Advocating for Alternative Incentives for a Proactive Pharmaceutical R&D System: A Prompt from COVID-19
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Citation

Acknowledgment
We would like to acknowledge Dr. Jeromie Ballreich from the Johns Hopkins Bloomberg School of Public Health for his feedback on the K2P document.
• To date, COVID-19 has infected over 5 million people worldwide, killed over 338,000, and is estimated to impact at least 40% of the world’s population.

• Over the past 2 decades, the world experienced 5 outbreaks and in every case vaccine development came in too late (examples: H1N1, Ebola, and Zika).

• The current pharmaceutical R&D model is highly market-driven and misaligned with public health needs.

• Pharmaceutical companies have an economic incentive to invest in R&D only when there is a sufficient and predictable market. There is little incentive for drug companies to develop products for diseases that do not have large markets or that affect low-income populations.

• Current market-driven incentives, such as tax credits or priority review vouchers, do not unbind incentives from expected profit and do not guarantee accessibility for developing countries.
• There is a need to alter the R&D incentive structure so that emerging infectious diseases that might turn into pandemics in the future will be prioritized by the various entities involved: public funders, philanthropists, private drug companies, and international organizations.

• Alternative R&D incentives should improve the overall net present value for new projects, enable greater participation of private industry, and facilitate cooperation and synergies across players in the market. Incentives must be implemented in a set of complementary “push” and “pull” incentives to promote proactive R&D for the next pandemic.

• Academia, public sector, biotech industry, international organizations, philanthropists and governments each have a role in advancing and advocating for a sustainable R&D system.

• This document presents key recommendations to improve the pharmaceutical R&D system, building on learnings from previous emerging infectious diseases and international best practices.
Advocating for Alternative Incentives for a Proactive Pharmaceutical R&D System

K2P

Until now, among the most recent cases, the world has been affected by the COVID-19 pandemic, which has affected more than 338,000 people and has been estimated to have caused the death of more than 5% of the world's population. In all cases, the development of the vaccine took place very late (e.g., ebola, zika virus and H1N1 influenza) in the context of the current model of pharmaceutical research and development, which still prioritizes the interests of the market, which is not consistent with the needs of public health.

Companies are encouraged to invest in pharmaceutical research and development only when there are sufficient markets. While companies are less motivated to develop products for diseases that do not have large markets or that affect the low-income population.

Current commercial incentives, such as tax incentives or priority review vouchers, do not guarantee exclusivity and do not guarantee access to developing countries. There is a need to change the incentives for pharmaceutical research and development, giving priority to infectious diseases that may become pandemics in the future from various stakeholders: the public funders, donors and pharmaceutical companies, and international organizations.

These incentives should improve the overall value of new projects, enable greater industrial participation, and support cooperation and integration among all key actors in the market, according to a comprehensive approach to strengthen the proactive research system for the next pandemic.

This document presents key recommendations to improve the pharmaceutical research and development system, based on previous experiences and best practices internationally.

The fundamental challenges, as defensive strategies or measures to be taken, include the need to adapt the current regulatory framework to the reality of the pandemic, the need for transparency and accountability in decision-making processes, the need to foster a culture of innovation and entrepreneurship, and the need for stronger partnerships with stakeholders.
Preamble

Despite the pharmaceutical industry being a trillion-dollar business and the significant investment in research and development (R&D) by governments and the pharmaceutical industry, the COVID-19 pandemic has highlighted that the system is unable to proactively address the needs for vaccines, testing and treatment for unpredictable and novel viruses. This puts into question the incentives of the pharmaceutical industry—does the industry have the appropriate financial incentives to invest in unpredictable outbreaks responsible for the high burden of disease? Are viruses responsible for pandemics on the radar screen of the large pharmaceutical companies aside from the time when the outbreak has already occurred? A reform in the incentive system for pharmaceutical R&D is needed to mitigate the impact of the next pandemic.

The clinical effect of COVID-19 may impact at least 40% of the world’s population[1]. The economic consequences will affect everyone. To date, more than 5 million cases and 328,000 deaths have been recorded worldwide and the numbers will increase[2].
Selection Process

We ran the following search strategies to identify the relevant literature.

