Vaccines Europe analysis of vaccine production lead times

Executive Summary

Background: Since technological developments and the response to the COVID-19 pandemic have the potential to impact vaccine manufacturing, this research was conducted on mRNA and viral vector-based COVID-19 vaccines in Q4 2022 using similar methods to a Vaccines Europe analysis of vaccine production lead times in 2015-18. In 2024, the paper was updated to include data on protein-based COVID-19 vaccines, based on information available up to the end of May 2024.

Results: Based upon interviews with industry subject matter experts, production lead times under pandemic-emergency conditions were estimated to be 3.5–6 months for viral vector, 2.5–5.5 months for mRNA and 5-11 months for protein-based COVID-19 vaccines. Differences between mRNA and viral vaccines were accounted for by the upstream manufacturing process (1.5–3 months for viral vector and ~1 month for mRNA-based vaccines), reflecting the time for cell culture, bioassay validation, and quality requirements for viral vector manufacturing.

Discussion/conclusions: The pandemic imposed variable effects on the supply of COVID-19 vaccines. Factors accelerating time to market due to the pandemic included early investment in manufacturing and advanced agreements to support at-risk and/or in-parallel processes, prior to standard regulatory authorisations. Additional factors improving time to market included unprecedented collaboration and partnerships among vaccine manufacturers, regulators and control laboratories, simplified presentations, in-process inspection controls, and simplified administrative procedures and paperwork. Some of the factors accelerating production lead time during the pandemic could be adopted further and applied in a non-pandemic situation, such as further international harmonisation of regulatory processes, simplification of package requirements, and early dialogue between key stakeholders. Constraints inherent to vaccine manufacturing limit the ability to further accelerate production lead times, and the time needed to make vaccines available to end users does not principally depend on manufacturing. Steps excluded from this analysis include lengthy high-risk R&D, and quality assurance of materials and equipment; post-release testing; supply, shipment, and vaccine administration to end users. Accelerated lead times achieved during the pandemic were minimally impacted by production lead times and largely made possible by exceptional repurposing of pre-existing technology platforms and unprecedented investment in research, development, and manufacturing scale-up, as well as the use of concepts such as Continuous Improvement initiatives, leveraging Lean Manufacturing, Value Stream Mapping and Operational Excellence. While new vaccine platforms and lessons from the pandemic have the potential to impact production lead times, sustained investment across vaccine types and technology platforms remains essential to address the challenges of communicable diseases, as no one platform is likely to be suitable for all pathogens.

Introductory Statement

Ensuring the availability of safe and efficacious vaccines is a public health priority. Manufacturers review their manufacturing processes in the light of scientific developments and in response to challenges such as the COVID-19 pandemic. An analysis of vaccine production lead times to improve vaccine availability was conducted in 2015-18. The research found that vaccine production, from the start of manufacturing until release of the first lot by the manufacturer, took between 18 and 24 months, or more than 36 months for some very complex multivalent vaccines.[1] A few vaccines, such as monovalent hepatitis B and seasonal influenza vaccines, had shorter production lead times (12 months for influenza vaccines and 12 to 18 months for hepatitis B) (**Table 1**).

Factors identified as affecting vaccine supply included long and complex manufacturing processes and quality controls; unpredictable timelines for lot release; complex global regulatory life cycle management; diversity of presentations, packs and labels in the EU; unpredictable demand; and suboptimal budget and procurement practices. Pasté *et al.*[1] recognised that these factors may not necessarily apply to COVID-19 vaccines. Vaccines Europe conducted this follow-up research in the last quarter of 2022, to analyse the production lead times of some of the first COVID-19 vaccines, including ones based on mRNA and viral vector–based vaccine technologies. In 2024, the paper was updated to include data on protein-based COVID-19 vaccines, based on information available up to the end of May 2024.

Overall, the original analyses and the following updates are intended to allow stakeholders to consider production lead times when drafting policies that concern vaccines and vaccination. Given that the development, manufacturing, and approval of COVID-19 vaccines occurred under exceptional circumstances, we have projected how the situation might differ when these technologies are further developed and deployed under non-pandemic conditions. Vaccines Europe will provide regular updates on those developments.

Methods and Terms of Reference

This follow-up research followed the methods and principles of the 2015-18 analysis by Pasté *et al.* [1] published in 2022 and examined the following stages of vaccine manufacturing: upstream manufacturing; formulation; fill, finish, control and release. The analysis was based on five 1-hour video teleconferences with a total of eight subject matter experts from five separate industry organisations/vaccine manufacturers identified and selected by Vaccines Europe.

