THE UNIVERSITY OF CHICAGO
MARKET SHAPING ACCELERATOR

Response to Project NextGen: Potential Market Shaping Strategies for Vaccine Development Request for Information

August 10, 2023

We welcome BARDA's intention to invest substantial resources in promoting the development of next-generation vaccines for Covid-19 and future variants. Our estimates suggest that the annual expected cost of pandemics exceeds $700 billion (Glennerster et al., 2022). The large economic and mortality losses from pandemics mean that investing in reducing the costs of future pandemics, whether a new wave of Sars-CoV or an outbreak of a new pathogen, is likely to generate large expected returns even if the expenditures required are substantial. In the specific case of additional waves of Sars-CoV, we have estimated that the value of a universal Sars-CoV vaccine would be somewhere in the range of $700 billion and $1 trillion (Kelly et al., 2023). However, the presence of certain market failures (detailed below) entails that the return to the private sector from investing in next-generation vaccines will be below the social return, and thus that there will, without government intervention, be too little investment.

We also welcome the intention to complement existing push support for vaccines (such as paying for trials) with pull support (paying for outputs and outcomes). Pull support has the benefit of incentivizing producers that BARDA might not be aware of, encouraging competition between potential vaccine producers, and linking payment to what BARDA cares most about—a successful vaccine.

In this response to BARDA's July Request for Information (RFI), we start by setting out some general principles underlying our response to many of the specific questions raised in the RFI. We then provide more detailed responses to specific questions raised. We do not attempt to answer all the questions as some are best answered by medical/biological experts, focusing on those where economic principles can provide the most insight.

Our analysis of the proposed scenarios outlined in the RFI suggests that funding a grand prize linked to the successful commercialization of a vaccine with optimal TPP characteristics is the highest priority use of BARDA's funds. We encourage BARDA to work with other parts of the US government with procurement or other authority who could commit in advance to purchasing vaccines that meet the TPP criteria, reducing the demand risk firms face. Additional considerations on the structure of the prize are provided below.

We are certainly willing to provide more detail on any of the proposals made in this submission and engage in longer-term analysis on costing if that would be helpful.

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I. General Principles

A. Focus resources where market failures are largest.

Understanding specifically where the returns to private sector developers and distributors deviate from the benefits to society as a whole is important in determining where and how to focus limited BARDA resources. The main drivers of divergence are the following:

i) R&D that others can copy. The benefits of some innovations can be almost entirely captured by the firm making the innovation: for example, incremental improvements in a specific vaccine. Others (even in the presence of patents) can lead to improvements in competitors' vaccines: for example, a new vaccine platform or a new way to deliver a vaccine. These more general innovations are particularly undersupplied by the market. Many of the "optimal" characteristics are R&D improvements that other firms can learn from. Firms may fully capture the benefit of the "threshold" characteristics (adapting an existing booster for a new strain would mainly benefit that firm).

Implication: consider which of the threshold characteristics are really market failures. Focus more of the funding on optimal characteristics.

ii) **Reduced transmissibility.** Much of the benefit of reduced transmissibility goes to those not taking the vaccine. The person taking the vaccine (and their insurer) will care about some of the external benefit (e.g., reducing transmission to family members) but much of it they won't value (e.g., reduced transmissibility to non-family members or those covered by a different insurance program). It is also much more expensive to test for reduced transmissibility (trials must have a much larger sample size).

Implication: funding to incentivize reduced transmissibility is a high priority within the $5bn envelope.

iii) Improvements that reduce implementation costs. In a typical market, producers have proper incentives to improve their product to reduce user costs. In the case of vaccines, such improvements might include immunizations requiring only a single dose, more heat stable, a longer shelf life, etc. The presence of insurance changes the calculus somewhat because the person who chooses the product does not pay all the costs: the doctor or patient may choose the vaccine that is best for them without taking into account, for example, storage costs. If two vaccines are equivalent, insurance companies could say they will only reimburse the one with lower implementation costs; this is much more likely outside the US where there is more

coordination in purchasing. Patients care about one vs. two doses so there may already be sufficient incentive to achieve this benchmark.

Implication: insurance coverage reduces the extent to which developers think about the costs of administering vaccines when trading off different innovations to pursue, but they are not as large as some of the other market failures, reducing the priority for funding.

iv) Scale of production. Even when a vaccine innovation has been approved, private and social incentives are not aligned; firms would prefer to sell at a profit margin above cost, reducing quantity relative to what is socially optimal. In addition to the standard result in economics that producers undersupply when there is not perfect competition, vaccine producers also face social pressure to keep prices down when they produce mass-market vaccines while niche products for highly vulnerable consumers can command very high prices. Given the high fixed cost and lower variable costs of producing vaccines, ideally, government support is tied to lower prices in the long run. (There is a question of whether the current envelope is sufficient to achieve this goal.)