In Google Scholar, we used the following search terms “pharmaceutical R&D systematic review”, “pharmaceutical R&D incentives systematic review”, “R&D financing systematic review”, “R&D incentives for infectious diseases” and “R&D incentives for COVID-19”.

In Pubmed, we search for: “(((pharmaceutical[Title/Abstract]) AND R&D[Title/Abstract])) AND (((incentives[Title/Abstract]) OR investment[Title/Abstract]) OR financing[Title/Abstract])”, “(((LMIC[Title/Abstract]) OR developing countries[MeSH Terms]) OR neglected[Title/Abstract])) AND (((pharmaceutical[Title/Abstract]) AND R&D[Title/Abstract])) AND (((incentives[Title/Abstract]) OR investment[Title/Abstract]) OR financing[Title/Abstract])”, AND“(((R&D[Title/Abstract]) OR innovation[Title/Abstract]) AND emerging infectious diseases[Title/Abstract]”.

We prioritized systematic reviews, followed by peer-reviewed articles, governmental and international organization reports and lastly media articles. Our search resulted in a total of 71 publications. Articles were reviewed until information saturation was reached.

This document, explains the drivers behind current R&D incentives and summarizes key alternative incentives that have been proposed to improve the pharmaceutical R&D system. Pandemic preparedness, emerging diseases that have not yet turned into pandemics as well as neglected tropical diseases share similar features of being unattractive to big pharma because of a lack of viable market at the time[3]. Most of the literature on pharmaceutical R&D reform has focused on existing neglected tropical diseases that affect the world’s poorest populations. Less is known about the best strategies to address emerging pathogens that might turn into pandemics in the future. Building on the learnings from neglected tropical diseases, recommendations for action for academia, public sector, biotech industry, international organizations, philanthropists and governments of developing and emerging countries were developed, to inform strategies for future pandemics.
Emerging infectious diseases are defined as “outbreaks of previously unknown diseases, known diseases that are rapidly increasing in incidence or geographic range in the last 2 decades, or persistence of infectious diseases that cannot be controlled”[8].

Investment in pharmaceutical R&D is not based on priority public health needs or the burden of disease[3,7]. The current market-driven system incentivizes pharmaceutical companies to develop the most profitable products rather than the products that would have the greatest public health impact or therapeutic benefit. There is a need to alter the R&D incentive structure so that emerging infectious diseases that might turn into pandemics in the future will be prioritized by the various entities involved: public funders, philanthropists, private drug companies, and international organizations.
Emerging Infectious Diseases Not a New Problem

Emerging infectious diseases are challenging because it is not possible to predict the nature of the disease in advance and when and where it will break out. Over the past 2 decades, the world experienced 5 outbreaks and in none of the situations was a vaccine available in time to mitigate the impact: Severe acute respiratory syndrome-related coronavirus (SARS-CoV) in 2003–2004, H1N1 “swine flu” in 2009, Middle East respiratory syndrome coronavirus (MERS-CoV) since 2012, Ebola virus in 2014–2016 and from 2018 onward, and Zika virus in 2015–2016[9].
Timeline

Pathogen detection, WHO public health emergency of international concern (PHEIC) declaration, and vaccine development events during the H1N1, Ebola and Zika outbreaks.

H1N1 emerged in April 2009. Within four months of the WHO declaring H1N1 a public health emergency of international concern (PHEIC), four vaccines were FDA-approved and shipped globally. However, it was already too late. The death toll was estimated at 151,700 to 575,400 worldwide during the first year of the pandemic[9].

Ebola emerged in 2014 in a West African village and quickly spread to neighboring countries. It was declared a PHEIC by WHO in August 2014 and ended in December 2015. Even though Ebola was a familiar pathogen and 15 vaccines had been in pre-clinical development for over a decade, it took a year to initiate clinical trials of the first vaccine[10]. By the time positive phase III trial results were reported, the Ebola epidemic had ended. Estimated death toll was 11,300[9].
Zika was discovered decades before it re-emerged in 2016. It had not been considered a public health priority because it was thought to cause only sporadic and mild symptoms in Africa and Asia. In 2015, Zika broke out in Brazil and was later declared a PHEIC in February 2016. Two companies partnered with the US government to develop vaccines, however not in time; Zika ended in November 2016. More than 2000 babies were impacted with irreversible microcephaly or other neurological disorders[9].
COVID-19 Pandemic

