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Rapid-response manufacturing of adenovirus-vectored vaccines

The Coalition for Epidemic Preparedness Innovations (CEPI) has proposed a '100-day mission', or 'moonshot' aspiration, for compressing the time to launch a new vaccine to 100 days from pathogen identification[1]. Alongside this is the recognition of the importance of the second hundred days – that is, rollout of a new vaccine at large scale. Vaccine platform technologies with known safety, immunogenicity, manufacturing and distribution characteristics will be critical to meeting these challenges.

Many features of preclinical and clinical development of new vaccines are independent of the platform technology. Manufacturing and distribution comprise the major points of divergence in the pathways to deployment of vaccines based on different platforms. Here, we show that 'rapid response' manufacturing of adenovirus-vectored vaccines can enable compressed development timelines that are competitive with those of other platforms, and we discuss the implications of improved vaccine manufacturing for future outbreak response and equity of access to vaccines.

Adenoviral vectors offer a rapidly adaptable and deployable platform with proven safety and efficacy, and particular advantages in achieving equitable access. The Vaxzevria (ChAdOx1 nCoV-19) COVID-19 vaccine from Oxford and AstraZeneca, based on a chimpanzee adenovirus platform, is estimated to have saved around six million lives in 2021, more than any other COVID-19 vaccine[2]. A review of 79 real-world effectiveness studies confirmed its high efficacy against death or severe disease[3]. Thrombosis with thrombocytopenia syndrome occurred rarely in recipients of adenovirus-vectored vaccines and appears even rarer in datasets from outside Europe and North America[4,5]. In many contexts – including emergency response to pathogens with high mortality and no existing vaccine – the frequency of this syndrome would have little impact on the risk/benefit balance of vaccination.

With AstraZeneca and other industrial partners, we developed a simple manufacturing process that produced more than 3 billion doses across a network of facilities in 12 countries on 5 continents[6]. Production cost was low, and the vaccine's suitability for refrigerated rather than frozen storage enabled distribution to hard-to-serve communities, notably in low- and middle-income countries[7].

Alongside these positive features, however, adenovirus manufacturing has had two notable disadvantages. First, the time it took to prepare viral seed as a starting material for production delayed the availability of initial batches for clinical trials. In 2020, the first-in-human use of an mRNA SARS-CoV-2 vaccine happened 63 days after the publication of the pathogen sequence[8]. The first clinical batch of ChAdOx1 nCoV-19 was not released until a month later. Second, volumetric productivity (number of doses per liter of bioreactor capacity) is estimated to be at least an order of magnitude higher for mRNA vaccines than the roughly 2,000 doses per liter achieved for ChAdOx1 nCoV-19 (refs. [6,9]). This necessitated a greater 'footprint' for manufacturing adenovirus-vector drug substance (bulk vaccine).

We recently published work seeking to address these disadvantages[10]. We showed that streamlining viral seed production could enable release of a first vaccine batch for clinical trials within 60 days of the sequence of a new pathogen becoming available and the release of a first large-scale commercial batch within 100 days (Fig. 1a). We showed also that intensifying the upstream process (that is, cell culture and viral replication) could quadruple volumetric productivity compared to the process used for commercial production of ChAdOx1 nCoV-19. The improved process produces approximately 8×10^{14} viral particles (VP) of purified drug substance per liter of bioreactor culture, sufficient for >10,000 doses of drug product[10].