Implication: rewards for development should be supplemented with conditions linked to scale.

B. Consider the interaction of BARDA actions with other parts of the government

BARDA's proposed pull incentives are not the only incentives or players in the system that encourage next-generation vaccine development. BARDA is already paying for vaccine trials through push funding. When designing a new incentive program, considering the total incentive is important.

Government is also a large purchaser of vaccines. BARDA should discuss cooperating with federal healthcare insurance programs to establish a commitment in advance that vaccines that meet the TPP criteria would be covered (eligible for insurance reimbursement). Similarly to an Advance Market Commitment, this would signal to firms that there will be a market for their products (reducing the demand risk they face).

The RFI envisages potentially rewarding firms for developing vaccines that are covered by major insurers. This is unlikely to be an optimal way to incentivize firms—it potentially involves one part of the federal government (BARDA) rewarding firms conditional on the actions of another part of the federal government (federal healthcare insurance programs). Prior coordination would make more effective use of the federal government's ability to shape markets.

Implication: BARDA should coordinate the Project NextGen program with other government healthcare stakeholders.

C. The criteria for using interim payments vs grand prizes.

Generally, it is better for funders to tie prizes to the achievement of the desired final outcome rather than an intermediate step. In awarding a prize for the target outcome, the funder can be agnostic among different routes of achieving the final objective, while defining an intermediate step might inadvertently preclude some approaches. In addition, intermediate payments can distort incentives. For example, consider an innovator choosing between approaches A and B. A is much more likely to pass stage 2 but is less likely to pass stage 3, while B is more likely to pass stage 3. A prize upon the success of stage 2 could incentivize them to put more effort than they should into approach A.

There are two reasons why, despite the typical advantages of targeting final outcomes, interim payments are sometimes useful: when there are major distortions in the private capital market and when an intermediate innovation could benefit many different firms.

Milestone payments provide incremental financing for firms. This is useful if promising innovations find it hard to access commercial financing even when there is a clear, large government-guaranteed reward for achieving the innovation. This is unlikely to be the case here, in particular for near-term innovations. BARDA BAA's Area of Interest on NextGen vaccines provides funding awards for phase 2b efficacy trials, which substantially decreases the interim financing an innovator has to raise. Once a vaccine has successfully cleared phase 2b trials, the vaccine has a significantly higher probability of reaching approval (MacPherson et al., 2020). A sufficiently large grand prize would likely provide sufficient incentives for private finance to cover the remaining cost of phase 3 clinical trials, licensure, and capacity scaling as long as the remaining risk of technical failure is not very high (it is appropriate that some ideas are not pursued at this stage based on an assessment of technical risk). This suggests little need for a milestone payment between phase 2b and commercialization. There are several well-established routes for raising private funding: larger firms can fund out of internal resources; larger firms can buy out or arrange deals with smaller firms; and smaller firms can raise external funding from financial backers based on their phase 2 trials.

A more compelling reason for using milestone payments would be if there are intermediate innovations that would benefit multiple firms: for example, an immunoassay that can accurately measure transmission reduction, mucosal immunity, breadth, and duration of protection. In this case, sharing information publicly once the milestone is reached would be a public good and could reduce the cost of development for many vaccines. Intermediate prizes could be awarded to the development of technologies that would be useful to others on condition that the innovation is made publicly available to be used in a variety of vaccine trials.

There is a final practical budget reason for milestone payments which is that innovations may take place after the timeline for a given appropriation. Putting money in a separate entity, cooperating with a philanthropic partner who has more flexible funding timelines, or paying out to the firm that is furthest along are also partial solutions to this challenge as is the portfolio approach we discuss below.

Implication: generally, grand prizes are preferable to interim awards for incentivizing the final outcome. Interim prizes should be reserved for special use cases.

D. *Take account of the existing* commercial incentives.

The existing market demand for SARs-CoV vaccines and boosters provides a commercial incentive for firms to be investing in next-generation vaccines. Seventeen percent of the U.S. population (56 million) received the most recent bivalent boosters developed by Pfizer and Moderna (CDC), and both companies have also announced that they plan to sell their boosters for $110-130 per dose once commercialized (AP News; Reuters). Given that public and private insurance providers are likely to continue to cover the cost of the vaccine, a new vaccine has the potential to capture some or all of a $5 billion market (estimating ~50m people get vaccinated at ~$100 per dose). For those covered by insurance, the efficacy of the vaccine rather than the price is likely to dominate which vaccine they demand (or their doctor recommends).

