vaccine companies understand their target market, navigate the dynamic landscape, and identify potential partners, buyers, and competitors.

In conclusion, this perspective chapter highlights the importance of a well-designed supply chain logistics and a well-defined business ecosystem for new vaccine companies venturing into the world of natural vaccines. The challenges and opportunities presented in this chapter are intended to assist these companies in making informed decisions and building a foundation for successful vaccine development and distribution. As the world adapts to the changing landscape of infectious diseases, the pursuit of natural vaccines and innovative delivery methods holds immense promise [12–14]. By creating a seamless supply chain and understanding the market dynamics, vaccine companies can play a pivotal role in shaping the future of global health and disease prevention.

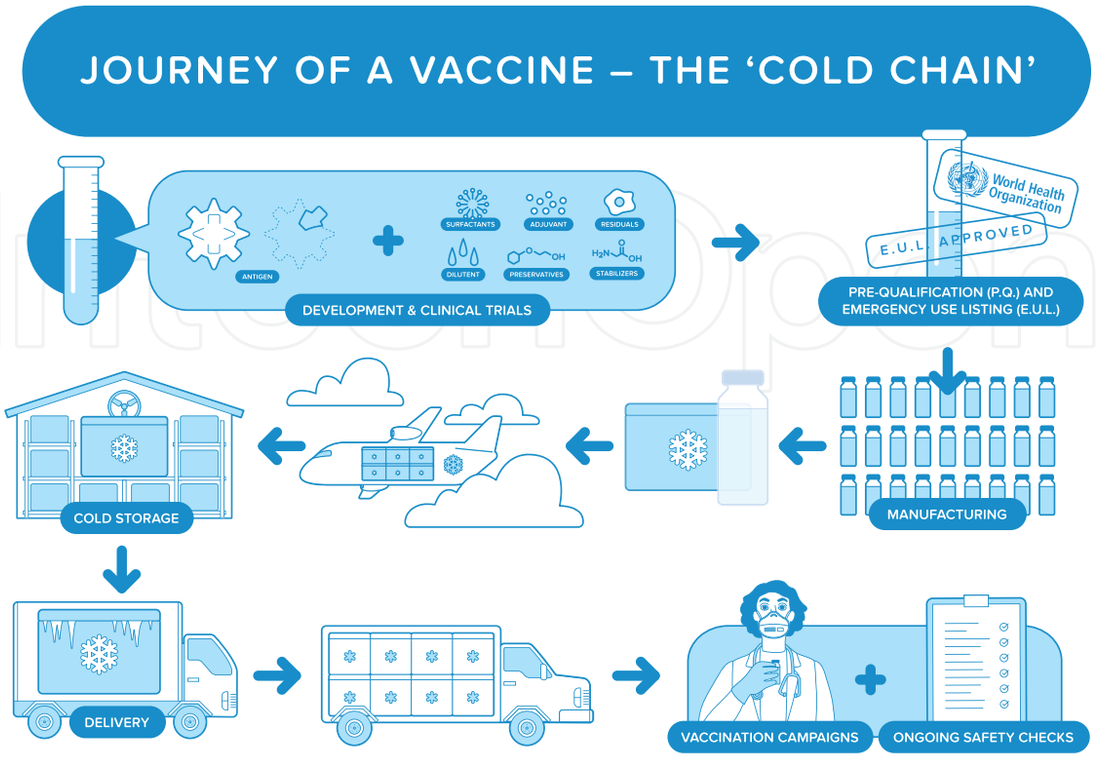

Figure 1.
Traditional journey of a vaccine. Taken from [8].

2. Understanding the current vaccine market and the existing supply chain

To design an effective supply chain for natural, non-invasive vaccines (e.g., orally- or nasally-delivered), it is crucial to gain a richer understanding of the current vaccine market and the traditional supply chain that supports it. The existing competitive landscape provides valuable insights into the requirements and complexities of vaccine distribution, highlighting the need for innovative approaches to facilitate widespread accessibility, acceptability, and efficient delivery. The vaccine market has witnessed significant growth and transformation in recent years due, in part, to the need for a rapid development and distribution of the COVID-19 vaccine. Vaccines play a vital role in preventing the spread of infectious diseases and are one of the most cost-effective public health interventions. However, despite their immense benefits, challenges persist in achieving global vaccination coverage. Factors such as inadequate funding, distribution inefficiencies, and logistical hurdles have impeded accessibility to vaccines [12, 13].

Traditionally, the vaccine supply chain has followed a sequential model that encompasses various stages from manufacturing to distribution, further broken down in **Figure 1**. This model involves multiple stakeholders, including manufacturers, regulatory authorities, distributors, healthcare providers, and ultimately, the end-users/-vaccine-recipients. The supply chain process begins with vaccine production, where manufacturers develop, test, and produce vaccines in accordance with regulatory requirements and quality standards. This design and clinical trial stage involves stringent quality control measures to ensure the safety and efficacy of novel vaccines, including three phases of clinical trials which can take many years to complete [15]. If the vaccine makes it past all these checks and reviews, approval will be granted by regulatory authorities, at which point large-scale production and distribution can begin.

Vaccines undergo packaging and labeling processes to meet specific requirements for distribution and administration. These requirements range from single or multiple-use vials to blister packs and syringes. Once the vaccines are packaged, they move into the distribution phase, which involves logistics and transportation to various destinations around the world. This phase includes considerations such as cold chain management, storage facilities, and inventory management. The 'cold chain' refers to the continuous temperature-controlled supply chain that ensures vaccines are stored, transported, and distributed at the appropriate temperatures to maintain their potency and effectiveness. Since almost all vaccines currently on the market need to be stored at refrigerator temperature or below, cold chain logistics poses perhaps the most significant supply chain challenge in maintaining product efficacy, integrity and potency throughout the distribution network [16]. This challenge will be explored in greater detail in the following sections.

Additionally, the distribution phase requires coordination with healthcare providers, vaccination centers, and public health agencies to ensure vaccines reach their intended recipients. Timely and accurate information sharing, inventory management, and forecasting play crucial roles in ensuring the availability and accessibility of vaccines at the point of administration [17].

Delineating the current vaccine market and the intricacies of the traditional supply chain enable us to better identify opportunities for innovation and devise strategies to overcome existing limitations. The insights gained from examining the current vaccine landscape lay the foundation for designing an efficient and resilient supply chain for natural, non-invasive vaccines.

2.1 Impact of vaccine supply chain management on global population health

Although the economics of a global supply chain is likely to result in greater profitability when everything works smoothly, the adverse impact of poorly designed supply chains on global population health cannot be overemphasized. The human cost of a failed supply chain can be significant. For example, some essential medications used daily in emergency departments and outpatient clinics may suddenly be in short supply, including medicines to control blood pressure, sedatives required for patients on ventilators, analgesics for pain control, antibiotics, normal saline [18]. Similarly, the beneficial impact of vaccines on global population health is often impaired by poorly designed and executed distribution systems, resulting in supply chain constraints that adversely impact vaccination campaigns [6]. This results in prolonged vaccine stockouts resulting from forecasting errors [19], wastage of vaccines due to excessive freezing or thawing following temperature deviations [20], and suboptimal coverage of target populations [21, 22]. This inefficiency and waste disproportionately affects low- and lower middle-income regions of the world where immunization budgets are already stretched thin, these constraints lead to missed opportunities to protect populations against preventable diseases.

