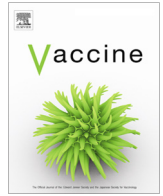




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# Enabling emergency mass vaccination: Innovations in manufacturing and administration during a pandemic



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## 1. Introduction

The global reach of infectious disease pandemics typically necessitates a similarly ubiquitous public health intervention: mass vaccination. The development and large-scale deployment of a vaccine requires substantial investment and a coalition of stakeholders to undertake research and development (including phase I to III clinical trials), manufacturing, and widespread administration. Recent efforts by national and international funders and researchers to advance the state of vaccinology for pandemics and other infectious disease emergencies have focused largely on expediting the R&D phase [1]. There has been comparatively less attention paid to modernizing, optimizing, and therefore accelerating other aspects of the vaccine enterprise—namely, manufacturing, distribution, and administration. The current COVID-19 pandemic plainly underscores the need to vastly accelerate mass vaccination in every phase.

We have conducted two qualitative research studies on vaccine manufacturing and administration capabilities in the context of infectious disease emergencies and have authored two forthcoming reports (*Mass Vaccination 2.0: A Survey of New Technologies and Strategies* and *Vaccine Capacity for Global Pandemics: Manufac-*

*turing and Distribution*). Here, we seek to apply findings and lessons from that work to inform the vaccine response to COVID-19.

## 2. COVID-19 emergence & vaccine candidates

No vaccine is licensed for the prevention COVID-19; however intensive R&D efforts have commenced. The WHO convened experts to develop a global research and development strategy for COVID-19, including vaccine development [2]. There are currently about 60 vaccine candidates in the preclinical development stage, including RNA, DNA, protein subunit, vector, and inactivated vaccines. Several are currently in phase I clinical trials [3].

While it has been suggested that a SARS-CoV-2 vaccine might be available as early as 12–18 months from research initiation, industry stakeholders have voiced concern regarding animal model development, time to clinical trial start-up and data assessment, adequate manufacturing scale-up, regulatory concerns for vaccines developed using platform technologies, and the provision of sufficient funding to support development and procurement [1]. In addition, an evaluation of the regulatory landscape may help to identify opportunities to expedite the evaluation and emergency licensure of vaccine candidates without sacrificing safety or efficacy.

## 3. Vaccine manufacturing

As a result of limited commercial markets and technical manufacturing challenges, innovation for vaccine manufacturing has

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been slow, and capacity has been difficult to change. Unlike other pharmaceutical products, which have large commercial markets to justify the expense of manufacturing capacity, vaccines have limited markets, often with governments or NGOs such as GAVI as the only purchasers [4]. In the case of the Ebola rVSV-ZEBOV-GP vaccine developed by Merck, approval by regulatory authorities took years to achieve, and concerns about the ability to rapidly scale-up manufacturing in response to a worsening Ebola epidemic in the Democratic Republic of the Congo prompted discussions about reducing the vaccine dosage or using the vaccines sparingly [5]. Notably, in the context of COVID-19, the Gates Foundation and CEPI have publicly committed to supporting the construction of new production facilities for the top vaccine candidates for COVID-19, before they are validated in clinical trials and licensed [6].

Traditional approaches to scaling up access to vaccines for epidemic response have included use of stockpiles, repurposing existing manufacturing plants and building new production facilities [7,8]. Stockpiles by definition do not store vaccines for novel pandemic pathogens, and repurposing or building new plants can take months to years.

To prepare for pandemics and shorten the mass vaccination timeline, vaccine manufacturing needs to move beyond current approaches. Countries with sufficient resources need to invest in new technologies, processes, and governance to be able to rapidly immunize a large proportion of the global population. Three inter-related approaches would permit rapid scale-up of vaccine manufacturing. First, the continued refinement and use of platform technologies can shorten the pre-clinical phase of development [9]. Indeed, annual seasonal influenza vaccines are rapidly developed from a platform that requires replacement of a subsection of the vaccine matched to the circulating strain(s). From a more technologically advanced perspective, vaccine approaches such as viral-vector, peptide-based, DNA- and mRNA-based vaccines may offer true “plug-and-play” capabilities and thus appear to be a particularly promising platform technology [9].

There will also be a need to consider and address the practicalities of ownership, operation, and sustainable financing of any additional manufacturing capacity. Fortunately, there have been several recent examples such as the expansion of global influenza vaccine capacity under the WHO's global influenza strategy, the establishment of Centers for Innovation in Advanced Development and Manufacturing (CIADM) in the United States, and other models of public private partnership. An analysis of these and other models could be undertaken to better understand their relative strengths, weaknesses, and to identify opportunities for improvement.