This potential market size is likely large enough to incentivize firms to invest in commercializing near-term threshold vaccines even without an additional prize. However, where commercial incentives might fall short of the social optimum is in achieving a sufficient stockpile or capacity level that could allow the vaccine to be rolled out quickly in case a more dangerous than expected variant arises. The market demand for a Covid booster is uncertain due to uncertainty over the health impact of the next SARs-CoV variants. A particularly bad variant could spark a surge in demand for vaccines. There is immense social value in having a stockpile of vaccines available to quell an emerging outbreak (Jarrett et al., 2021). Private firms have some incentive to have stocks available to deal with a surge in demand but they do not internalize the disruption to society if a bad variant leads people to reduce their mobility absent sufficient vaccine supply. Typical vaccine payments lead the supplier to earn the same revenue whether the vaccine is sped to consumers or trickles out more slowly to them.

To be clear, here we are referring not to the speed of invention, for which the race to win a prize would provide strong incentives (more on this below). Rather, we are referring to investments firms make in stockpiling and capacity that could speed rollout to the population in the event of a resurgence of Covid.

The ideal intervention needed to resolve this market failure is a funder with the ability to procure a stockpile of vaccines. BARDA should consider partnering with other organizations to incentivize necessary scaling.

Implication: BARDA's proposed prize pull funding is not well suited to address the market failure associated with near-term vaccines: limited commercial incentives to build stockpiles and/or install large capacity to accelerate rollout.

E. The number of winners should balance incentives for speed and quality of the product.

Awarding the prize solely to the first vaccine to meet TPP criteria (as specified by either the near-term or optimum program) would incentivize initial research and development speed but not provide an incentive for other developers to continue innovating a potentially better product. Additionally, it would substantially raise the risk faced by developers because they get nothing if a competitor beats them by just a few days. Awarding the prize solely based on the quality vaccine risks rewarding a "me too" innovation: the innovator who makes the initial breakthrough gets no reward while a follow-on vaccine that slightly improves on the first vaccine reaps all the prize (Kremer and Glennerster, 2004). It also fails to incentivize speed to market and appropriate scaling.

BARDA should therefore set a defined time window after the first vaccine is commercialized in which successful products can be considered for the award. The window should be long enough to reduce perverse incentives for vaccine developers to cut corners to beat other vaccines to the finish line by trivial amounts of time. Additionally, the window should be short enough to prevent "copycat" or "me too" vaccines from taking the prize. A window of six months or a year could be considered appropriate, but BARDA may have additional expertise to inform this decision.

Implication: the winner should be chosen from the pool of successful vaccines to be commercialized within a defined window of time after the first vaccine becomes available.

F. Incremental awards based on optimal attributes.

Our reading of the existing proposal is that there would be a grand prize for a vaccine that met all of the optimal targets. Several optimal characteristics are valuable enough individually to warrant incentivizing, such as reduced transmissibility and pan-sarbeco effectiveness. The social benefit of a universal SARs-CoV vaccine has been estimated to be in the range of $700 billion to $1

trillion, far exceeding the cost of funding the innovation (Kelly et al., 2023). Setting a prize only if all the optimal targets are met risks a firm that has ideas to meet one target but not others, not pursuing their idea. An alternative approach is to set multiple definitions for success. This would simultaneously incentivize firms to innovate across multiple attributes.

BARDA could determine success upon commercializing either type of vaccine: one that reduces transmission by 90% and/or one that is pan-sarbeco effective. This would allow developers that are well suited to work on a singular attribute to be incentivized to continue their work, even if the other attribute is not within their reach.

The commercialization of either product would trigger the start of the window as discussed in General Principles Section E. Then, BARDA would select the prize winner from the best vaccine among those commercialized in the window that meets one or the other criterion or both. The estimated innovation timeline must be similar for both qualifications; otherwise, firms working on the attribute with a longer time horizon would be discouraged from attempting to win the prize. Presumably, a vaccine meeting both criteria would almost certainly be judged better than a rival meeting only one.

A modification of this approach would tie the size of the prize to how many of the attributes a vaccine achieved. If the first vaccine achieved only one of the characteristics in the optimal TPP there would still be money left over for a vaccine that achieved another optimal TPP characteristic. This would encourage ongoing innovation toward the optimal TPP profile, but would also face the opportunity cost of an allocated budget sitting unspent.

Implication: allow for flexibility in the contract to allocate awards based on the successful development of a subset of optimal attributes.