We now describe techno-economic modeling of commercial-scale implementation of this improved manufacturing process (Fig. 1b). Models were constructed and evaluated using Biosolve Process 8 software (Biopharm Services). We modeled a facility with a cell expansion seed train using a 200-liter '$n-2$' bioreactor for alternating seeding of each of two 200-liter perfusion-capable '$n-1$' bioreactors, in turn servicing two 2,000-liter production bioreactors and a single downstream purification train. The following assumptions were based on our published data[6,10]: cell doubling time 36 h; upstream process productivity 1.5×10^{12} VP mL^{-1}; benzonase nuclease concentration 100 units mL^{-1} during harvest; clarification filter loading up to 1×10^{12} cells m^{-2}, corresponding to 75 L m^{-2} with peak cell density 1×10^{7} cells mL^{-1} and a 33% safety factor; clarification product recovery 66%; anion exchange membrane binding capacity 1×10^{16} VP L^{-1}; anion exchange recovery 90%; tangential-flow filtration filter loading 2×10^{16} VP m^{-2}. Concentration in the tangential-flow filtration stage was limited to 0.33 × the bioreactor volume, corresponding to an expected product concentration of 2.2×10^{12} VP mL^{-1}. Costs were based on Sartorius and Biosolve's proprietary databases. The resulting model, after redaction of the proprietary itemized cost information, is provided as Supplementary Table 1.

This bioreactor configuration could provide a batch around every 3.5 days (Fig. 1c). This more than doubles facility output as compared to a facility lacking perfusion in the seed train and using a single production bioreactor, while requiring a proportionately small increase in footprint. Using perfusion for more cell expansion at $n-1$ reduces the cycle time of the production bioreactors. A single purification train remains sufficient to process the output from both production reactors. The downstream process could be executed with moderate modification to the equipment used for global production of ChAdOx1 nCoV-19. Although the volumes of buffer required for AEX are large as compared with other process stages, these are likely to be manageable for many facilities by using buffer concentrates and in-line dilution technology. We have not, to date, optimized the final tangential-flow filtration to minimize the required membrane area, and our model here uses cautious assumptions based upon our unoptimized experience. The projected tangential-flow filtration membrane area of 84 m^2 per batch is large, highlighting the