Second, flexible manufacturing and regulatory processes coupled with platform technologies would further expedite the availability of new vaccines. Currently vaccine production sites are highly specialized - a traditional approach to reduce costs and meet regulatory requirements. Many existing manufacturing plants are thus limited in their ability to be repurposed to produce different vaccines.

Third, governments and agencies should prioritize investments in geographically distributed manufacturing, to increase production and therefore access on a global scale. Globally, the majority (80%) of vaccines are manufactured by five companies based in the US and Europe [10], often geographically distanced from areas where vaccines are needed the most, both for childhood immunization programs and for outbreaks that are likely to spread quickly. Geographically distributed manufacturing capacity can also help to increase resilience in the vaccine supply chain by avoiding possible manufacturing disruptions after natural disasters or more localized outbreaks and epidemics.

We recognize that significant investments in terms of time and resources have been devoted to these goals and that progress has

been made, but additional financial support from governments, nongovernmental organizations and philanthropic organizations will be required to fully realize the vision of a world able to rapidly produce millions or billions of doses of a vaccine targeted against a novel pathogen like the one we now face.

#### 4. Vaccine administration

Most vaccines, including those intended for use during mass vaccination campaigns, are currently administered by a healthcare worker via needle and syringe. This practice is well understood by vaccinators, familiar to vaccinees, and it will undoubtedly be the one used for any successful COVID-19 vaccine. However, this approach to vaccine administration has drawbacks, as rapidly mobilizing a sufficiently large trained vaccinator workforce is challenging [11], particularly during a pandemic. We propose that a combination of new technologies and strategies could be implemented to expedite mass vaccination for COVID-19.

Potential alternative routes of vaccine administration include liquid oral formulations and intranasal mists. Oral vaccines (e.g., cholera, polio, and rotavirus) and intranasal live attenuated influenza vaccines have been used globally, particularly for mass vaccination during outbreaks and epidemics [12]. Novel next-generation administration technologies include microneedle array patches (MAPs), integrated reconstitution administration devices, tablets and sublingual oral gels, and next-generation jet injectors [12].

These technologies are in the developmental pipeline and are reasonably well characterized. However, substantial investment will be needed to manufacture these products and make them available for use. Additionally, the regulatory, logistical, and financial landscapes that support traditional vaccine development and administration would likely need to be modified to incentivize and facilitate the development and eventual wide-scale use of next-generation vaccine administration technologies.

Certain alternative administration technologies may enable the emergence of new strategic approaches to mass vaccination. Streamlined Vaccine Administration (SVA), a proposed framework in which vaccine administration may occur without the involvement of a healthcare provider, could enable self-administration or administration facilitated by community health workers. We believe administration techniques not reliant on extensive training can ease staffing constraints associated with mass vaccination. As one example of this emerging public health practice, self-administration has been previously demonstrated to be successful and well tolerated with the use of leave-behind second doses of oral cholera vaccine [13]. However, implementation challenges remain; for instance, self-administration could be associated with a degree of noncompliance or incorrect usage.

Most SARS-CoV-2 vaccine candidates would be administered using the traditional injectable route, and such products should be developed and deployed as quickly as possible. However, the CDC and other public health agencies should assess the feasibility, associated costs, societal acceptability, and implications for public health practice of an SVA-enabled mass vaccination campaign using alternative routes of administration such as oral tablets. This evaluation could include a combination of epidemiologic and economic modeling, operations research, and a social and behavioral health component. We would suggest that this novel approach could improve the reach and timeliness of mass vaccination campaigns across high-, middle-, and low-income countries during the COVID-19 pandemic, and should be supported by governments, researchers, and funders. Such campaigns should ultimately proceed, however, only if the associated vaccines prove to be safe, effective, and logistically feasible to implement.

Even if this approach does not prove viable during the COVID-19 pandemic due to financial, regulatory, or practical constraints, the development of new tools and strategies that enable more rapid vaccination campaigns should be prioritized to bolster preparedness for future high-consequence outbreaks.

## 5. Conclusion

COVID-19 demonstrates a clear need for a more rapid and adaptive pandemic vaccine enterprise. Vaccine research and development programs should be designed to optimize downstream processes that permit rapid scale-up while maintaining the standards of safety and efficacy that we expect of routine vaccines. However, the safety profile of any vaccine candidate is critical and should not be sacrificed in the name of expedited industrial or public health processes.

Higher levels of sustained public support, technological development, and coordination with private sector stakeholders are needed to modernize the pandemic vaccine enterprise in ways that better protect public health and safety during infectious disease emergencies. This modernization effort should be supported as a core component of national and international health security, as it would ensure that population-level protection is achieved as soon as possible once a safe and effective vaccine has been developed.

## Declaration of Competing Interest

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

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