Article:
Newall, A.T., Beutels, P., Kis, Z. et al. (2 more authors) (2023) Placing a value on increased flexible vaccine manufacturing capacity for future pandemics. Vaccine, 41 (14). pp. 2317-2319. ISSN 0264-410X

https://doi.org/10.1016/j.vaccine.2023.02.065

Placing a value on increased flexible vaccine manufacturing capacity for future pandemics

Newall AT[1], Beutels P[1,2], Kis Z[3, 4], Towse A[5], Jit M[6,7]

Article type: Invited short commentary

Affiliations Authors
[1]School of population health, Faculty of Medicine, UNSW Sydney, Australia.
[2] Centre for Health Economics Research & Modelling Infectious Diseases, Vaccine & Infectious Disease Institute, University of Antwerp, Belgium
[3] The Sargent Centre for Process Systems Engineering, Department of Chemical Engineering, Faculty of Engineering, Imperial College London, London, UK
[4] Department of Chemical and Biological Engineering, The University of Sheffield, Sheffield, UK
[5]Office of Health Economics, London, UK
[6]Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK
[7]School of Public Health, University of Hong Kong, Hong Kong SAR, China

Corresponding author
Anthony T Newall

Email: a.newall@unsw.edu.au

Mailing address: School of Population Health
University of New South Wales
UNSW Sydney 2052
Australia

Word count 1382
Key words Pandemic preparedness; Pandemic; Cost-effectiveness; Vaccine development; Vaccine manufacturing; Health Technology Assessment.

The COVID-19 pandemic has highlighted the enormous health, social and economic costs that can result from a global pandemic. It has also illustrated that even when vaccines can be rapidly developed for a novel pandemic-causing infection there are substantial challenges to rapidly mass-manufacturing vaccines to meet global demands. Many of these challenges to the rapid mass-production of vaccines are not unique to a pandemic vaccine but COVID-19 has demonstrated the substantial health and economic costs of delays in a pandemic situation. In the case of COVID-19 the lack of capacity in many countries to make novel vaccines was a significant bottleneck in the manufacturing process. The faster that safe and effective vaccines can be mass-manufactured for an emergent infectious threat, the greater the potential to reduce the global health and economic burden. This raises the question of what steps can be taken to help make rapid mass-production of vaccines easier in the event of future pandemics.

The existing resources in place to manufacture non-pandemic vaccines (including equipment, facilities, and human capital) can play a critically important role in the ability to respond to an emerging pandemic. This is because it takes significant time to create new capacity, so the use of existing resources forms a key element in tackling emerging threats. For example, constructing, equipping, validating and starting up a new vaccine manufacturing facility takes several years [1]. Moreover, the training of specialised manufacturing and quality control staff, and manufacturing of the required equipment cannot be done rapidly at scale. While there are important challenges to the adaption of existing manufacturing resources to develop and produce a new vaccine, the long lead times to create and expand production capacity mean that the magnitude and type of existing vaccine manufacturing capacity can be critical.

An important issue when discussing vaccine manufacturing capacity is the technology utilised. In planning for a future pandemic, benefits may emerge from trying to ensure that there is flexibility of vaccine manufacturing capacity. Vaccine production platform technologies (e.g. the RNA platform) offer the possibility to rapidly develop new candidate vaccines and mass-produce these vaccines once approved by the regulatory authorities. By definition, platform technologies allow the production of multiple vaccine products against multiple diseases using the same production process, raw materials, personnel, facilities and quality control methodologies. This disease-agnostic nature of platforms is a substantial advantage compared to conventional disease-specific vaccine production modalities. The development and mass-production of new vaccines can be further accelerated by re-using the manufacturing platform *knowledge* being generated, which can serve as prior knowledge when producing new vaccines [2]. In the case of RNA vaccines, production is associated with high variable costs (due to expensive raw materials) and relatively low fixed costs (due to small scale facilities)[3], thus the RNA vaccine platform is likely to be more cost-effective for maintaining surge or slack capacity for future pandemic response. Other platform technologies may also be potentially useful in the future, for example, the DNA vaccine platform, if the intra-cellular DNA delivery challenges are solved [4].