G. Costing pull incentives of vaccines

The optimal size of the pull incentive depends on the value of the health and economic benefits that derive from accelerating vaccine development, the number of firms competing for the award, the distribution of their costs, and the probability that they would succeed. Snyder et al. 2023 explain how to integrate those factors via an optimal mechanism that induces firms to reveal their true development and production costs. The authors show that the optimal mechanism can be implemented as a simple reverse auction.

However, if program constraints prevent BARDA from employing such a mechanism, there are general economic principles to ground an estimated needed size of a grand prize.

i) Gap between social and private benefits. The vaccine characteristics in Table 1 of the RFI have very different social benefits. Some of these could be calculated: for example, the saving from reduced incidence of side effects and the reduced storage costs for more heat-resilient vaccines. As discussed above in Section A, some of these are already likely to be rewarded on the market via a higher price. The benefits of a pan-sarbeco vaccine have also been estimated to be somewhere between $700 billion and $1 trillion (Kelly et al., 2023).

ii) Difficulty of challenge/cost of innovation. The harder the problem, the more expensive the cost of innovation and the larger the prize needs to be. Because investments are undertaken with certainty but success and winning are not certain, the prize must more than cover costs; it must cover the costs scaled up in inverse proportion to the chance of successful innovation and the chance of beating other successful rivals for the prize (which depends on the number and competitiveness of rivals). In general, the size of the prize should be between an estimate of these scaled-up costs and the social benefit of the innovation. The optimal prize trades off giving away too much surplus to firms with too high a prize against incentivizing too little innovation effort. Given the high social value of many of the vaccine innovations specified by Project NetGen relative to the total program budget (only a portion of which would be available to fund prizes), we suspect that making the prize too large is less of a danger than providing innovation incentives that are too weak.

iii) Speed. When speed of innovation is of the essence (as amid a pandemic), it is important to set the incentive level such that a large number of firms work on the approach simultaneously even if the probability of success of the marginal firms is low and/or does not contribute much to the overall probability that at least one succeeds. In calmer times, the approach can be altered. Then more attention can be paid to pulling in firms with a reasonable chance of success but not very longshot firms.

iv) Number of firms. In general, if more firms are competing for a prize, the prize has to be larger to offset the lower chance that a given firm beats its rivals to the punch. However, the number of firms competing reacts to the size of the prize and should not be seen as set. The best way to think about this is how many firms BARDA wants to compete (see speed above), and then determine the appropriate size of the prize.

Implication: root the calculation of the necessary size of the prize in established economic principles.

H. Design features unattractive to firms impact the necessary size of the prize.

Including TPP requirements such as price caps and required manufacturing capacities reduce firms' expected commercial returns from a new vaccine, which will need to be accounted for in the size of the grand prize to avoid dulling incentives too much.

Currently, BARDA proposes a price per dose of less than $10, which is significantly lower than the price per dose the U.S. government paid for the Pfizer and Moderna bivalent boosters ($30.48 and $26.36 respectively; Kates et al., 2023). Further, both companies have also announced that they plan to sell their boosters for $110-130 once commercialized (AP News; Reuters). Given 17.0% of U.S. adults received the bivalent booster (CDC), a prize of over $5 billion would be needed to bridge the gap between the commercial market incentive and BARDA's price restriction.

Additionally, a price cap needs to exceed firms' marginal cost of production of a dose to incentivize increased production. If the price cap is too low, firms lack any financial incentive to produce doses beyond those committed to in the prize contract.

Implication: BARDA should factor in the need to increase the prize to offset a tighter price cap when determining the price-cap level.

II. Responses to RFI Questions

A. Establishing the Objective

2. Are there any target performance levels that should be modified and why?
The target price per dose may be unrealistic given the size of the award. Refer to General Principles Section H for details.

7. Are there any other features of the TPP that may improve availability in low-middle income country settings, expanding the global reach of vaccines that may be eligible for prizes?
Price is a major factor that would improve the availability of vaccines to low-middle income countries. Requiring successful vaccines to be sold to GAVI at a restricted price would greatly expand access to the vaccine for the world's poorest countries. However, if the restricted price is well below firms' anticipated production costs, forcing GAVI sales could require a much larger grand prize to avoid dulling incentives. BARDA could consider looking for partnering organizations to help increase the size of the prize funds in that event.

There was considerable concern in the early stages of Covid-19 vaccine development that low- and middle-income countries would not be able to distribute vaccines requiring very low-temperature storage. In the end, most countries were able to distribute Covid-19 vaccines, even those requiring very low temperatures, although this distribution was not cheap.