The following five steps provide practical solutions and strategies to avoid constrained distribution/supply and ensure that global vaccine supply chains are better prepared for large demand surges arising from pandemics, epidemics, or disease eradication efforts, largely based on lessons learnt from the COVID-19 pandemic [23]:

1. Adequate consideration of supply chain & logistics during vaccine development

    a. Global logistical constraints around cold chain infrastructure, dosing schedule, and type of syringe/delivery device are important factors that must be taken into account when developing vaccines

    b. Considerations such as thermostability, dose volume, number of doses, and type of syringe/device for administration should be given prominence in pre-pandemic R&D programs

2. Stable & diversified supply of raw materials & components

    a. The governance structure, technical capabilities, and partnership modalities of the vaccine procurement marketplace need to be carefully configured and adequately resourced to solve the material sourcing problem for new and existing manufacturers, especially during a period of high demand and constrained supply

    b. Careful consideration should be given to ensuring that such a marketplace can be maintained during inter-pandemic periods and that trade barriers do not stymie its usefulness during pandemics and large health emergencies

3. Cold-chain investments as a long-term health system investment

    a. In some instances, the lack of ultra-cold chain equipment at the subnational levels has resulted in a more direct distribution system for

some COVID vaccines. This more direct distribution model should be explored as a permanent option for routine vaccines. Besides improving efficiency and reducing cold chain requirements, this would enhance operational readiness for fast response distribution during disease outbreaks or pandemics.

b. COVID-19 vaccine distribution in many countries also relied on special arrangements for shipment preclearance, airspace clearance, advance documentation sharing, and sharing assets across public and private agencies. There should be an assessment of whether these ad-hoc measures for the distribution of COVID-19 vaccines can be made more systematic.

4. Immunization supply chain data systems, demand forecasting & tracking vaccine wastage

   a. A robust system that provides real-time information on vaccine stock and temperature/conditions of storage throughout the supply chain is critical to ensure the efficient distribution of vaccines, both for routine immunization and during a pandemic.

   b. Such systematic collection of immunization supply chain data in real-time also facilitates better demand forecasting.

   c. Mature supply chain stock tracking systems can also provide data on vaccine wastage, and this can help to inform specific interventions to minimize such wastage.

5. Investing in the people who manufacture & deliver

   a. During a pandemic, the shortage of trained biomanufacturing personnel can negatively impact vaccine production. A critical need is to establish a network of different types of training and capability-building providers who have an on-the-ground presence.

Supply chains were originally designed for a different era in immunization [24]. There has since been slow advancement with relatively low levels of investment. By 2020, vaccines comprised 40% of the average immunization budget in low- and lower middle-income countries [25], and this budget has since continued to grow. There is a need for significant changes to be made in the design and management of supply chains, including the flow of information and funding from end to end across the vaccine supply value chain [6].

There is a dearth of supply chain managers, particularly in low-and middle-income countries (LMICs), that have been adequately trained to improve supply chain performance [26], despite the increased availability of supply chain management and logistics education and training programs [27]. Recent evidence indicates that appropriately trained supply chain personnel can indeed have a significant positive impact on supply chain performance [28–31].

To date, very few countries have attained average scores exceeding the desired threshold of 80% for the Effective Vaccine Management (EVM) process, which benchmarks supply chain performance against best practices in nine areas of vaccine

management [32]. Some countries have developed exemplary oversight mechanisms for monitoring performance and recommending policy changes geared toward improving supply chain performance [33].

The success of immunization programs and campaigns is heavily dependent on the accuracy and completeness of data collection systems, which are prerequisites for forecasting vaccine requirements as a preamble to the delivery of vaccines where they are needed. Lydon et al. [19] determined that vaccine stockouts lasting one month or longer occur in one of every three countries globally, and about 89% of these national stockouts compromise vaccine availability at the service delivery level. Electronic data systems have been successfully piloted and scaled in developing countries, leading to reduced stockouts and increased vaccine availability after 13 months of consistent use [29], and data on vaccine wastage and session size has been used to determine optimal dose-per-vial [34].

In navigating these complex issues related to vaccine supply chains, international alliances and organizations like Gavi, the Vaccine Alliance, play a crucial role. By providing a platform for cooperation, funding, and equitable distribution, they help mitigate the impact of international tensions, geopolitical events, and vaccine distribution disparities on vaccine supply chains and access [35]. Emerging vaccine companies often look to such organizations as key partners in addressing these challenges.

2.2 Importance of cold chain integrity

Ensuring the integrity of the cold chain is paramount in vaccine supply chains. Hanson et al. [20] determined that accidental freezing or thawing still occurs in about a third of storage facilities in wealthy and lower-income countries alike, and Azimi et al. [36] determined that cold chain equipment is failing in 20% and underperforming in 50% of 55 Gavi-eligible countries. As mentioned above, this level of equipment and process failure leads to enormous amounts of waste which would otherwise be potentially life-saving vaccines for people in need. Innovations in cold chain equipment for immunization supply chains are providing solutions to these problems at many different levels [37], including the use of formulations that can withstand freezing or thawing [38], methods for extending supply chains and improving immunization coverage and equity through controlled temperature chain use of vaccines [39], and use of cold chain equipment that is designed to avoid undesired freezing or thawing and to operate successfully in areas without reliable access to electricity [37]. These innovations are not only improving the efficacy of vaccines but also enhancing global equity in immunization coverage.

3. Introducing the steps of a natural vaccine supply chain - A sample case

To gain a comprehensive understanding of the natural vaccine supply chain, with a specific focus on FruitVaccine, Inc.[1], it is vital to provide a more detailed introduction to the crucial stages and their direct connection to our case study (see **Figure 2**).

This section will elucidate the critical steps in the natural vaccine supply chain. We will begin by delving into the research and development (R&D) phase, highlighting how FruitVaccine's approach in this stage contributes to the success of the supply