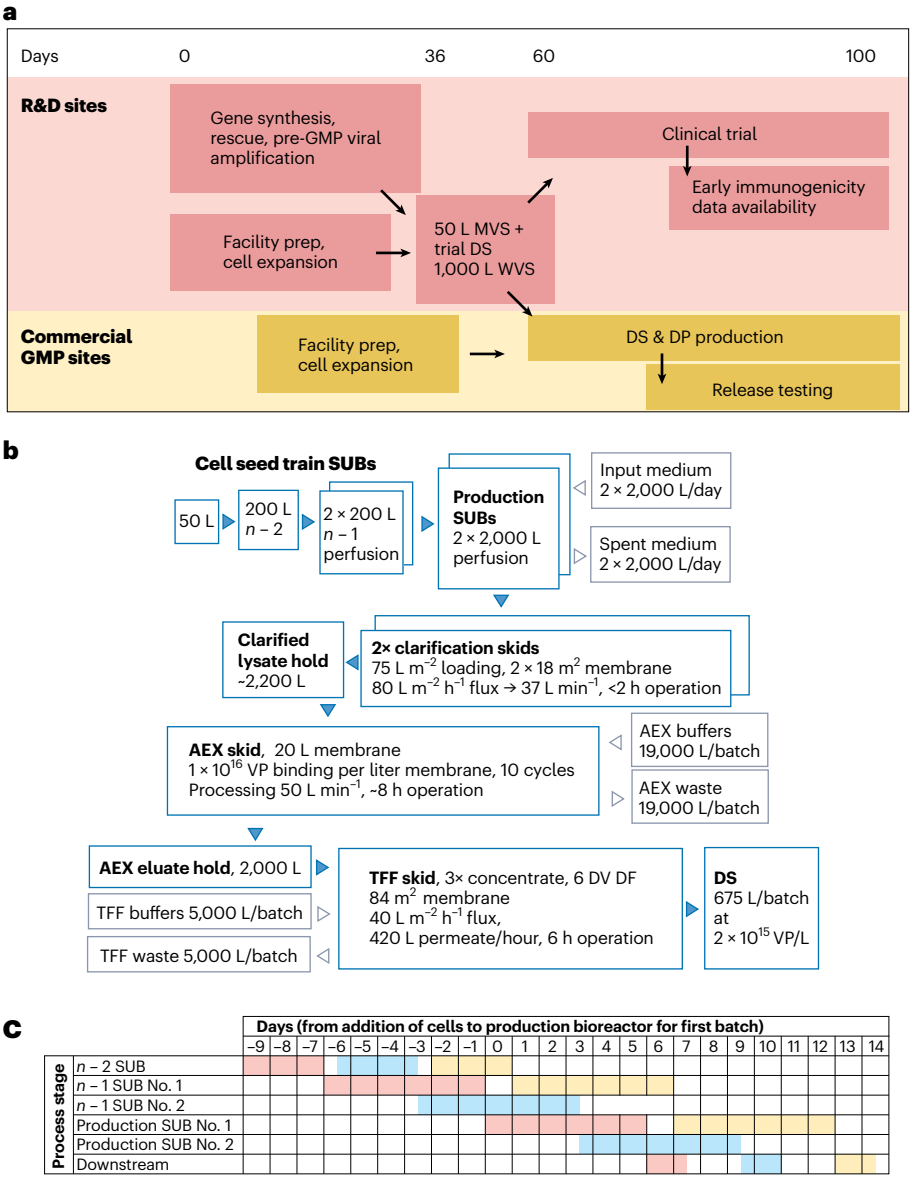

Fig. 1 | Accelerated high-productivity adenovirus manufacturing. a, High-level overview of development campaign combining seed production, supply of vaccine to clinical trial, execution of clinical trial, and large-scale manufacturing, enabling release of the first commercial-scale batch at day 100. **b**, Equipment, product and materials flow in modeled facility. **c**, Illustrative production schedule, showing use of two $n-1$ reactors, two production bioreactors and a single downstream purification train. Pink, blue and yellow shading indicate first, second and third batches respectively. AEX, anion exchange; DP, drug product; DS, drug substance; DV DF, diavolumes of diafiltration; GMP, Good Manufacturing Practice; MVS, master virus seed; SUB, single-use bioreactor; TFF, tangential-flow filtration; WVS, working virus seed.

need for such optimization, but could nonetheless be achieved either using a custom tangential-flow filtration skid or multiple cycles on off-the-shelf skids.

Assuming 70% facility usage, a single such facility is predicted to produce approximately 1.3 billion doses per year, with a cost of goods of drug substance below $0.11 per dose (lower than that of the fed-batch process used to produce ChAdOx1 nCoV-19). This corresponds to output of roughly 900 doses per liter of installed bioreactor capacity per day. Capital expenditure to construct and equip such a facility would be approximately $43 million, with operating expenditure of less than $110 million per year.

Under an alternative assumption of short-term maximum-capacity operation for emergency response, we estimate that eight such facilities (that is, total installed bioreactor capacity of 32,000 L) could provide a total of 1 billion doses per month. Although substantial, this would be smaller than the network of facilities that produced ChAdOx1 nCoV-19 in 2021. We believe several existing facilities (including a number in low- and middle-income countries) would be suitable.

These results have a number of implications for preparedness for future pandemics.

In our work to improve the adenovirus manufacturing platform, we focused initially on three time-based metrics: time from pathogen-sequence availability to release of the first clinical trial batch, the first commercial batch, and the billionth dose. In contrast to the situation in 2020, we believe that both adenovirus manufacturing and other platform technologies are now capable of meeting the CEPI '100-day' aspiration. Completing preclinical and clinical development in substantially shorter periods than this seems unlikely. Within the second hundred days, our modeling suggests that a well-prepared all-out global effort using a realistically sized manufacturing network could release over 3 billion doses. This would be sufficient to provide a first dose to a large proportion of the global population and represents a level of output that took over two years for any COVID-19 vaccine program to achieve.

Between 2020 and 2022, there has been a step change in the speed of technically feasible vaccine manufacturing. Now, rather than being a question of technical feasibility, delivering such manufacturing speed is mostly a question of finance and preparation, including mitigating risks of failure and preparing template regulatory filings in advance. A fully validated version of the process we have described, preferably including an independent parallel 'backup campaign' for seed production and supported by rapid-turnaround platform analytics, would in our view provide high confidence of success.