A bigger challenge to the distribution of boosters in low- and middle-income countries is that there is not a tradition of regular adult vaccination, for example for flu. This means that when Covid is not top of mind, there is likely to be relatively limited demand, and arguably for many low-income countries Covid is not the main health priority. However, there might well be a surge in demand from middle-income countries if another wave arrives as deadly as, say, the Delta variant. The most important steps that the United States can take to support low- and middle-income countries' access to Covid vaccines therefore include the following:

i) Increase capacity to produce improved vaccines at large scale (e.g., make prizes contingent on large-scale production).

ii) Work with funders like the World Bank to ensure that low- and middle-income countries can obtain financing to ramp up vaccine production in future waves. (We recognize this is not the role of BARDA.)

B. Measuring the Product's Ability to Meet the Objective

3. What trials, assays, tests, processes, etc. will need to be developed to be able to prove a product can meet or exceed optimal product attributes? This can include approaches to lower cost, improve reliability, and expand accessibility of existing assay tools such that their use in large scale clinical trials may be more feasible or to establish entirely new types of assays/tools. Please provide specific feedback for each attribute.

As discussed in General Principles Section C, intermediate prizes should be avoided unless aimed at innovations that benefit multiple firms. Sharing the technology once the milestone is reached would be a public good and could reduce the cost of development for many vaccines. The milestone would need to be contingent on publicly sharing the results of the innovation.

An appropriate target could be the development of immunoassays that can accurately measure transmission reduction, mucosal immunity, breadth, and duration of protection. A key attribute of the optimal TPP is the vaccine's ability to reduce transmission. A clinical trial on the efficacy of transmission reduction would require a very large sample size to study both the individuals who received the vaccine and their close contacts. Such a study would be costly and time intensive. Hence, developing an immunoassay that could accurately measure transmission reductions would reduce the cost of vaccine development and expedite time to market.

C. Prize Award Amounts and Structure

Scenario 1

1. ***Should BARDA make awards based on award of a BLA or after 1 year of commercialization?***

BARDA should award its grand prize based on the final outcome they would like to incentivize. To reach BARDA's goal of ensuring next generation SARs-CoV vaccines are "available and accessible," commercialization should be tied to accessibility metrics. This would entail requiring a certain quantity of doses be available at a set price level. Rewarding such an availability target would help reduce the demand risk resulting from uncertainty about future outbreaks. BARDA has already outlined in the TPP a price cap of $10 and a requirement of the ability to scale to produce 100 million doses within 100 days (though the price cap may need to be revised in light of the value of the prize pool; refer to General Principles Section H for details). Awards should be administered upon demonstration of these criteria; awards based on BLA approval may not go far enough to guarantee access to the vaccine.

2. ***Should BARDA consider awarding multiple winners, first to finish, or some other criteria?***

Refer to General Principles Section D.

3. ***Is a grand prize likely to stimulate private investment in R&D? Why or why not? What would be an appropriate measure of successful commercialization?***

A grand prize of sufficient size is likely to stimulate private investment in R&D. Firms will make investment decisions based on the expected value of the return to their investment. A grand prize allows developers to have an increased payout upon developing a successful product, thus increasing their expected return, as well as increasing the certainty of a payout. If the expected payout from their investment in R&D exceeds their costs, private investors will choose to invest in vaccine development.

Successful commercialization should be tied to the demonstration of vaccine accessibility. This would require firms to sell the vaccine within the price cap set forth by the TPP and demonstration of ability to scale capacity in the case of a surge in demand (possibly brought on by the onset of a new spike in cases). The award could be given after a certain duration of time of the vaccine on the market at the given price or after a specified number of doses are made available.

Additional payout conditions, such as pricing and scale requirements, would require a larger grand prize. These factors impact the expected returns from commercialization which in turn would need to be compensated for by the prize to meet the criteria.

Scenario 3

1. What should BARDA set as the interim and grand prize pay outs and why?

Refer to General Principles Section C for a discussion on the appropriate use cases for interim payouts. Our view is that interim payouts are likely not needed in pharmaceutical development because the industry is well-capitalized. The exception is for intermediate goods that could be used by many firms. The appropriate size of payment for this interim good should be somewhere between i) by the gap between the private return (i.e. what a company that develops the intermediate good could sell it for) and the social return (what it's worth to society) and ii) the likely cost of developing such an intermediate product if it succeeds multiplied by the risk of failure.

If BARDA thinks the firms working on vaccine development are unlikely to be able to raise capital on the private market despite evidence of a promising approach, the size of the interim payments should be determined based on the amount of liquidity needed for the candidate vaccine to finance the next stage of progress. For example, if BARDA awards an interim payment after phase 2 of clinical trials, the award should be large enough to allow for financing of phase 3 trials and the costs associated with BLA approval.