[1] fruitvaccine.org

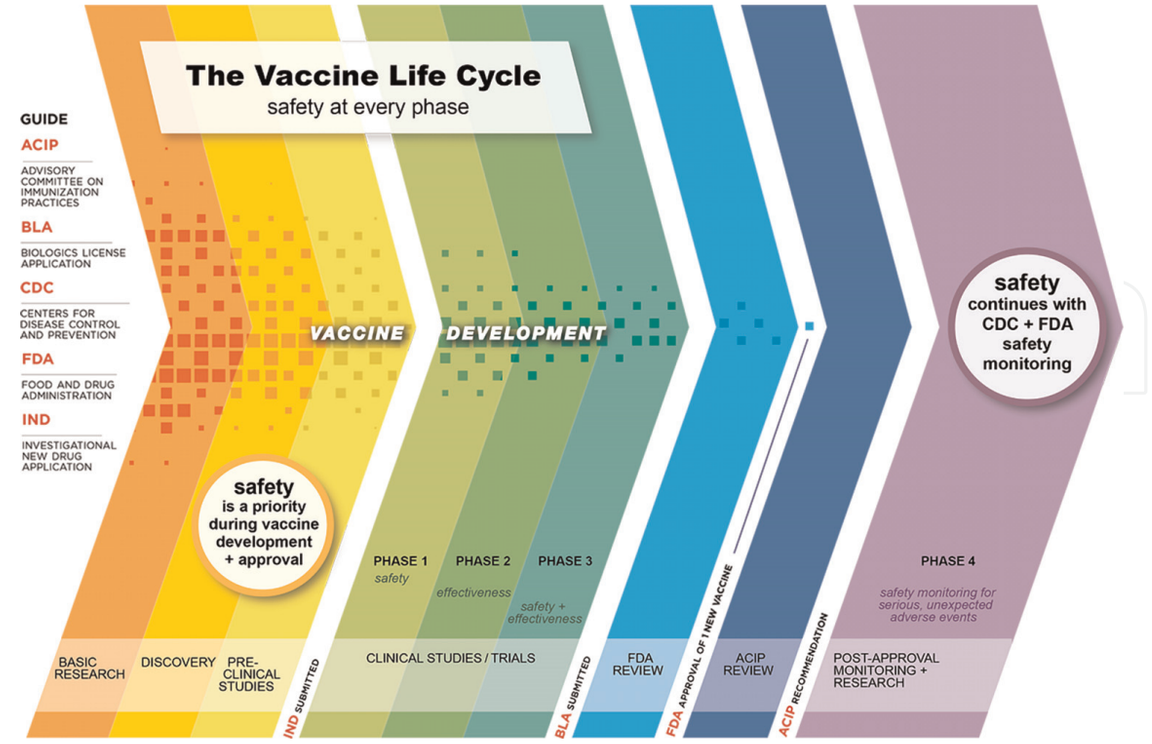

Figure 2.
The vaccine life cycle. Taken from [9].

chain. Following that, we will explore the process of plant cultivation and fruit growth within greenhouses, emphasizing FruitVaccine's innovative methods in this critical component. The subsequent discussion will revolve around the manufacturing of various vaccine formats and finish off by delving into the packaging and distribution segment, underscoring how FruitVaccine optimizes these processes to allow for global vaccine access and coverage [12–14]. This comprehensive overview will provide a clearer connection between the steps of the natural vaccine supply chain and our case study, FruitVaccine, offering valuable insights into the complexities and innovations that drive the success of this unique approach to vaccine development and distribution.

3.1 Research and Development (R&D)

The initial stage of the supply chain for plant-created vaccines involves extensive research and development efforts. In the R&D stage, the primary goal is to design and develop effective vaccines and to enhance the efficiency and cost-effectiveness of large-scale vaccine manufacturing processes while maintaining the integrity and immunogenicity of vaccine antigens extracted from the plants. To illustrate, the scientists and researchers at FruitVaccine have been working continuously since 2017 on the transgenic process to create vaccines in the form of fruiting cherry tomato plants. Multiple growing cycles, test batches, and preclinical studies have been conducted to test various factors of the vaccine and to evaluate its safety and efficacy. This stage is crucial for determining the most effective vaccine formulation and dosage, ensuring adherence to regulatory requirements and quality standards.

During the R&D phase, rigorous testing is conducted to validate the vaccine's effectiveness in stimulating the desired immune response. FruitVaccine's flagship

product that has been in development and testing is a vaccine against the human respiratory syncytial virus (hRSV). hRSV causes an infectious disease that affects all humans, especially infants, the elderly, and immunosuppressed individuals due to their weakened respiratory systems. It infects over 64 million people each year globally and results in over 160,000 deaths [12, 40]. Various methods, such as molecular biology techniques and genetic engineering, are employed to optimize the gene function of vaccine antigens in these tomato plants. These techniques enable the production of higher yields of specific proteins, ensuring the efficacy and stability of the vaccine in processing and manufacturing.

Vaccine R&D requires large inflows of time, resources, and funding to sustain research efforts. FruitVaccine is fortunate to have been recognized by local and international organizations for breakthroughs in the field of immunization. In late 2020, FruitVaccine was awarded a research grant from the National Science Foundation Division of Industrial Innovation and Partnership [41]. Further, it was also selected for the All-SBIR NSF-iCorp program which took place in Fall, 2021. These grants have played a pivotal role in advancing our research efforts and bringing our innovative vaccine products closer to the market, reinforcing the commitment to global health and immunization.

In addition to vaccine development, R&D efforts focus on improving production processes and establishing protocols for large-scale manufacturing. The research team strives to develop efficient and cost-effective methods for extracting and purifying the vaccine antigens from tomato plants while maintaining their integrity and immunogenicity [12–14]. R&D provides the foundation for subsequent stages in the supply chain.

3.2 Natural vaccine-plant cultivation

Before delving into the specifics of natural vaccine-plant cultivation, it is crucial to emphasize the paramount importance of this phase in the production of plant-created vaccines. Natural vaccine-plant cultivation is the heart of the process, where genetic material is translated into tangible resources for vaccine production. It serves as the bridge between innovative research and the manufacturing of vaccines that can improve global health. Moreover, it plays a vital role in supporting environmental sustainability with greenhouse cultivation, which is a cornerstone of the FruitVaccine project. These controlled environments enable year-round cultivation and require less land and resource use, among other benefits that will be explored.

Plant-created vaccines require a suitable carrier for the genetic material of the vaccine, and plants such as tomatoes serve this purpose. Within FruitVaccine, these plants are grown in controlled laboratory and greenhouse environments. Greenhouse cultivation offers several advantages, including year-round production, protection from pests and adverse weather conditions, and the ability to optimize growing conditions for maximum yield and quality-control.

While the R&D of the transgenic tomato plant is done within the laboratory, the greenhouse is where plants are carefully nurtured and monitored to ensure optimal growth. This process includes providing appropriate nutrition, managing temperature and humidity levels, and implementing other beneficial horticultural measures. The cultivation process involves the careful selection of tomato varieties that provide the necessary protein activity for vaccine production. Greenhouse cultivation allows for better control over environmental conditions, leading to more consistent and

predictable plant growth. This cultivation facilitates a reliable supply of raw materials for vaccine testing and manufacturing and reduces the risk of variability in the vaccine product.

Since the company is in its early stages, greenhouse cultivation is primarily done by the team of researchers responsible for the vaccine's R&D in the lab setting. Small plots of greenhouse space are currently being used to test batch viability and crop yields. Furthermore, the greenhouse environment enables the implementation of sustainable practices in tomato plant cultivation. By utilizing efficient irrigation systems, integrated pest management techniques, and optimized nutrient delivery, the FruitVaccine team strives to minimize resource usage and reduce environmental impact. This goal aligns with the company's commitment to sustainable and eco-friendly production methods, ensuring that the entire supply chain adheres to environmentally responsible practices.

As the company progresses from the R&D phase to larger-scale production, additional greenhouse space will be allocated to accommodate the increased demand for tomato plants. The next section considers partnerships with key stakeholders and the different options available in that space.

3.3 Manufacturing of different vaccine formats

The manufacturing stage is a pivotal phase in the supply chain, where the harvested fruits are transformed into various vaccine formats, each serving to allow for greater accessibility or efficient distribution to target populations. This phase plays the role of creating the product that will be sold and distributed around the world. Different vaccine formats, including chewable pills, oral drops, vaccine puree, and nasal spray, are tailored to accommodate the varied preferences and requirements of individuals as well as more efficient accessibility and distribution, outlined further in the next section [42].

Chewable pills offer a convenient and user-friendly vaccine format. In the manufacturing process, tomato plants are harvested, and the resulting fruit is processed into chewable pills. This process involves drying and compressing the fruit using specialized machinery that ensures uniformity of size and shape. This manufacturing process enables accurate dosing and adherence to quality standards, resulting in consistent and reliable vaccine creation.