More than twelve drug companies are currently racing to develop a COVID-19 vaccine[11] – which would need at least 12 to 18 months to be ready for regulatory approval and even longer to be disseminated on a mass scale and reach developing countries; similarly, many companies are testing and repurposing existing drugs to treat COVID-19. Even though COVID-19 is a novel strain of the coronavirus, the process of developing a vaccine or drug could have shortened if earlier pursuits of relevant R&D had not been discontinued. During the SARS-CoV and MERS outbreaks, several vaccine candidates were in the development pipeline but were eventually discontinued because both diseases were rapidly controlled by governmental measures resulting in the fading of the urgency of the situation. A SARS-CoV vaccine was finally developed in 2016 (more than 10 years after the outbreak), however, did not find private or public funding for human clinical trials due to the absence of critical need and thus the disappearance of a viable market[11].

Since the market for a COVID-19 drug became evident over the past 3 months, 200 drugs have undergone clinical trials, 10 out of 100 candidate vaccines are in phase I-II clinical trials, and $5.5 billion has been invested for the COVID-19 response by the public sector and philanthropists.
Current R&D System: Challenges, improvements and incentives

Drivers behind current R&D incentives

Several reasons have led to a mismatch between pharmaceutical industry priorities and actual need:

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<th>Profit motive</th>
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| Investment in R&D is highly dependent on expected profit. Pharmaceutical revenue is a product of price and volume. Consequently, drug companies are encouraged to set the highest prices possible to maximize profits[7,12]. Combined with patents that prolong the product’s market exclusivity and delay generic competition, this system results in undesirable consequences: patients lack access to the drug if they cannot afford it, and products that impact rich populations are the most likely to be developed even if there are already available treatments and the new product is only slightly different (example: me-too drugs)[7,13].

There is little incentive for drug companies to develop products for diseases that do not have large markets or that affect populations with low purchasing power (low and middle-income countries). Outbreaks are unpredictable, often start in low-income countries, and may not last long enough to make up a sufficient market for a new drug[3]. In addition, vaccines are costly to develop because they incur, on average, a 94% risk of failure[9] and typically cost up to $1 billion in capital investment[10]. Therefore, companies face high uncertainty and limited data when assessing the feasibility of developing products for emerging infectious diseases that have not yet turned into large-scale outbreaks or for neglected diseases that impact low-income populations, and the opportunity cost of capital for pharmaceutical companies is high given that they can invest the resources to develop new products for high-income markets[14]. |
Mismatch with R&D processes

Governmental and philanthropic R&D funding does not align well with typical R&D processes. Drug and vaccine development processes are lengthy and risky; scientists often reach dead ends with one investigation but discover leads to another promising product. Current R&D grants are often short-term (5 years), unpredictable and earmarked to specific diseases, therefore not flexible enough to accommodate for the inherent fluidity of the drug development process[14].

The experiences with the Ebola, Zika and H1N1 outbreaks highlighted that public funding to support vaccine development in advance of the outbreak is limited, funding tends to be short-term and stop after the outbreak is over and often covers a limited portion of the development costs[9].

Mismatch with global health priorities

R&D that is needed does not always reflect R&D that is undertaken. In 1990, a study demonstrated that only 10% of global R&D expenditure was allocated to diseases that comprise 90% of the global burden of preventable deaths; which is known as the “10/90” gap[7]. This mismatch is still relevant today; in 2016 low-income countries received only 0.01% of the global annual funds for R&D, while 85% of the grants were allocated to research in the U.S[15].

Lack of a global forum

The benefits and costs of R&D should be shared globally among nations. However, there is currently no such global forum that can coordinate global efforts, continuously map R&D priorities, and hold nations accountable for their fair share of early-stage R&D investments[7].
Improvements to date:

The establishment of the WHO R&D Blueprint and the Coalition for Epidemic Preparedness Innovation (CEPI)

The WHO formed the R&D Blueprint after convening a broad global coalition of scientists and regulators. The WHO R&D Blueprint is “a global strategy and preparedness plan that allows the rapid activation of R&D activities during epidemics” [16]. Under the R&D Blueprint, the WHO publishes and annually updates a list of priority emerging infectious diseases for which there is a need for accelerated R&D. Diseases are prioritized based on the severity of the public health risk posed and the lack, or insufficiency, of countermeasures against them.