Maintaining and funding pandemic-response vaccine manufacturing capacity during non-pandemic times is a challenge yet to be solved. Keeping outbreak-response vaccine manufacturing facilities entirely idle during non-pandemic times is difficult as workforce skills will be lost, and capital goods will depreciate. A more feasible option is to increase flexible vaccine manufacturing capacity. In the case of RNA platform technology, flexible capacity could be utilised during non-pandemic times to produce RNA-based candidates for clinical trials and routine RNA-based vaccines and therapeutics (after approval by regulatory authorities). These flexible facilities could have parallel RNA production lines which could then be redeployed for outbreak-response manufacturing when needed. However, it will be essential to limit disruption in manufacturing other life-saving vaccines/therapeutics if these flexible production facilities are redeployed for outbreak-response manufacturing. This might potentially be achieved by, for example: 1) managing strategic buffer stockpiles of routine vaccines,

2) maintaining extra capacity in non-outbreak times by over-scaling a proportion of manufacturing facilities and using this excess capacity/scale for outbreak-response manufacturing. In an extreme situation of a very severe emergent pandemic then consideration may need to be given to prioritisation in manufacturing (e.g. reduction in production of some other products to allow greater production of a pandemic vaccine).

One way to increase flexible vaccine manufacturing capacity is to recognise and place a value on flexible non-pandemic manufacturing capacity as insurance for a future pandemic. That is, to recognise that the funding of flexible non-pandemic vaccines may not only bring benefits from the disease being prevented, but also has an additional benefit in increasing the resting stock of resources that could potentially be used in a pandemic. At present, all else being equal, the financial incentives to produce conventional vaccines are the same as those to produce more flexible platform-based vaccines, as the potential spill over benefits from more flexible vaccines are not currently valued [5]. While global pandemics of the magnitude of COVID-19 have not been common over the last century, the sheer scale of costs involved, which have been estimated in the trillions of dollars for COVID-19 [6], means that insurance is likely to have significant value. The social value of accelerating vaccine supply in a pandemic has been estimated to be in the trillions of dollars [6].

Methods have been proposed to estimate the potential future value (i.e. ex ante value, most notably so called “option value”, including insurance value [7, 8]) of medical innovations. The benefits of having flexible vaccine production platforms available that can be quickly repurposed for pandemic vaccine production, can be potentially valued using techniques that try to estimate how much society should be willing to pay (e.g. using contingent valuation) for this benefit or estimate by macroeconomic model-based scenario analysis the value (benefits) of faster deployment of a pandemic vaccine. For instance, if COVID-19 pandemic vaccine production had been faster after regulatory approval reaching more populations around the globe, the value of that faster pace would be large, as it relates to worldwide improved wellbeing, economic activity, and disease prevention [6]. At the same time more rapid manufacturing of a pandemic vaccine may reduce inequities in global vaccine distribution and population health.

The decision making around the funding of non-pandemic vaccines in many countries is heavily influenced by economic assessment [9]. However, the creation of additional flexible manufacturing capacity as insurance for a future pandemic is not currently formally valued as part of this evaluation process. Recognition of this value could potentially involve countries with the greatest financial means paying more for non-pandemic vaccines (or funding vaccines for sub-populations who would otherwise not be cost-effective), where their production provides pandemic insurance value that enables more rapid roll out of pandemic vaccines should the need arise. It will be important, when expanding the economic assessment to include option value to avoid double counting benefits [10], and contractual arrangements would need to be in place to ensure that any additional manufacturing capacity could be utilised in an emergency. Through the inclusion of this option value, these vaccines would be more likely to be cost-effective and funded (or funded for a wider population), and consequently increase flexible vaccine manufacturing capacity for a future pandemic emergency.