2. Should BARDA base interim pay outs on positive clinical trial data or simply on their completion?

If doing interim payments, BARDA should base interim pay outs on success in clinical trials rather than on their completion. Payment upon success transfers the risk of technological failure from BARDA to the firms. As firms have private information on their likelihood of success and cost of clinical trials, this scheme would prevent investment in clinical trials for vaccines that have no realistic chance of succeeding.

3. How many interim prizes should BARDA consider?

Refer to General Principles Section C for a discussion on the appropriate use cases for interim payouts.

***4. Would an interim pay out spur continued investment by private investors or company internal resources to continue with development*?**

Interim payouts introduce the risk of companies who have a high chance of reaching the interim goal but very little chance of reaching the final goal being rewarded. In light of this risk, pull mechanisms are most effective when the payout is linked to the desired outcome rather than partial completion. See General Principles Section C for a detailed discussion on why grand prizes are preferred to interim payouts in this context.

Questions Regarding Pull Incentive Structures

1. ***What should BARDA set as the grand prize payout and why? *Please provide number and the economic reasoning behind the selected amount, considering costs of development and potential ROI from product once marketed***

Outside of the proposed pull program, the size of the commercial booster market creates an incentive for the development of next-generation Covid-19 vaccines. Refer to General Principles Section D for an explanation of why a prize is not well suited to overcome the key market failure associated with near-term "threshold" vaccines: limited incentives for capacity scaling and stockpiling. However, a prize could be used to increase the number of firms investing in the development of optimal TPP characteristics, which are undervalued by the market because they confer greater benefits to public health than individual protection (which is the main attribute consumers and insurers are willing to pay for).

The immense societal benefit from reduced transmission or universal SARS-CoV vaccine would likely be orders of magnitude larger than the cost of development (Kelly et al., 2023). Hence, the optimal amount of funding to incentivize as many participants as possible to be innovating in this space is likely in excess of the entirety of Project NextGen's budget of $5 billion.

However, even a grand prize in the range of Project NextGen's budget or a reasonable fraction thereof can be worthwhile, increasing the number of firms investing in attempting to commercialize a vaccine with optimal TPP attributes. A grand prize would need to be large enough to cover the costs of R&D (that are not already subsidized by direct push funding) multiplied by the inverse of the chance of successful innovation and the chance of out-competing rivals who happen to also be successful (which in turn depends on the number of other companies participating). BARDA is best positioned to perform the exact calculation by drawing on their expertise and experience, but we include a generic estimation below to illustrate concepts.

To estimate the potential cost needed for R&D, BARDA could draw on its experience from the funding of the development of mRNA vaccine technology. If BARDA's BAA provides funding support through phase 2b clinical trials, the costs in question are phase 3 trials and manufacturing scaling. In a comprehensive review of the funding sources for mRNA vaccine technology development through commercialization, Lalani et al. (2023) reported that BARDA provided $1.7 billion in clinical trial support to Moderna for phases 2 and 3, the NIH funded separate clinical trials for $490 million, and $108 million was invested in manufacturing and basic science. BARDA would have greater insight into the costs of phase 3 trials, but for illustrative purposes, we assume $800 million would be a reasonable estimate of phase 3 and manufacturing costs.

To estimate firms' risks, BARDA should consider the candidate vaccines' chance of success and the number of firms participating. If push funding available through BARDA's BAA covers phase 2 clinical trials, the source of risk is phase 3 trials. A review of vaccine timelines for emerging or reemerging viral infectious diseases found that 61.6% of vaccines successfully transition from phase 3 trials to FDA approval (MacPherson et al., 2020). Even if the vaccine is successfully developed, it still may lose out on the prize money to other successful firms. If 10 firms were participating in the prize competition, each with a 61.6% chance of success, then each successful firm would only have a 16.7% chance of winning the prize.

Hence, to compensate for the $800 million in costs and 10.3% chance of winning, the prize would need to be nearly $8 billion ($800 million times the reciprocal of the 10.3% chance). However, the expected commercial payout from capturing a portion of the Covid booster market could defray some of these scaled-up costs, so the prize need not cover the whole amount. The expected commercial returns from a successful vaccine are partially determined by the price cap BARDA enforces as part of the TPP.