After the overwhelming impact of the Ebola epidemic, CEPI was established in 2017 as a global partnership between public, private, philanthropic, and civil society organizations. Its mission is to finance, coordinate, and accelerate the development of vaccines against emerging infectious diseases and enable access to these vaccines for people affected by outbreaks[10]. CEPI was originally funded by Norway, Japan and Germany, the Bill & Melinda Gates Foundation and the Welcome Trust, and has so far financed eight of the leading COVID-19 vaccine candidates currently in clinical trials. CEPI estimates that developing three candidate vaccines for COVID-19 will require a $2 billion investment[17], which will require funding from all available sources[18–20].
The WHO R&D Blueprint list included 8 pathogens: Crimean-Congo hemorrhagic fever (CCHF), Ebola virus disease and Marburg virus disease, Lassa fever, Middle East respiratory syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS), Nipah and henipaviral diseases, Rift Valley fever (RVF), Zika and an unknown Disease “X”[21].

As of December 2019, CEPI had committed to investing up to $706 million in vaccine development. This includes 19 vaccine candidates against its priority pathogens (Lassa fever virus, Middle East respiratory syndrome coronavirus, Nipah virus, Chikungunya, Rift Valley fever) and three vaccine platforms to develop vaccines against Disease X, a novel or unanticipated pathogen.
R&D financing

Neglected infectious diseases affecting primarily developing countries and emerging infectious diseases comprise unattractive markets to pharmaceutical companies and are largely financed by philanthropic donors instead.

Traditionally, most R&D financing has come from two sources[14,18]: 1) governments (the NIH in the US, the Medical Research Council in Great Britain, and the Agence Nationale pour la Recherche Scientifique in France) provide grants to academic researchers to develop the early-stage basic science, 2) private for-profit drug companies invest in promising molecules and run the product through additional clinical trials up to final approval and manufacturing.

Therefore, the current system relies heavily on market incentives, with 60% of all R&D funding coming from for-profit firms[7]. Even though public and philanthropic donors contribute to the remaining 40% of funding[7], it is the private firms that ultimately carry the product through phase III clinical trials determining whether the product comes to market. Among the funds invested in the R&D Blueprint pathogens in 2016, Ebola virus disease received 43%, Zika virus disease received 32%, and SARS-CoV received 8%[22], while coronavirus infection research was allocated only 0.6% of the grants[15].

In the context of neglected diseases, the private sector chips in a considerably smaller percentage: in 2018, private drug firms contributed only 17% of the total of $5 billion invested by all funders in basic R&D for neglected disease, while the public sector and philanthropic organizations contributed 64% and 19% respectively[3].
Market-driven R&D incentives

Market-driven incentives to invest in developing products that may not have a viable market otherwise do exist, however, they do not address the inherent issue of tying investment motivation to expected revenues. They also do not include price controls to ensure affordable access to the end product.

Examples of incentives provided to pharmaceutical industry from the U.S. to encourage R&D:

- Empirical evidence shows that offering a tax credit for R&D expenses increases private R&D investment[23]. The Orphan Drug Tax Credit, an incentive offered within the U.S. Orphan Drug Act (ODA) to encourage the development of rare disease drugs, has been successful, albeit with caveats that allow companies to game the system. While the number of orphan drug FDA approvals in the US increased from 1 to 503 over a 35-year period [24], the ODA has also allowed companies to seek orphan status for blockbuster drugs treating very common conditions that affect large patient populations rather than true rare diseases, while 90% of 7000 rare diseases still lack any treatment[25].