Quality control testing is rate limiting for vaccine availability. The timeline we have suggested (Fig. 1a) allows 16 days for release testing of the first clinical trial batch and 35 days for testing the first commercial batch. The difference is due to performing 28-day in vitro culture-based assays for adventitious viral agents and replication-competent adenovirus for commercial material, whereas nucleic acid-based assays (supported by 14-day in vitro assays) are used for

clinical trial material. Full validation of PCR- or next-generation-sequencing-based methods for detecting contaminants could bring forward the release of the first commercial batch to day 80 or sooner.

Further improvement is probably possible. However, any vaccine platform that can achieve 100 days to the first commercial batch, produce 1,000 doses per liter of bioreactor capacity per day and cost <$1 per dose of drug substance is likely to be competitive from a manufacturing perspective. Further improvement may provide relatively marginal benefits. Leading vaccine platforms have now attained levels of manufacturing speed and facility productivity at which other factors are probably more important. Such considerations include safety, tolerability, efficacy, stability, cost, programmatic suitability, individual recipient preference, and manufacturer willingness to support technology transfer beyond their own facilities. There are likely to be valid scientific reasons for selecting different vaccines in different contexts.

Future epidemics are inevitable. Having diverse vaccines (including adenoviruses) promptly available is necessary to protect public health and prosperity. It would in our view be economically attractive to maintain a network of regional facilities 'warm-lit' (prestaffed, prestocked with materials and prefinanced) for manufacturing any adenovirus-vectored vaccine on billion-dose scale, as a global public good. On the basis of our modeling, it might cost less than $220 million a year to finance a global facility network capable of providing a billion doses of an adenovirus-vectored vaccine to a wide range of countries in well under 200 days from identification of a novel pathogen. This estimate is based on holding a sufficient stockpile of materials and consumables to produce 1 billion doses (55 batches, each providing about 18 million doses, with materials and consumables costing roughly $1.3 million per batch) and renewing stocks every 12 months. Some materials and consumables will have shelf lives greater than 12 months, reducing costs, but warehousing costs are not included. Rapid response requires using pre-existing facilities — for instance, those of contract manufacturing organizations that make other vaccines or biologicals between epidemics — and negotiating contracts for emergency 'walk-in' rights in the event of a pandemic. Using existing facilities would reduce capital and labor costs, although these are predicted to constitute a minor part of the total cost of vaccine production. A key uncertainty is the cost of walk-in emergency availability of a facility. Between pandemics, this would require maintenance of staff training and process validation, perhaps requiring intermittent execution of the process, and — critically — would preclude use of the facility to make products for which an interruption of a few months could not be tolerated. Our estimate assumes that such walk-in capacity could be procured for around $11 million–$16 million per facility per year, which, over five years, is close to the total capital and labor cost of a purpose-built facility. Greater cost effectiveness might be achieved at a facility that used a similar process to make another viral vector for a non-pandemic indication, or by concentrating the eight production trains in a smaller number of facilities.

Costs of establishing such warm-lit networks are substantial but correspond to only ~0.002% of the $12.5 trillion global cost of the COVID-19 pandemic (as estimated by the International Monetary Fund[11]), or around 0.4% of global spending on COVID-19 vaccines in 2021 (ref. [12]). Which entity might fund and commission such a network for adenoviruses or indeed any other vaccine platform is an open question for global policymakers, as this extends beyond CEPI's core role of supporting research and development.

Data availability

Data generated and analyzed during the current study are available from the corresponding author on reasonable request.

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Competing interests

C.C.D.J. and A.D.D. are named inventors or contributors to intellectual property assigned to Oxford University Innovation relating to the ChAdOx1 nCoV-19 vaccine manufacturing process and will receive a proportion of proceeds from out-licensing of the intellectual property. A.D.D. has received research and consultancy income from AstraZeneca.

Additional information

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