A semi-structured questionnaire was used to gather lead time information for respective viral vector and mRNA COVID-19 vaccines; all industry subject matter experts were sent a pre-interview briefing document and were asked to base estimates, where applicable, on actual lead times for their own COVID-19 vaccines, accounting for externalities that impacted production and avoiding theoretical or notional lead-time estimates.

In 2024, the paper has been updated with information on protein-based COVID-19 vaccines based on data collected in writing from the Vaccines Europe members manufacturing these medicinal products.

[1] Pasté M *et al*. Addressing vaccine supply challenges in Europe: Expert industry perspective and recommendations. *Health Policy*. 2022;126:35–42.

In keeping with the original research and in accordance with EU competition law, no confidential data, trade secrets or other sensitive information concerning the manufacturers, their processes, products, or portfolios was disclosed to participants or the public as part of this analysis.

Targeted Literature Review

Since the 2015-2018 analysis by Pasté *et al.*[1] other authors have reported qualitative and descriptive estimates of vaccine manufacturing as "complex, time consuming and costly,"[2] with production lead times estimated to range between 0.5 and 3 years in 2019.[3] A systematic review of 25 vaccination campaigns, including vaccine production and procurement, reported that "vaccine production and planning is carried out over a long period, sometimes over a year."[4] However, these secondary research reports did not address production lead times in detail, nor did they consider COVID-19 vaccine technologies or their manufacture during the pandemic. Moreover, Pasté *et al.,* in their detailed primary analysis, demonstrated that the production lead time for many vaccines is commonly greater than 1 year (from 12 to over 36 months).[1]

We found no primary literature specifically estimating the production lead times of COVID-19 vaccines during the pandemic, nor research estimating production lead times of vaccines based on mRNA or viral vector technology platforms. Thus, in keeping with the analysis by Pasté *et al.*,[1] the primary research reported here addresses production lead times of COVID-19 vaccines in a detailed manner under the unique conditions of the pandemic.

Primary Research: Results and Discussion

When considering viral vector and mRNA technology platforms separately, overall production lead times were 3.5–6 months for viral vector and 2.5–5.5 months for mRNA-based COVID-19 vaccines. The main differences in production lead times between viral vector and mRNA-based COVID-19 vaccines were accounted for by the upstream manufacturing process, which was 1.5–3 months for viral vector and approximately 1 month for mRNA-based vaccines. This difference chiefly reflects the time for cell culture, bioassay development/validation, and quality requirements for manufacturing viral vectors, for which there are biological, regulatory and equipment constraints.

For protein-based COVID-19 vaccines, the overall production lead times were estimated between 5 and 11 months.

The final control-and-release stage was similar for mRNA, viral vector and protein-based COVID-19 vaccines (1–3.5 months). There were no meaningful differences in lead times for the other stages, including formulation, filling, labelling, packaging, and storage, which account for 1 week - 3 months of the overall production lead times and are dependent on overall scale and capacity.

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[2] Plotkin S, Robinson JM, Cunningham G, Iqbal R, Larsen S. The complexity and cost of vaccine manufacturing - An overview. *Vaccine*. 2017;35(33):4064-4071.
[3] Kis Z, Shattock R, Shah N, Kontoravdi C. Emerging Technologies for Low-Cost, Rapid Vaccine Manufacture. Biotechnol J. 2019;14(7):1-2.
[4] Lopes J.M. *et al.* Optimization methods for large-scale vaccine supply chains: a rapid review. *Ann Oper Res.* 2022;316:699–721.

These lead times are shorter than the overall 12 to 36-month production lead times estimated for a range of vaccines in 2018 by Pasté *et al*.[1] (**Table 1**). The primary manufacturing stages accounted for a major part of the lead time differences between viral vector, mRNA vaccines and the vaccines reported by Pasté *et al*.[1]

Table 1. V*accine production lead times for selected vaccines*

Example vaccines	**Production lead time* (range, months)**
Previously reported analysis (Pasté *et al*. 2022)†	
Complex multivalent vaccines (e.g., pertussis-containing vaccines, meningococcal and pneumococcal conjugated vaccines)	18 to >36†
Monovalent hepatitis B vaccine	12–18†
Seasonal influenza vaccine	~12†
Results of the present analysis	
Monovalent COVID-19 mRNA vaccine	2.5–5.5
Monovalent COVID-19 viral vector vaccine	3.5–6
Monovalent COVID-19 protein-based vaccine	5-11

*From the start of production until the release of the finished product by the manufacturer
† Pasté *et al*. in: Addressing vaccine supply challenges in Europe: Expert industry perspective and recommendations. *Health Policy*. 2022;126:35–42.