- The Priority Review Voucher (PRV) program, originally enacted in 2007, allows the FDA to grant a PRV to the developer of a drug or vaccine for a neglected disease of a low-income population[26]. The PRV is valued at $100 million to $300 million and can be transferred to another product within the same company’s portfolio or to another company to speed up FDA review by 4 months[14,27]. Between 2007 and 2019, 31 PRVS were granted by the FDA, starting with a malaria drug[14]. The evidence on PRV’s success is mixed; several studies found little effect of PRV on R&D investment, and researchers have cautioned about the risks of PRVs[27,28]. However, a recent Government Accountability Office report found that all drug companies surveyed in the report considered PRV as a criterion in their drug development decision-making[29]. The main risks of PRVs are that as more PRVs are granted, PRVs will decline in value [29], and PRVs might allow for drugs that do not have clinical urgency to be fast-tracked through the FDA which may compromise the adequate assessment of safety and efficacy[29].
Even though market-driven incentives such as tax credit and PRV may achieve ‘short-term gains’, evidence has shown that they suffer from a variety of unintended consequences and do not lead to sustainable improvement[27,28]. More importantly, they are not sufficient to get pharmaceutical companies to invest in vaccine development. A different set of incentives, separate from expected profit, is needed to ensure a sustainable stream of R&D[13].
Alternative R&D Incentives

More than 40 incentives were identified in the literature synthesis conducted that are typically characterized into “push” and “pull” categories[6,14,26,30–32]. Push mechanisms help subsidize early-stage product development; firms receive the incentive regardless if their R&D effort results in a product. Pull mechanisms guarantee an amount of revenue for the drug company after the product is developed, ensuring that investments are only made in productive R&D.

In the context of pandemics, the problem with push and pull incentives is that past push incentives did not help avert COVID-19’s impact or any of the previous outbreaks over the past 2 decades and pull incentives are limited by the inability to predict the market size before the outbreak has occurred and could be wasteful in the absence of an outbreak. Previously proposed frameworks that have evaluated the viability of different incentives have stressed on market criteria: the incentive should improve the overall net present value for new projects, enable greater participation of private industry, and facilitate cooperation and synergies across players in the market[26].

Three of the most promising mechanisms identified in the literature were ones that met most of those criteria: Product Development Partnerships (push), large cash prizes (pull), and advance market commitments (pull) (Annex 1). These mechanisms can be used as part of a comprehensive approach to improve the proactivity of the R&D system in battling emerging infectious diseases and future pandemics.
The review of literature revealed that most studies are descriptive and empirical evidence on the effectiveness of different R&D incentives is scarce[6,14,26,30–32]. No single option was deemed superior to all others - most studies recommended implementing a combination of different and complementary incentives: push mechanisms to subsidize early-stage research, and pull mechanisms to bring products to market[6,26,33].

Recommendations

The current R&D model in the pharmaceutical industry is highly market-driven and misaligned with public health needs. The COVID-19 pandemic is an opportunity to establish a new sustainable R&D financing system for a wide range of emerging as well as neglected infectious diseases[34-36].
Advocating for Alternative Incentives for a Proactive Pharmaceutical R&D System
Academia

- Investigate which push/pull mechanisms are most promising in the context of emerging infectious diseases.
- Conduct qualitative interviews with key stakeholders, including pharmaceutical executives, to identify and explore the barriers to implementation of promising mechanisms.
- Conduct quantitative economic modelling studies to estimate the impact of the implementation of promising interventions.

Public sector

- Public agencies of high-income countries - the NIH in the US, the Medical Research Council in Great Britain, and the Agence Nationale pour la Recherche Scientifique in France - should continue to invest in grants (push mechanisms) to subsidize early-stage research and encourage the participation of small to medium biotech entities and academic researchers.
- Increase public funding for large clinical trial costs run by larger private drug companies.
- Expand public funding for important Product Development Partnerships (PDPs) already established - like CEPI - to ensure continued and sustainable work towards proactive R&D for emerging pathogens (push mechanism).
- Offer prizes and advanced market commitments, in collaboration with philanthropists and international organizations, to incentivize the late-stage development of partially developed vaccines and therapeutics[6] (pull mechanism).
Biotech Industry

- Prioritize R&D incentives for the list of emerging pathogens under the WHO R&D Blueprint.
- Invest in rapid-response platforms and innovative technologies with the potential to fast-track the development and manufacturing of vaccines and therapeutics against previously unknown pathogens[37].
International organizations

- Foster a more open and transparent environment for research to take place even if protected by intellectual property[3] by promoting open data source platforms that facilitate communication and sharing of technologies, data and materials[38]. Such agreements share risks and reduce duplication of efforts. The Global Research Collaboration for Infectious Disease Preparedness is one example.