Assuming similar uptake rates as the bivalent booster dose, the demand for a new SARS-CoV vaccine would be roughly 55 million (CDC). Increasing BARDA's proposed price cap to $120 (the reported expected commercial price) would entail a market size of $6.6 billion. Because the optimal attributes confer greater social benefits to public health than individual protection, they may not fully capture the Covid booster market when they are successfully developed. Consumers, whether that be patients or insurance providers, base purchase decisions on individual benefits. Hence, even the best vaccine to emerge from the prize competition still may face a rival vaccine in the commercial market. Given this concern, it may be appropriate to assume that the prize winner would only capture 50% market share, worth $3.3 billion.

In this hypothetical, the grand prize initially estimated at $8 billion could be reduced to $4.7 billion because of the complementary commercial incentives. Imposing a much stricter price cap would require a much larger grand prize. An additional economic consideration not included in this stylized example is that firms need to more than break even to cover their cost of capital (estimates between 11% and 20%).

This estimation calculation depends on knowing (or being able to estimate accurately) the firm's costs. In reality, firms will know more about their costs (they will have private information). This will increase the necessary size of the prize. For example, if BARDA envisages attracting two firms to invest, the prize needs to be large enough to incentivize the firm with higher costs (the "marginal" firm pulled in). Since it cannot estimate the costs of this firm precisely, it will need to set a larger prize to ensure participation. The mechanism presented by Snyder et al. (2023) resolves this issue using a reverse auction.

2. ***If early-stage direct funding support (i.e., grants or contracts) was available, how would that affect the size of the prize payouts in scenarios 1, 2 and 3 above necessary to incentivize private industry participation?***

Additional direct funding support would decrease the necessary size of pull funding needed to incentivize innovation. The amount of pull funding needed is determined by the cost of R&D multiplied by the inverse of the probability of a successful vaccine and the probability of winning the prize given success (dependent on the number of firms participating). Early-stage direct funding would decrease the remaining cost of R&D and support the vaccine development to a phase with a higher probability of ultimate success. Both of these factors reduce the size of pull funding needed.

3. ***Would the change in prize pool be proportional to the amount of direct funding support? Please provide an explanation for your answer.***

An increase in the amount of direct funding does allow the funder some ability to reduce the prize pool without compromising innovation incentives, but the relationship between the amount of push funding and the amount of pull funding in a hybrid scheme involving both is far more complex than one-to-one.

One factor is that push funding is paid out to multiple firms, whereas pull funding is only paid out to the successful firm. Hence, the relationship between the two forms of spending is in part mediated through the number of participating firms. The number of participating firms is not predetermined but rather is influenced by the funding program's design. In particular, the proportion of funds allocated to push versus pull funding can influence the number of firms that choose to participate in the program. Additionally, push and pull funding each has its own advantages depending on a combination of factors including firms' risk tolerance, the distribution of the probability of success across firms, and asymmetric information.

In a scenario with risk-neutral firms that have the same probability of success, there is a one-for-one relationship between the size of direct funding support to all firms and the prize pool. A risk-neutral firm will be indifferent between receiving $1 or ⅕ chance of $5. However, in a scenario with risk-averse firms that have the same probability of success, pull funding will cost more — firms will need to be compensated for the risk of failure.

In a scenario where the government seeks to induce a diverse set of firms to invest including those with a lower probability of success, and cannot observe their probability of success, it will need to offer all firms a large pull incentive to induce the marginal firm to invest. Push funding based on reimbursing costs is likely to be cheaper in such a case.

However, incorporating pull funding will often reduce costs associated with the perverse actions of direct funding recipients that can make push funding very expensive. If firms can just take the money from the direct payment and run, the funder gets zero innovation for dollars spent. If the

funder cannot fully audit the reimbursement costs, the firm can embellish the reimbursement request with expenditures from other lines of business. If direct payments fully reimburse reported costs, firms have no incentive to cut costs and may even inflate reported costs to receive a markup. These actions can be disincentivized by conditioning payment on the success of the outcome using pull funding which requires firms to have "skin in the game."

4. ***Which of the scenarios would encourage the most participation by private industry and maximize chances for at least one product to be commercialized that meets optimal TPP?***

Scenario 2, a grand prize aimed at the optimal TPP, would maximize the chances at least one product is commercialized to meet the optimal TPP. See General Principles Section C for a detailed discussion on why grand prizes are preferred to interim payouts in this context.

5. ***Which scenario, if any or both, would fail to properly incentivize private industry to commercialize a vaccine that meets optimal TPP?***

Scenario 1 only incentivizes investment in the near-term threshold TPP. Since the development of the near-term vaccine does not further the necessary technological innovation of the optimal TPP characteristics, funding this scenario would not properly incentivize any progress toward a commercialized vaccine that meets the optimal TPP.

In insolation, scenario 3 would also fail to incentivize a commercialized optimal vaccine. Interim prizes would incentivize the completion of the milestone they are linked to, but they would not properly incentivize the final product. See General Principles Section C for details on why a grand prize is preferable to milestone payments.