Oral drops provide an alternative administration method for non-invasive vaccines, especially for those who are unable to use chewable pills due to health- and/or age-related difficulties. In the manufacturing process, tomato plants are processed to obtain the vaccine proteins, which are then formulated into a liquid solution suitable for oral administration. The solution will be carefully prepared, ensuring the appropriate concentration of vaccine proteins and maintaining stability throughout the shelf life of the product. Packaging and labeling of the oral drops will also be undertaken to ensure ease of use and accurate dosage administration.

Vaccine puree serves as another format that is particularly suitable for those who experience difficulty with chewing. The manufacturing process involves transforming the harvested tomatoes into a puree-like consistency. The vaccine puree will be packaged in appropriate containers, considering factors such as ease of use and accurate dosage administration.

Nasal spray provides another needle-free option for vaccine administration. Similar to how the oral drops are processed, vaccine components will be extracted from the

harvested tomatoes, which will then be formulated into a nasal spray solution. This formulation ensures the proper delivery of vaccine antigens through a fine mist sprayed into the nasal passages.

3.4 Packaging and distribution

The final stage of the supply chain involves packaging and distribution of the vaccines to ensure their safe and efficient delivery to healthcare providers, clinics, vaccination centers, and other key entities involved in the immunization process. Proper packaging with sustainable materials is crucial to protect the vaccines from environmental factors and maintain their stability. **Figure 3** shows an example of current cold chain packaging and how important it is for vaccine shipments to be properly packaged for distribution.

Packaging for natural, non-invasive vaccines typically involves sterile vials, bottles, or blister packs, depending on the vaccine format. These containers are designed to preserve the vaccine's integrity and prevent contamination. Labeling requirements, including batch numbers, expiry dates, and dosage instructions, are carefully adhered to for regulatory compliance and accurate usage information.

Distribution logistics play a vital role in ensuring vaccines reach their intended destinations in a timely and efficient manner. This includes transportation, warehousing, and inventory management to maintain the vaccine's cold chain integrity, especially for oral drops and nasal sprays that require cold storage. Collaboration with logistics partners, such as shipping companies and cold chain providers, is essential to facilitate the smooth flow of vaccines from the manufacturing facility to the end users.

The emergence of inovative alternative vaccine formats, notably the chewable pills and vaccine puree, presents a major, compelling advantage in their distribution: these novel formats eliminate the need for a stringent cold chain. Unlike delicate needle-based vaccines that require refrigeration, most commonly between 36°F and 46°F [43], from production to administration, chewable pills and vaccine puree are more

Figure 3.
Traditional vaccine packaging. Taken from [10].

stable at ambient temperatures. Packaging material, especially for the vaccine puree format, plays an important role. The USDA recommends maintaining temperatures below 85°F for optimal storage of canned products [44]. Notably, during land transportation, temperatures can fluctuate between −5.8 and 134.6°F. Exposure to direct sunlight can elevate the roof temperature of an unsheltered container to as high as 158 °F due to solar radiation [45]. While needle-based vaccines necessitate a stringent cold chain, the temperature for canned puree vaccines only needs to be maintained to prevent freezing-induced leakage and to stay below 85°F to ensure optimal efficacy. This breakthrough brings several benefits to vaccine distribution and accessibility. First, it allows for longer shelf life, reducing waste and ensuring greater availability, especially in resource-limited settings with limited refrigeration infrastructure. Second, wider and more flexible temperature requirements simplify transportation logistics, reducing costs and enhancing efficiency. This advantage is particularly significant in remote areas where access to medical facilities and refrigeration facilities may be challenging.

Effective distribution strategies prioritize equitable access to vaccines and consider factors such as geographical location, population density, and healthcare infrastructure. Collaboration remains a linchpin in ensuring effective vaccine distribution. The involvement of governmental agencies, non-governmental organizations, and international bodies in the distribution process is pivotal in creating a comprehensive strategy that reaches even the most remote or underserved areas.

In conclusion, the supply chain for natural, non-invasive vaccines involves several critical steps, including research and development, tomato plant cultivation in greenhouses, manufacturing of different vaccine formats, and packaging and distribution. Each stage requires meticulous attention to detail, adherence to quality standards, and collaboration with various stakeholders to ensure the safety, efficacy, and efficient delivery of vaccines to the intended recipients.

4. Integrating the supply chain

As emerging vaccine companies embark on the development and distribution of novel vaccines, the process's efficiency heavily relies on integrated supply chain management. This section explores the crucial factors that come into play during the integration phase, emphasizing the significance of coordination and ownership in crafting a successful vaccine supply chain.

4.1 Ownership and governance

The ownership structure and governance mechanisms within the supply chain play a pivotal role in the success and efficiency of emerging vaccine companies. A carefully considered ownership and governance framework can facilitate seamless coordination among stakeholders, optimize resource allocation, and enhance the overall performance of the value chain.

4.1.1 Intellectual property ownership

The research and development phase serves as the foundation for the entire supply chain, as it involves groundbreaking scientific discoveries, innovative vaccine formulations, and crucial preclinical and clinical trials. During this stage, emerging vaccine

companies typically retain full ownership and control over their intellectual property and vaccine candidates [46]. Owning the intellectual property rights allows the company to protect its innovations from potential competitors and negotiate licensing agreements with partners if necessary.

Maintaining ownership of the R&D process offers several advantages. First, it enables emerging vaccine companies to maintain control over research priorities, explore multiple vaccine candidates, and more easily adapt to changing market demands. Second, the company can leverage its discoveries for licensing agreements and strategic partnerships that can accelerate vaccine development and market entry. Furthermore, a clear ownership structure over intellectual property ensures streamlined decision-making processes and fosters a sense of responsibility among research teams.

This ownership structure was exemplified during the research and development of Johnson & Johnson's COVID-19 vaccine, where they maintained ownership of the vaccine's intellectual property. This ownership allowed them to collaborate with various partners to expedite production and distribution while protecting their innovations [47]. The ability to retain control over research priorities, adapt to rapidly changing market demands, and negotiate strategic partnerships significantly contributed to the vaccine's rapid development and deployment.

4.1.2 Cultivation ownership

The greenhouse cultivation of plants for vaccine production is a critical step in the supply chain. During this stage, emerging vaccine companies may explore different ownership models to efficiently scale production capacity while ensuring quality control.

One option is for the company to maintain full ownership and operation of the greenhouses, granting them complete control and flexibility over the cultivation process. This ownership model enables emerging vaccine companies to optimize growing conditions, respond swiftly to changing market demands, and implement sustainable practices aligned with their vaccine development needs. In-house ownership also ensures stringent QA/QC, or quality assurance and quality control measures, with direct oversight of every stage of cultivation, from seed to harvest. This level of control is particularly vital when producing vaccines that require consistent and precise measures of vaccine antigens. Additionally, for companies heavily invested in research and development, owning and operating greenhouses facilitates seamless integration between laboratory work and plant cultivation. Researchers can directly monitor the plants and make adjustments based on ongoing R&D findings, promoting a more efficient and iterative vaccine development process. Furthermore, in-house ownership allows the company to protect its proprietary methods, cultivation techniques, and research discoveries related to plant-created vaccine production, securing a competitive advantage in the market.

On the other hand, emerging vaccine companies may consider partnerships with specialized greenhouse operators, acting as a contract development manufacturing organization (CDMO), as an alternative approach. Collaborating with an experienced CDMO in this capacity can offer rapid scale-up opportunities without the initial delays and capital expenditures associated with establishing new greenhouses [48]. Established greenhouse operators have existing facilities, optimized processes, and skilled staff, enabling accelerated vaccine production. Access to their expertise reduces the burden on the company's internal resources and provides valuable insights into best practices and technological advancements in cultivation techniques.