- Establish and manage open-licensing agreements or voluntary patent pools to share manufacturing rights for pandemic technologies. Examples include the Medicines Patent Pool and the recent Open COVID Pledge[39,40].

- Strengthen WHO’s role as a convener, to coordinate the R&D development efforts across scientists, funders, developers and regulators across the world.

- Strengthen the WHO Global Observatory on R&D Financing which provides a useful platform for monitoring investments in R&D financing, to further facilitate information sharing, priority setting, prevention of error duplication and coordination of various R&D funding mechanisms globally[41].

- Consider establishing a “pooled fund” of countries’ and funders’ donations governed by a distinct entity allowing the sharing of R&D risks and cost, and to help finance prizes or advance market commitments. Among the proposed pooled funds are a global R&D fund and a Global Vaccine Development Fund[41].

- Ensure that all research entities abide by the standards set in the WHO roadmaps of the priority pathogens.

- Promote R&D and capacity building in LMICs where emerging infectious diseases usually originate.
Philanthropic organizations

- Reinforce investment in existing PDPs like CEPI based on the WHO Blueprint priority pathogens[21,42].
- Guarantee markets in LMICs through AMCs for therapeutics developed in other developing countries instead of waiting for developed countries to offer what is left of their therapeutic products[6].
- Offer prizes for priority pathogens for final products produced in high and low income countries[6,41].
- Direct R&D efforts of universities, firms and public research institutions to address all potential pathogen threats.
Governments of developing and emerging countries

- Share responsibility with developed countries by contributing to funding R&D organizations or to pooling funds. These assigned budgets should be mandatory yet based on each country’s capacity[41].

- Call on national research entities to invest in emerging infectious disease research since those usually emerge first in LMICs[43].

- Coordinate local R&D efforts to ensure synergies[40].

- Encourage the sharing of data and pathogen strain among research institutions within a country[42].

- Endorse surveillance and reporting of new emerging diseases and possible outbreaks[44].
### Annex 1

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<th>Mechanism</th>
<th>Product Development Partnerships (PDP): collaborative agreements to share R&amp;D risk and reward between the public and philanthropic sectors and private drug companies</th>
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| **Description & examples** | - PDPs are non-profit organizations that play the role of mediators between the public, private and philanthropic sectors [14,26].  
  - Governmental and philanthropic grants supply R&D funding for specific products. The arrangement usually obligates the drug company to provide the end product at an affordable price to developing countries. Historically, each PDP has focused on a specific neglected disease, and worked on taking the new product from inception to pre-clinical and clinical research so that “efficacy and feasibility of large-scale manufacturing are demonstrated to both companies and developing country purchasers”.  
  - A successful example is the meningitis vaccine project which supported the development of the vaccine and its scale-up in African countries[12]. Other examples of PDPs include the Drug for Neglected Disease Initiative (DNDi), Medicines for Malaria Venture (MMV), the Global Alliance for TB Drug Development, and the International AIDS Vaccine Initiative (IAVI)[14,30].  
  - Such partnerships are already taking form in the race of developing a COVID-19 vaccine; GSK is sharing its adjuvant technology with the University of Queensland in Australia, which is funded by CEPI[34]. |
| **Benefits** | - PDPs allow the funder to specify the R&D priority and guide development, pool expertise, and appeal to small drug companies that may lack sufficient capital[26,30].  
  - PDPs are not dependent on the market size of the product[26,30]. |
| **Potential risks** | - The financial risk lies heavily on the funder, coordinating and managing the interests of multiple stakeholders in the PDP can be challenging, and  
  - PDPs have been criticized for lack of sufficient transparency and clear governance structure[26,30] and for investing in modifying existing treatments rather than inventing new ones[30]. |
| **Uncertainties concerning future outbreaks** | - The applicability of PDPs has been examined mostly in the context of existing neglected diseases; it is unclear how well they would function in the context of future pandemics not yet known.  
  - It is unclear to what extent private pharmaceutical companies would engage if PDPs’ affordable/equitable access policies threaten intellectual property rights. For example, the original equitable access policy of CEPI mandated that CEPI would have access to pre-existing intellectual property used in developing the vaccine to ensure it could exercise its “step-in” rights when needed (the right to license and use intellectual property developed with CEPI funds for vaccine production). This provision had to be revoked later in December 2018 after the objection from J&J, Pfizer and Takeda. |
**Mechanism** | **Prize: multi-million cash reward for the development of a new product**
---|---
**Description & examples** | • Prizes have been frequently proposed as a mechanism to reward the development of new drugs or vaccines that are therapeutically important but may not be commercially lucrative[7,14,39,45].
• The prize would be payable only on the condition that the firm makes the vaccine available to patients at low or zero cost, and generic competitors would be allowed to enter the market as soon as the original product is launched[45].
• Prizes are particularly attractive in the context of neglected diseases or for solving scientifically challenging problems (for example, proof of concept for an AIDS vaccine)[7,14,45].
• A prize can be a lump sum payment granted upon the delivery of the first successful product or a series of incremental milestone prizes paid at various stages of the R&D process[26].
• Some have proposed a prize of $500 per person for a COVID-19 vaccine; assuming full uptake in the U.S, the total cost to the federal government would amount to $165 billion, less than 3.5% of the federal budget[46].