A sufficiently large prize in scenario 2 would incentivize private industry to commercialize a vaccine that meets optimal TPP.

6. ***Should BARDA consider having partial awards for meeting some but not all TPP attributes?***

Yes, partial awards could be beneficial, refer to General Principles Section F for details.

7. ***Are there other pull incentive structures beyond prize awards that would be better at incentivizing private industry to develop next generation COVID-19 vaccines than those mentioned in Scenarios 1, 2, or 3?***

An Advanced Market Commitment would allow BARDA more power over price setting, a key attribute to guarantee the availability and accessibility of a developed vaccine. See answers below in Section D for details.

8. ***How should BARDA factor in risk of technological failure into the incentives?***

Pull funding mechanisms have the advantage of firms bearing the risk of technological failure. This is appropriate as firms are better informed about their probability of success or failure.

However, a larger risk of technological failure would increase the needed size of the prize to incentivize investment.

9. ***How should BARDA define and determine successful commercialization and why? One example could be successful achievement of BLA. Another could be whether major insurers reimburse for vaccination or whether it's available at major healthcare systems and/or pharmacies.***

Ideally, if there is sufficient funding, successful commercialization should be tied to the demonstration of vaccine accessibility. This would require firms to have the vaccine available for sale at the agreed price and demonstrate the ability to scale capacity in the case of a surge in demand (possibly brought on by the onset of a new spike in cases). The award could be given after a certain duration of time of the vaccine on the market at the given price or after a specified number of doses are sold. BARDA has included similar provisions in the TPP: a price cap of $10 and the demonstrated ability to scale to 100 million doses in 100 days.

However, low price caps and large manufacturing requirements impact the needed prize size due to increased scaling costs and decreased expected commercial revenue. Refer to General Principles Section H for further details on how unattractive design features impact the necessary size of the prize.

Features of the Award Structure

Collaboration Opportunities

1. ***Should BARDA consider collaborations with organizations that might include offering Advance Market Commitments (AMCs) or complementary prizes? In this case, for international procurement, a procuring organization provides an advanced market commitment to purchase specific volume of bulk or fill finish vaccine, over several years.***

Yes, BARDA should consider collaborating with organizations that could offer an AMC. As discussed above the size of the prize might not be sufficient to compensate for the suggested price case. By committing to purchase or subsidize future purchases, the sponsors of an AMC could secure price and supply commitments from firms. The Advance Market Commitment for Pneumococcal Vaccine included a long term price cap that applied even after the fund was exhausted (Kremer et al., 2020; Kremer et al., 2022). Firms may be willing to agree to such conditions because the AMC would reduce the demand risk firms face and help cover their fixed costs.

Procurement would also allow for stockpiling of vaccines which would ensure vaccines are more quickly available upon the emergence of another variant. Stockpiling vaccines plays an important role in the ability to respond quickly to quell emerging outbreaks (Jarrett et al., 2021).

2. ***What volume of an AMC is likely to increase private participation or stimulate private investment? How does payment value of the vaccine influence this answer?***

Kelly, Glenerster, and Snyder (2023) provide a rough estimate that an AMC of $4.3 billion would be sufficient to stimulate investment in a universal coronavirus vaccine. This estimate assumed that the goal of the AMC was to make the universal Covid vaccine available to anyone in the U.S. who wanted one, which was estimated at a third of the population. It should be refined.

An AMC subsidizes vaccine purchases in return for pricing close to (above) marginal cost. The subsidy is intended to help cover the fixed costs of R&D and manufacturing capacity. An AMC would need to subsidize a sufficiently large quantity to cover firms' fixed costs and induce investment. In return for providing a larger subsidy (increasing the overall AMC fund) the sponsors could secure greater commitments on capacity and supply or on price (including in the tail period after the AMC fund is exhausted).

3. ***Are there specific conditions of an AMC that might be attractive or unattractive for participation among vaccine developers (e.g., price cap, guaranteed AMC vs payment once doses delivered, top-up payments etc.)?***

Generally, conditions of an AMC that are unattractive to firms provide some desirable features to the sponsor. For example, specifying a price cap per dose ensures greater accessibility to the vaccine, but it reduces a firm's ability to charge a price significantly above its costs. Additionally, firms would prefer a guaranteed AMC, but a co-payment or top-up mechanism (where AMC subsidy matches consumer purchases) ensures firms produce a product that is attractive to the intended consumers. Unattractive requirements can be compensated for through larger "top-up" commitments to increase the expected payout to successful firms.

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