While partnering with greenhouse operators provides advantages in rapid scale-up and access to expertise, it also comes with some trade-offs. Companies may have less direct control over cultivation conditions and processes, relying on the partner's decisions and responsiveness to changing demands. Additionally, the collaboration introduces an element of dependency on the greenhouse operator, and disruptions or disagreements with the partner could impact the company's ability to meet production targets. Careful agreements and confidentiality measures are necessary to protect the company's intellectual property and research discoveries when collaborating with greenhouse operators.

The choice between in-house ownership and partnerships with greenhouse operators in the cultivation of plant-created vaccines requires careful consideration of the company's financial capabilities, expertise, research integration needs, and long-term growth strategy. Depending on what stage of rollout the company is in, it might be wise to maintain cultivation in-house until ramp-up and widespread distribution agreements are reached, at which point contracting agreements could be negotiated with growers in strategic locations. Greenhouse ownership and cultivation is not new in the vaccine industry. Many major companies such as GSK grow critical raw materials within greenhouses, allowing them to maintain ownership and control of every step of the cultivation process [49]. Companies also often contract with CDMOs to buy these raw materials so they can manufacture and distribute their vaccine to the world. As stated, both of these are very viable options and depend on the multitude of factors mentioned to make the proper decision. Striking the right balance between control, resource optimization, and collaboration will be critical for emerging vaccine companies to achieve efficient and successful vaccine production and market entry.

4.1.3 Manufacturing and production ownership

The manufacturing stage in the supply chain for emerging vaccine companies involves transforming raw materials into various vaccine formats suitable for different administration methods. Two primary approaches are commonly considered: in-house manufacturing and partnerships with contract manufacturing organizations (CMOs).

As discussed above, in-house manufacturing allows emerging vaccine companies to have direct control over the production process, ensuring stringent QA/QC measures. Additionally, it offers flexibility in adapting to changing market demands and adjusting production schedules, accordingly, enabling efficient responses to unforeseen events. However, in-house manufacturing requires significant upfront capital investment in equipment, personnel, and infrastructure [50]. Managing a manufacturing facility demands expertise in pharmaceutical production, which may necessitate additional hiring or specialized training. The scalability of in-house manufacturing could also pose challenges, particularly for smaller companies with limited resources.

Collaborating with CMOs offers an alternative approach to vaccine manufacturing. Working with specialized CMOs allows companies to access expertise and capabilities in vaccine production without heavy capital investment. CMOs are experienced in vaccine manufacturing, and this partnership can expedite the process of scaling up production capacity to meet market demand. Partnering with CMOs reduces financial risks associated with setting up and maintaining a manufacturing facility, allowing the emerging vaccine company to allocate resources more strategically to other critical aspects [51]. However, it also means relinquishing some direct control over

manufacturing processes, potentially impacting the company's ability to respond quickly to changing market conditions or research priorities. Intellectual property concerns may also arise during collaboration, necessitating careful agreements to protect proprietary information.

Emerging vaccine companies must carefully assess their capabilities, the resources available to them, and their desired level of control in order to make the proper choice. For a startup in the non-invasive space such as FruitVaccine, short-term contracting on the operational level could strike the right balance by outsourcing some of the manufacturing processes, while maintaining control over the more crucial ones, such as QA/QC. This strategy would allow a trial period with the CMOs in order to see if longer term, more collaborative contracting agreements would be viable in the future once the company has reached a more stable state.

4.1.4 Packaging and distribution ownership

The final stage in the supply chain for emerging vaccine companies involves packaging and distributing the vaccines to ensure their safe and efficient delivery to healthcare providers, clinics, vaccination centers, and other key entities involved in the immunization process. Proper packaging with sustainable materials is crucial to protect the vaccines from environmental factors and maintain their stability during transportation and storage.

Some emerging vaccine companies may choose to handle packaging and distribution in-house, allowing them to maintain direct control over these critical processes. In-house packaging provides the company with the flexibility to tailor packaging designs to its brand identity and specific vaccine formats. This level of control ensures that packaging materials meet the highest quality standards and comply with regulatory requirements for vaccine storage and transportation. Additionally, in-house distribution gives the vaccine company the ability to optimize logistics and streamline the supply chain to meet demand efficiently. By managing the distribution process internally, the company can establish strategic partnerships with shipping companies and cold chain providers, where needed, to ensure the vaccines' safe and timely delivery. However, in-house packaging and distribution require substantial investments in logistics infrastructure, warehousing, and personnel.

Smaller vaccine companies with limited resources may find it challenging to set up and maintain a comprehensive distribution network. In such cases, outsourcing distribution may be a more feasible option. Outsourcing packaging and distribution to third-party logistics providers is a viable alternative for emerging vaccine companies. Collaborating with specialized distribution partners allows the company to leverage the expertise and established networks of these providers, reducing the burden of managing complex logistics operations. Outsourcing distribution can be cost-effective for smaller vaccine companies, as they can benefit from the efficiency and economies of scale offered by the logistics partner [52]. This option provides access to established distribution networks, enabling the vaccines to reach a broader market and diverse geographical regions. However, outsourcing distribution also means relinquishing some control over the logistics process. The vaccine company must carefully choose a reliable and reputable logistics partner to ensure that the vaccines are handled with the utmost care and adhere to strict temperature requirements, especially for vaccines requiring a cold chain.

An emerging vaccine company may also adopt a hybrid approach, combining in-house and outsourced packaging and distribution strategies. For example, the

company may choose to handle packaging in-house for better control over branding and quality. Simultaneously, they may collaborate with a specialized logistics provider to manage the transportation and distribution aspects, leveraging the exchange partner's expertise and established networks.

It is quite common to have third-party logistics (3PL) or fourth-party logistics (4PL) companies handle part or all of the packaging and distribution supply chain. These logistics providers are often well established and trusted in their industry and can offer considerable savings over in-house distribution [53]. Writing an effective and flexible long-term contract could offer an array of synergies and pave the way for a mutually beneficial sustainable partnership.

It is important to note that scaling demands synchronicity across all stages from cultivation to distribution, as focused scaling—such as expanding cultivation without a corresponding adjustment in packaging and distribution—can lead to inefficiencies and wastage. However, scaling the entire process, particularly as a company transitions into mass production, entails a substantial financial commitment that might be beyond the company's immediate means. During this juncture, an intricate predicament emerges, necessitating a delicate balance between maintaining control, mitigating financial risks, and safeguarding intellectual property concerns. The decision whether to retain a step in-house, engage with a specialized external entity, or even establish new partnerships hinges on a meticulous and comprehensive cost analysis. Ultimately, the resolution of this conundrum necessitates a comprehensive cost assessment, guiding companies toward a strategic choice that aligns with their unique circumstances and long-term aspirations.

4.1.5 Governance mechanisms

Alongside ownership considerations, establishing effective governance mechanisms is vital for successful vertical coordination within the supply chain [54]. Clear governance structures define decision-making processes, roles, and responsibilities of different stakeholders, and ensure that the interests of all parties align with the overall objectives of the emerging vaccine company.

Governance mechanisms should promote transparency, accountability, and mutual trust among stakeholders. Regular meetings, performance evaluations, and collaborative forums facilitate open communication, enabling prompt decision-making and issue resolution. Furthermore, a robust governance framework safeguards against potential conflicts of interest and ensures compliance with regulatory requirements and industry standards [55]. Compliance with ethical guidelines and industry best practices instills confidence among stakeholders, regulatory bodies, and end-users.