**Benefits** | • A prize allows funders to direct the R&D agenda, rewards only successful products, and presents a strong incentive to drug developers to carry a product through phase III clinical trials[12,45].
• In the absence of monopoly patent rights during a pandemic, large cash prizes offset the disincentives for drug companies to invest in a vaccine[2].
• Prizes may not require substantial changes in regulatory infrastructure[26]; in 2010, the U.S. Congress passed legislation (15 U.S. Code § 3719. Prize competitions) for federal agencies to run prize competitions and since then, over 1000 prize competitions amounting to more than $300 million have been administered[46].

**Potential risks** | • There is difficulty in pre-specifying the product and in setting the appropriate amount; ideally it would be based on the product’s therapeutic value[12,45].
• Most of the risk is borne by the drug developer, thus might leave out small drug companies that do not have the initial funds to start the R&D process[26].

**Uncertainties concerning future outbreaks** | • Given the huge uncertainties related to future pandemics and the high risk of failure in vaccine development, it is unclear how pharmaceutical firms perceive the potential value of prizes and what their barriers to up-take are.
Mechanism | Advance Market Commitments (AMC): an agreement to purchase the product upon successful development at a pre-set price
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Description & examples | • An AMC represents an agreement in which a funder guarantees the drug manufacturer that they will purchase the product at a pre-set price[14,26,30] once the product is successfully developed.
• Using AMCs funded by the Gates Foundation and partners, two pneumococcal vaccines have been developed and delivered to more than 183 million children across 59 countries[46].
• GAVI relies heavily on AMCs to provide medication to low-income countries for discounted prices[47].

Benefits | • AMCs minimize risk for the drug developer by guaranteeing a minimum viable market[26,48].
• AMCs provide drug companies with a sense of security while ensuring affordable access to patients in need[26,48].
• The payment is made only once a successful product has been developed, thus minimizing the risk of failure for the funder[26,48].

Potential risks | • Similar to prizes, the challenge lies in determining the end-product specifications beforehand – which is especially challenging in the context of future pandemics – and in setting the appropriate price - too low would be insufficient to stimulate companies to develop the drug, and too high might be an inefficient use of resources[26,48].
• AMCs assume that companies have the necessary upfront funding to develop the drug, which is often not the case for small drug companies[26,48].
• While AMCs guarantee a purchase price, they have not typically guaranteed a purchase volume, which leaves drug companies partially dependent on sales volume to ensure profit maximization[26].

Uncertainties concerning future outbreaks | • A deeper understanding is needed to formulate AMCs to develop products for diseases that have not yet emerged.
• More clarity is needed about the types of technologies for which AMCs would be appropriate, for example establishing ways to predict which animal pathogens are most likely to produce zoonotic diseases, platforms that would speed up vaccine development and testing, and therapeutic products that could work for a wide array of diseases[49].
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