The unique conditions created by the COVID-19 pandemic, imposed variable effects on production lead times and overall supply of COVID-19 vaccines. Development and approval of packaging and labelling was simplified, but could be further optimised, as within the EU there is significant diversity in packaging and label requirements. While outside the scope of this analysis, delays due to supply of starting materials (e.g., raw materials and disposables) were consistently cited by COVID-19 vaccine manufacturers as factors impacting production during the pandemic. Security of supply from global sources, a paucity of available sources, trade restrictions and increased demand were reported to have contributed to unpredictability and interruptions in the provision of starting materials, with plastic consumable/disposable items and specialised cell culture media as major factors impacting mRNA and viral vector–based vaccines manufacture.

Vaccines manufacturing lead-times are mainly driven by the technology platform characteristics and stringent GMP quality control requirements. Within these parameters, and never compromising on the quality of the vaccines manufactured, manufacturers are striving to optimize the manufacturing lead times. These efforts are captured in the manufacturers' Continuous Improvement initiatives, leveraging Lean Manufacturing, Value Stream Mapping and Operational Excellence concepts. [5]

[5] Value Stream Mapping: Operational Excellence Explained. January 2022. Available at: https://www.processnatives.com/operational-excellence-glossary/value-stream-mapping-operational-excellence-explained

Factors accelerating time to market due to the pandemic included early investment in ramping up manufacturing at risk through industry investments and advanced procurement and/or direct funding agreements globally. Additional factors improving time to market cited by manufacturers included the unprecedented collaboration and partnerships among vaccine manufacturers e.g., to maximise the efficient allocation of manufacturing capacity. Collaboration and flexibility of regulatory authorities included sharing information into rolling reviews of accessible data to allow faster approvals while maintaining robustness of approval procedures; streamlining regulatory processes e.g., universal QR codes to link to the appropriate paperwork in different countries; simplified presentation and packaging options (such as acceptance of one multidose presentation and a single language across the EU); increased capacity of ultra-low-temperature refrigeration; in-process inspection controls; and simplified administrative procedures and paperwork.

Conclusions

Taken together with the analysis by Pasté *et al.*,[1] the estimates of production lead times should support vaccination policy and decision making by relevant stakeholders. This analysis suggests the COVID-19 pandemic had variable effects on production lead times and supply of COVID-19 vaccines.

Vaccine manufacturing is typically developed and optimised over several years, but vaccine manufacturers focused efforts on rapidly ramping up manufacturing capacity to meet the unprecedented emergency demand during the COVID-19 pandemic. Some of the factors accelerating manufacturing lead time during the pandemic could be adopted further and applied in a non-pandemic situation, such as international harmonisation of regulatory processes, package requirements, simplification of administrative procedures and early dialogue between key stakeholders.

Aside from the pandemic, differences between vaccine production lead times for the various vaccines were mainly due to the specifics of the upstream manufacturing stages. Production lead times for all vaccines remain constrained by the same highly complex, time-consuming, capital-intensive nature of vaccine manufacturing. These constraints, inherent in vaccine manufacturing, limit the ability to accelerate production lead times. Vaccine quality for COVID-19 vaccines is controlled through the same multiple processes to guarantee production quality and consistency, as any human vaccines, with regulations and quality standards continually evolving to comply with Good Manufacturing Practice principles.

It should also be noted that the time needed to make vaccines available to end users does not depend principally on production lead times. Steps excluded from this analysis include lengthy and high-risk R&D, purchase, testing and quality assurance of starting materials and equipment; testing conducted after release; and the supply, shipment, and administration of vaccines to end users. The accelerated supply of vaccines during the pandemic was largely made possible by repurposing of pre-existing technology platforms and unprecedented investment in research, development, and manufacturing scale-up.

Since conditions differ under non-pandemic circumstances, it may be necessary to estimate COVID-19 vaccine production lead times on an ongoing basis under non-pandemic conditions and to include other vaccine types and technology platforms recently approved or currently in development.

While new vaccines and lessons from the pandemic have the potential to impact production lead times, sustained investment across vaccine types and technology platforms remains essential to address the challenges of communicable diseases, as no single platform is likely to be suitable for all pathogens.