4.2 Market analysis

4.2.1 The target market

For emerging vaccine and biomedical companies, identifying the target market is a critical aspect of the supply chain strategy. The target market comprises the specific groups or populations for whom the vaccines are developed and intended. The choice of target market depends on various factors, including the vaccine's intended use, the disease it aims to prevent or treat, and the availability of competing products.

The target market may encompass various segments, such as age groups, geographical regions, and risk factors [12].

Vaccine companies must conduct extensive research and engage in epidemiological studies to identify areas with the highest disease burden and unmet medical needs. Furthermore, understanding the demographic characteristics and healthcare infrastructure of potential target populations is crucial in determining the most effective distribution and marketing strategies. By focusing on a well-defined target market, emerging vaccine companies can optimize resource allocation and tailor their products to meet specific needs, increasing the likelihood of successful market entry.

4.2.2 A dynamic market landscape

The vaccine market is constantly evolving, influenced by factors such as advances in medical science, changing disease patterns, evolving regulatory requirements, and shifting public health priorities. As an emerging vaccine company, understanding the dynamic nature of the market is essential for effective supply chain planning.

In the early stages of a company's entry to the market, the market may be relatively small, with limited competition and niche opportunities, especially if the company's product is a novel one that has not yet entered the market. As the vaccine gains approval, the competitive landscape may shift rapidly due to changing demand, new entrants, and shifts in public health policies. Emerging vaccine companies must be agile and responsive to these changes, continuously evaluating market dynamics to adapt their supply chain strategies accordingly.

In the first few years of market entry, emerging vaccine companies may experience a growth phase as they gain momentum, expand their distribution networks, and establish a brand presence. During this period, demand may increase significantly, necessitating strategic partnerships with logistics providers and manufacturers to scale up production and distribution capabilities. Successful market entry may also attract potential buyers and partners, presenting opportunities for strategic alliances and collaborations [12].

It has been estimated that over 90% of clinical drug development results in failure, primarily attributed to factors such as "lack of clinical efficacy, unmanageable toxicity, poor drug-like properties, and lack of commercial needs and strategic planning." [56]. Therefore, emerging vaccine companies must be prepared for potential challenges and uncertainties in this dynamic landscape. Despite promising research and development efforts, not all vaccine candidates may successfully navigate the regulatory approval process or meet market demands. As a result, effective resource allocation and risk management are critical for ensuring long-term sustainability and adaptability.

Additionally, the evolving landscape of public health priorities can significantly influence market dynamics. Outbreaks of infectious diseases, global health crises, or changes in vaccination recommendations by health authorities can dramatically impact demand for specific vaccines [57]. Being proactive in monitoring these changes and engaging in effective stakeholder communication can position emerging vaccine companies to seize opportunities and respond to emerging challenges.

The vaccine market is a dynamic and ever-changing landscape that requires strategic foresight, adaptability, and resilience from emerging vaccine companies. Continuous market analysis, strategic partnerships, and sound risk management are essential components of a successful supply chain strategy. By understanding and navigating the dynamic market landscape, emerging vaccine companies can

contribute meaningfully to global health initiatives while establishing a robust and sustainable presence in the vaccine industry.

4.2.3 Buyers and competition

Buyers in the vaccine market include governments, healthcare institutions, and organizations responsible for vaccination programs. Additionally, the private market may involve pharmacies, healthcare providers, and individual consumers [12, 58]. For vaccine companies, securing partnerships and contracts with governments and health agencies is of paramount importance, as these entities play a central role in vaccine procurement and distribution.

Competition in the vaccine market can come from various sources, including established pharmaceutical companies, biotechnology firms, and other emerging vaccine companies. While large pharmaceutical companies may have extensive resources and global reach, emerging vaccine companies can carve out their niches by focusing on specialized vaccines, unique formulations, or addressing unmet medical needs. Staying competitive in the vaccine market requires differentiation through factors such as product efficacy, safety profiles, administration methods, and affordability. Moreover, continuous innovation and strong partnerships with healthcare providers and advocacy groups are essential for gaining market traction and achieving long-term success.

An in-depth market analysis is crucial for emerging vaccine companies to effectively navigate the complexities of the vaccine supply chain. Identifying a target market, understanding the dynamic market landscape, and evaluating buyers and competition are essential steps in developing a robust supply chain strategy that can lead to successful market entry and sustained growth. By staying agile and responsive to market changes, emerging vaccine companies can position themselves for success in the highly competitive market.

5. Challenges and opportunities

5.1 Barriers to entry

One of the primary barriers to entry for emerging vaccine companies lies in navigating the complex and stringent regulatory landscape. The vaccine industry is heavily regulated by government agencies such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the World Health Organization (WHO). These agencies have rigorous requirements for vaccine safety, efficacy, and quality to protect public health. Complying with these regulations requires significant resources, expertise, and time. Emerging vaccine companies must conduct extensive preclinical and clinical trials to demonstrate the safety and effectiveness of their vaccine candidates. These trials involve large-scale testing on human subjects and require adherence to Good Clinical Practice (GCP) guidelines. Additionally, regulatory approval processes can be lengthy, with the average time to market of new drugs averaging 10–15 years (see **Figure 4**), adding further challenges to market entry [59]. Delays in obtaining regulatory clearance can hinder the timely launch of vaccines and may also increase development costs. This barrier to entry of time to market is widely considered the toughest one for emerging companies to climb. Due to the importance of speed and agile development, there is significant work being

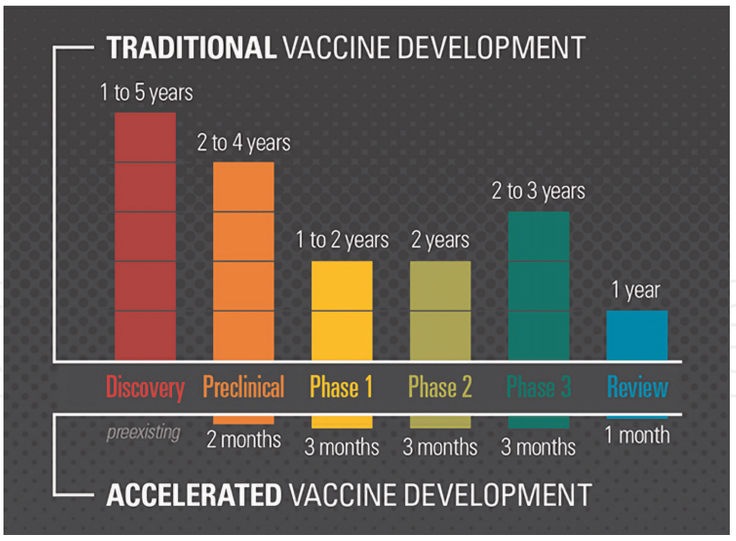

Figure 4.
Vaccine development timeline. Taken from [11].

done to shorten the timeline to market of vaccines. We saw this happen with the greatly expedited development of the COVID-19 vaccine, where many front runners were able to streamline clinical trials and regulatory approvals in the face of a global pandemic [60]. While these companies were primarily major pharmaceutical suppliers already, it does show the potential of much more rapid market launches for emerging companies if the same treatment can be applied to them. These extensive timelines and uncertainties in vaccine development underscore the significance of a well-planned supply chain strategy that can adapt to market demands and challenges throughout this lengthy journey.