It may be that the insurance value varies substantially depending on the manufacturing method used and the probability that adding capacity to a given platform will be helpful for future pandemic vaccines. For example, the insurance value of funding vaccines using rapid-response platforms (e.g. the RNA platform) may be greater as compared to more conventional and slower vaccine production processes. However, given the uncertainty of a future threat, there may also be benefits to having diversity in manufacturing capacity, for example, maintaining capacity for outbreak-response manufacturing of whole inactivated viral vaccines, bacterial vaccine production modalities,

recombinant protein vaccines and adenoviral vectored vaccines. Consideration could also be given to the potential biosecurity risks of different vaccine technologies [11].

Placing an appropriate value on different forms of vaccine manufacturing to help combat a future emergent threat is a complex challenge. However, it is a challenge worth addressing given the importance of increasing future pandemic preparedness. To date there has been very limited research on how to determine what this value would be for pandemics or for other infectious disease emergencies. As indicated above, conceptual methods exist that can be built upon to focus on the specific issue of valuing the speed of global vaccine deployment in times of crisis. This may at least partly imply revisiting the valuation and funding (e.g. through drug reimbursement committees) of non-pandemic vaccines, if this could lead to expansion and/or innovation of flexible vaccine production platforms. We hope this commentary can inspire research in this regard.

Conflicts of interest

PB reports the University of Antwerp received compensation for a consultancy for Pfizer, and research grants funded by Merck and by the European Commission Innovative Medicine Initiative, all unrelated to this paper.

The Office of Health Economics is a not-for-profit which receives research and consulting income from a variety of sources including pharmaceutical companies. AT has also received personal consulting fees from pharmaceutical companies.

All other authors declare that they have no known conflicts of interest.

Funding source

No funding was received to support this specific article.

Acknowledgements

MJ was supported by the NIHR Health Protection Research Unit in Modelling and Health Economics (HPRU-2019-NIHR200908) and in Immunisation (HPRU-2019-NIHR200908). The views expressed are those of the authors and not necessarily those of the UK Department of Health and Social Care, NHS, NIHR or UK Health Security Agency.

PB and MJ acknowledge funding from the European Union's Horizon 2020 research and innovation programme - project EpiPose (Grant agreement number 101003688). This work reflects only the authors' view. The European Commission is not responsible for any use that may be made of the information it contains.

References

1. Plotkin, S., et al., *The complexity and cost of vaccine manufacturing - An overview.* Vaccine, 2017. **35**(33): p. 4064-4071.
2. Daniel, S., et al., *Quality by Design for enabling RNA platform production processes.* Trends in Biotechnology, 2022.
3. Kis, Z., et al., *Pandemic-response adenoviral vector and RNA vaccine manufacturing.* NPJ Vaccines, 2022. **7**(1): p. 29.
4. Blakney, A.K. and L.G. Bekker, *DNA vaccines join the fight against COVID-19.* Lancet, 2022. **399**(10332): p. 1281-1282.
5. Monrad, J.T., J.B. Sandbrink, and N.G. Cherian, *Promoting versatile vaccine development for emerging pandemics.* NPJ Vaccines, 2021. **6**(1): p. 26.
6. Athey, S., et al., *Expanding capacity for vaccines against covid-19 and future pandemics: a review of economic issues.* National Bureau of Economic Research. Working Paper 30192, 2022.
7. Fornaro, G., et al., *Broadening the Concept of Value: A Scoping Review on the Option Value of Medical Technologies.* Value in Health, 2021. **24**(7): p. 1045-1058.
8. Lakdawalla, D., A. Malani, and J. Reif, *The insurance value of medical innovation.* Journal of Public Economics, 2017. **145**: p. 94-102.
9. Ultsch, B., et al., *Methods for Health Economic Evaluation of Vaccines and Immunization Decision Frameworks: A Consensus Framework from a European Vaccine Economics Community.* Pharmacoeconomics, 2016. **34**(3): p. 227-44.
10. Towse, A. *Real Option Value: Should We Opt In or Out?* Value in Health, 2022. **25**(11): p. 1818 – 1820.
11. Sandbrink, J.B. and G.D. Koblentz, *Biosecurity risks associated with vaccine platform technologies.* Vaccine, 2022. **40**(17): p. 2514-2523.