Vaccine development is a capital-intensive process that requires substantial financial resources. From research and development activities to clinical trials, manufacturing, and distribution, each stage requires significant funding [50]. However, many emerging vaccine companies may have limited access to capital compared to large, established pharmaceutical companies. Securing adequate funding is essential to sustain vaccine development efforts and navigate the long and costly R&D phase. Emerging vaccine companies often seek funding through various channels, such as venture capital, grants, public-private partnerships, and philanthropic organizations focused on global health. Lack of sufficient financial resources can hinder progress and limit the ability to scale up production and distribution capabilities. It may also lead to a competitive disadvantage against larger competitors with more extensive financial backing and greater economies of scale. It's been estimated that bringing a new drug to market costs anywhere from $314 million to $2.8 billion [61]. There's no telling the number of life-saving vaccines that have not made it to market simply because emerging companies could not afford to make it through the regulatory process.

The vaccine industry is dominated by a few large pharmaceutical companies with extensive experience, global reach, and long-standing partnerships with governments and healthcare providers. Competing against these established players can be challenging for emerging vaccine companies. Large companies often have significant resources, manufacturing capacity, and distribution networks that allow them to produce vaccines at scale and reach a broad customer base. They may also have existing vaccines with strong brand recognition and customer loyalty. To overcome this barrier, emerging vaccine companies must differentiate their products by

focusing on niche areas, targeting unmet medical needs, and leveraging cutting-edge technology. Collaborating with research institutions, governments, and international organizations can also open up opportunities for strategic partnerships and critical market access.

Manufacturing vaccines at the required scale and quality is a complex process that presents another barrier for emerging vaccine companies. Developing the capabilities for large-scale manufacturing and establishing a robust supply chain can be resource-intensive and time-consuming. Maintaining the cold chain for temperature-sensitive vaccines is particularly challenging, requiring specialized facilities, equipment, and logistics expertise. Ensuring the stability of vaccines throughout the supply chain is critical to maintaining their potency and effectiveness. To address this barrier, emerging vaccine companies may consider collaborations with contract manufacturing organizations (CMOs) or other established manufacturers. These exchange partnerships can provide access to existing manufacturing capabilities, scale-up expertise, and efficient distribution networks.

Intellectual property protection is also essential for emerging vaccine companies to safeguard their research and development investments and establish a competitive advantage. However, protecting intellectual property can be complex, and patent rights may be challenged or infringed upon by other players in the industry. Furthermore, obtaining sufficient market share for new vaccines can be a challenging process. Existing vaccines with similar target diseases or mechanisms of action may already have high rates of awareness and adoption, limiting the potential for market entry and pricing power of competing products. To mitigate this barrier, emerging vaccine companies must develop a robust intellectual property strategy and engage legal experts to secure patents and enforce their rights. They can also seek to differentiate their vaccines through improved formulations, delivery methods, or enhanced clinical outcomes.

Emerging vaccine companies often encounter significant challenges related to regulatory approvals, which can be influenced by geopolitical factors. The speed and ease of regulatory approval for vaccines can vary greatly between regions, and international tensions can complicate this process. This dynamic is well illustrated by the case of the SARS vaccine development in Asia. In the early 2000s, the outbreak of Severe Acute Respiratory Syndrome (SARS) presented a unique challenge for the Asian region. Countries in Asia were racing to develop a vaccine to combat this new threat. However, this situation was complicated by political tensions and a lack of international collaboration [62]. The lack of information sharing and cooperation due to geopolitical conflicts impeded progress and resulted in fragmented efforts. The ultimate response to the epidemic was delayed, emphasizing the intricate relationship between geopolitical events and vaccine development.

In conclusion, emerging vaccine companies face various barriers to entry in the vaccine industry. Navigating the complex regulatory landscape, securing adequate funding, competing against established players, establishing efficient manufacturing and supply chain capabilities, and protecting intellectual property are important challenges to overcome. By addressing these barriers strategically, emerging vaccine companies can increase the likelihood of their success, contribute to global health efforts, and make significant advancements in disease prevention and treatment.

5.2 Exit plan options

Developing a well-defined exit plan is essential for small vaccine companies to manage risks, maximize opportunities, and ensure a smooth transition in the face of

unforeseen circumstances or changing market dynamics. An exit plan outlines the company's strategy for concluding its operations or transitioning into new phases, safeguarding the interests of stakeholders, and maintaining the legacy of its innovative vaccine products. Several exit plan options can be considered, outlined below and in **Figure 5.**

5.2.1 Mergers and acquisitions

One viable exit plan for a small vaccine company is to merge with or be acquired by a larger pharmaceutical or biotechnology company. Mergers and acquisitions (M&A) can provide access to additional resources, distribution channels, and market expertise. By joining forces with an established player, the small vaccine company can enhance its product portfolio, expedite market entry, and tap into the acquirer's global presence [63]. There are countless examples of M&As in the vaccine industry, and this is, in large part, why the industry stays so small with huge companies controlling major portions of the market. For example, in 2022, Pfizer acquired the company ReViral, which was a pharmaceutical company specializing in developing therapeutics for RSV [64].

M&A transactions offer the potential for liquidity to shareholders, allowing them to realize the value of their investments. However, successful M&A negotiations require careful consideration of valuation, governance, and operational integration to ensure a seamless transition.

5.2.2 Licensing and technology transfer

Another exit option is to license the vaccine technology and intellectual property to larger companies or manufacturers. Licensing agreements enable wider distribution and market access while allowing the smaller vaccine company to focus on research

Figure 5.
Business exit plan options.

and development or other strategic priorities. One example of an effective technology transfer occurred in an " ... agreement between Biovac, a South African bio-pharmaceutical company, and the International Vaccine Institute (IVI), a non-profit international organization headquartered in South Korea, for the manufacture of OCV." [65] IVI was able to develop OCV, or the Oral Cholera Vaccine, at a much lower cost than Biovac and this agreement mutually benefits the two companies and also expands manufacturing capacity of the lifesaving vaccine, builds local capacity, and allows Biovac to focus more on their core competency of end-to-end production. This is one example of how international organizations can work together with private organizations across borders to provide more and more affordable vaccines to communities.

By licensing their vaccine technology, small companies can benefit from the expertise and distribution capabilities of the licensee, reducing the burden of manufacturing and distribution. This option can be particularly attractive when the small company lacks the resources to scale up production and distribution on its own.

5.2.3 Strategic alliances

Forming strategic alliances with established players in the vaccine industry can be an effective exit plan for small vaccine companies. Strategic alliances may involve joint ventures, co-development exchange partnerships, or collaborative research agreements. These alliances allow the small company to leverage the expertise and resources of its partners while contributing its innovative technology. A common occurrence during the COVID-19 pandemic, many of the leading pharmaceutical companies took on strategic alliances to quickly manufacture and produce vaccines. One such example was the partnership between BioNtech and Pfizer, allowing them to create a COVID-19 vaccine in record time using BioNtech's expertise in mRNA vaccines and Pfizer's reach and monumental manufacturing capacity globally [66].

Strategic alliances can provide access to global markets, expedite regulatory approval, and share risks and costs associated with vaccine development and commercialization. Establishing clear governance structures and defining roles and responsibilities is crucial for successful strategic alliances.

5.2.4 Gradual exit and continuation of research

In some cases, a small vaccine company may choose a gradual exit strategy while continuing its research and development efforts as a research-focused organization. This approach allows the company to wind down its commercial operations while maintaining its expertise and intellectual property.

A gradual exit enables the small vaccine company to transition its research projects to academia, government institutions, or non-profit organizations. It can serve as a legacy strategy, ensuring that the vaccine technology continues to contribute to scientific advancements and public health efforts.

It is essential for small vaccine companies to carefully evaluate their objectives, financial position, and market dynamics when determining an exit plan. Early planning for an exit strategy can help mitigate risks, optimize financial outcomes, and pave the way for a smooth transition that aligns with the company's long-term vision.

In conclusion, devising an effective exit plan is crucial for small vaccine companies to navigate the complex and competitive landscape of the vaccine industry.

By considering various exit options and proactively planning for the future, small companies can position themselves for success, make meaningful contributions to public health, and leave a lasting impact on global disease prevention and treatment.

5.3 Vaccine supply chain management and operation

5.3.1 Making the transition from risk management

One definition of the term "supply chain" applicable to vaccines and healthcare, in general, is: "*the network of organizations involved, through upstream and downstream linkages, in the different processes and activities that produce value in the form of products and services delivered to the ultimate consumer*" [67, 68]. Efficient vaccine supply chain management and operations are critical to ensuring the commercial viability of vaccines. This viability entails optimizing scarce resources to achieve maximum return on investment while ensuring there is minimum redundancy. This approach promotes operational sustainability amidst uncertainty and limited resources in times when there is no significant disruption to vaccine supply and demand [69]. However, during times of systemic disruption resulting from unforeseen increases in demand, such as epidemics or pandemics of vaccine preventable diseases, such efficiency-driven supply chain systems may be unable to keep pace with commensurate operational requirements to sustain requisite levels of vaccine manufacture and distribution. During such disruptions, there is a critical need to continue to supply high quality consumables, to maintain efficacy throughout the distribution process, and to uphold licensing requirements [70]. Following a disruptive event, a vaccine supply chain needs to rapidly regain its operational capacity through a sequence of activities, namely: preparation, absorption, recovery and adaptation, collectively referred to as "resilience" [71]. Supply chain resilience (SCR), a concept increasingly applied to healthcare, is focused on the speed and efficiency with which disruptions to supply chains can be addressed so that systems can return to their normal state. The COVID-19 pandemic has been one of the most disruptive events to healthcare supply chains, including those for vaccines, in modern times. SCR can be bolstered using concepts derived from systems engineering approaches to the design and improvement of supply chains, thereby enhancing their readiness to respond, recover, and grow from disruption [72]. Such disruptions within complex supply chains can result in critical failures.

"Resilience-by-design" and "Resilience-by-intervention" are two approaches that have been used by vaccine supply companies and governments alike to facilitate recovery post-disruption in critical supply chains without compromising normal supply chain efficiency [69, 73].

5.3.2 Efficiency-focused supply chain operations to resilience-by-design

The underpinning 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*" [69]. It is complementary to standard risk management and is focused on determining at which points disruption would have the greatest impact. Requisite processes are introduced to harden identified weak links and nodes in the vaccine supply chain, based on data from resilience analytics. Resilience-by-design may include one or more of the following strategies:

1. Contracting multiple suppliers of a critical consumable in different geopolitical regions.

2. Using interchangeable and generic materials when possible.

3. Instituting emergency operation management plans.

4. Adjusting supply chain structure, integrating certain transportation links.

5. Keeping an inventory buffer of critical path non-perishable raw materials.

The recent COVID-19 pandemic is illustrative of the importance of supply chain considerations [74]. In the race to develop a SARS-CoV-2 vaccine, some manufacturers did apply principles of resilience-by-design. A prime example of this is the impact of the batch failures of raw materials on the critical path of the Pfizer/BioNTech vaccine [48, 75]. The use of a resilience-by-design approach, appropriately informed by resilience analytics applied to the vaccine manufacturing supply chains, could have shed light on this critical node and the potential for its disruption to result in major impacts on system performance. The knowledge gained through the application of this process could have then been used as a basis for corrective actions.

Additional examples of resilience-by-design strategies undertaken by the biopharmaceutical industry, which leverage analyses of the supply chain to use internal company resources in order to facilitate recovery post disruption, include:

1. Moderna partnering with IBM to track vaccine administration for real-time supply chain data [76].

2. McKesson restructuring 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 [77].

5.3.3 Resilience-by-intervention strategies and systems engineering-based approaches

The underpinning 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*" [69]. 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. Unlike resilience-by-design, resilience-by-intervention leverages outside resources to facilitate recovery after disruption. It enables policymakers and regulators to perform an up-front quantitative evaluation of network points of failure, which in turn facilitates the assessment of feasible solutions to be weighed against societal goals. The first step is to quantify where disruption will have the greatest impact on network performance and the consequences of those impacts on society, which in turn facilitates strategic evaluation of corrective actions in the context of overarching policy objectives. In the vaccine supply chain, corrective actions may include one or more of the following approaches:

1. The use of federal or state stockpiles or vaccination centers

2. Emergency funding for manufacture ramp-up

3. Quicker transportation links

4. Public health campaigns

5. Quicker regulatory bureaucratic processes

The US government's COVID-19 Operation Warp Speed (OWS) is an example of resilience-by-intervention. Federal resources were invested in several vaccine manufacturers simultaneously, increasing the probability of success for at least one vaccine manufacturer. This decision addressed the need to fill a dosage quota in a short time span to address urgent public health needs. The emphasis on vaccine portfolio diversification, based on a variety of available platform technologies, was key to a risk management strategy based on resilience-by-intervention [75]. Other examples of resilience-by-intervention strategies include:

1. The Strategic National Stockpile: This provided for large quantities of ancillary equipment need for vaccination campaigns to be readily available "off-the-shelf", including hundreds of millions of syringes, needles, vials, fill-finish equipment, and supply kits.

2. The Cybersecurity and Infrastructure Security Agency (CISA)'s work with vaccine manufacturers to counteract any cyberattacks or threats to intellectual property.

3. The FDA's ability to expedite vaccine approval for public use through Emergency Use Authorizations (EUAs).

The demand for mass production of vaccines for global distribution continues to grow exponentially. As a result, there are increasing constraints on the supply of raw materials and other components that could have significant impacts on the ability to meet critical needs and to save lives during and following a disruptive event, such as an emerging epidemic or pandemic, as has been recently experienced with COVID-19. The introduction of systems engineering-based approaches to SCR, resilience-by-design and resilience-by-intervention strategies into vaccine supply chain management and operations can have a major impact on mitigating the risks associated with supply chain disruptions.

6. Conclusion

This perspective chapter has shed light on the pivotal role of supply chain logistics and business ecosystems in the development of natural vaccines with novel, safer, and non-invasive delivery mechanisms. With a focus on global health and population well-being, it has become evident that maintaining seamless supply chain integration is paramount to maximizing the potential for success in the vaccine industry. The case study presented in this chapter has provided valuable insights into the essential steps

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involved in the supply chain, from research and development to packaging and distribution. Moreover, a comprehensive market analysis has emphasized the significance of understanding target audiences and navigating the dynamic landscape of vaccine markets. The challenges and opportunities discussed have underscored the importance of resilience-based supply chain operations and strategic contingency planning, especially for success at the global scale. As new vaccine companies venture into this domain, the learnings from this chapter offer crucial guidance in shaping their approaches, emphasizing the potential transformative impact they can have on global health and disease prevention. By leveraging these key takeaways, these companies can make significant strides in bringing about a safer and healthier future for people worldwide.

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