

Vaccine Platforms: State of the Field and Looming Challenges



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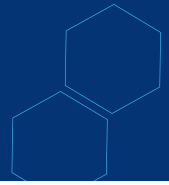
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Executive Summary



Background and Purpose of Report

To date, the pharmaceutical response to emerging infectious diseases and bioterrorism has been characterized by a “one bug, one drug” approach, where specific medical countermeasures—effective vaccines and therapeutics—are developed, manufactured, and deployed. However, over the past several years, platform technologies have been developed that could make it possible for multiple vaccines to be more rapidly produced from a single system.

The Johns Hopkins Center for Health Security conducted this project to elucidate the promise and challenges of vaccine platform technologies. The overarching aim of the project was to develop a state-of-the-art conceptual understanding of various vaccine platform technologies, with special attention to how they may speed development of vaccines for global catastrophic biologic risks (GCBRs) and emerging infectious disease outbreaks. This report describes major scientific and policy issues related to platforms and how they are understood in government, academia, and industry, and it provides recommendations aimed at helping realize the potential benefits of vaccine platform technologies.

Findings

Definitions of Vaccine Platform Technologies Vary

Among the various vaccines that currently exist or are in development, the criterion that classifies each vaccine candidate as a “platform”—or not—is unclear. For our project, a technology was defined as a platform if an underlying, nearly identical mechanism, device, delivery vector, or cell line was employed for multiple target vaccines. Platforms have the potential to lead to the development of multiple vaccines with one substratum-like component being amenable to the development of multiple disparate vaccines; they are pluripotent. There is clear cachet, from an investor and public relations standpoint, in being labeled a platform, irrespective of whether the underlying process is truly platform-based. As long as objective definitions and conceptual clarity are lacking, analyzing the promise and needed policy and science around platforms will be challenging. A sharper understanding of what constitutes a “platform” technology is needed.

A Spectrum of Platforms

There exists a spectrum of attributes possessed by certain vaccine technologies that render a vaccine more or less platform-based. The process under which a vaccine is manufactured qualifies it as platform-based. If it has the capacity to form the basis of myriad other vaccines using some conserved structure, it can be classified as a platform. The spectrum of different platforms ranges from viral vectored vaccines to nucleic acid vaccines. Thinking of platforms as being situated on a spectrum helps to minimize definitional disputes, as there are different variations of platforms. Overly restrictive definitions—such as limiting platforms to just viral-vectored vaccines—could become research and development obstacles.

Regulatory Agencies License Products, Not Platforms

Despite the potential manufacturing flexibility that platforms offer, regulatory agencies approve products, not platforms. Such agencies evaluate submissions as whole products intended for human use rather than as components. Each product submission, irrespective of its relationship to an existing platform, is viewed as a whole. But with increased use of a specific technology, regulatory agencies may over time become more comfortable with how such a technology works, the overall safety and efficacy profiles of the products produced, and history, allowing more rapid approval and less onerous approval decisions with each subsequent submission.

Rate-limiting Elements of Vaccine Development Can Be Diminished with Platforms

Much of the current discussion on the benefits of platforms centers disproportionately on aspirations that the regulatory process will be streamlined, but there is no plan for such a streamlining at this time. However, even without any new, special regulatory considerations being given to platform-based vaccines, the speed of the general platform-based approach—even if restricted to the pre-investigational new drug (pre-IND) phase—will likely have a significant measurable impact on vaccine availability.

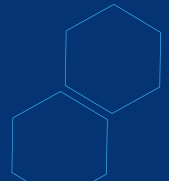
Platform Vaccine Technologies Could Minimize Risks Associated with Emerging Infectious Disease Countermeasures

Because a platform vaccine technology can be leveraged for multiple uses—both for emerging as well as routine infectious diseases—a platform can be a means of achieving economies of scale and lowering the risk of ventures in emerging infectious diseases. Platform vaccine technologies are a sustainable pluripotent infrastructure that can be applied to emerging infectious disease vaccines with minimal added financial risk, thereby diminishing costs of vaccine development.

Recommendations to Realize the Full Potential of Platform Vaccine Technologies

- Whether a vaccine receives a designation of being “platform-based” should not be a factor in the speed with which it is developed. Increasing the availability of vaccines (platform- and nonplatform-based) should be the overarching policy goal. Because of the enhanced awareness, value, and funding opportunities related to the ability to describe a vaccine as platform-based, companies may divert resources to making the case that their vaccine meets the criteria to be called a platform. By conceptualizing platforms as lying on a spectrum, and recognizing that more than one variety of platform technology exists, this type of strategic positioning may be minimized.
- The anticipated development speed of platform-based vaccines should not assume that regulatory streamlining will occur. The rapidity of development using platforms may largely be the result of the relative ease in reaching pre-investigational new drug (pre-IND) stages of development and may be very consequential even with standard regulatory timelines post-IND.
- The traditional approach to vaccine R&D should not be entirely supplanted by platform approaches. While platform-based approaches might be the future of vaccine development for many targets, there are infectious disease targets that currently exist or will likely emerge for which a traditional vaccinology approach might be most likely to succeed.
- An mRNA-based vaccine platform technique appears particularly promising in terms of ease of manufacture, adaptability to various targets, and biological delivery.
- Platform vaccine technologies, like all other emerging infectious disease (EID) medical countermeasures (MCMs), require special considerations given market conditions. Despite the economies of scale achievable via platform-based approaches, EIDs, by their very nature, will never represent a major market with large financial rewards and minimal opportunity costs. Dedicated programs by governments, nongovernment organizations, and philanthropies will likely play major roles for the foreseeable future in the development, uptake, and use of vaccine platform technologies.

Introduction



The prospect of severe infectious diseases with pandemic potential has triggered significant interest in developing the capacity to rapidly accelerate the development and manufacturing scale-up of medical countermeasures (MCMs) against such threats.¹⁻³ Among MCMs, arguably the highest impact interventions involve vaccines. Vaccines can be used in various ways to dampen or extinguish an outbreak—and ultimately to prevent such outbreaks from occurring in the first place.

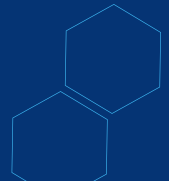
The 2018-19 outbreak of Ebola virus disease in the Democratic Republic of the Congo (DRC) has seen vaccines used as postexposure prophylaxis (PEP) of contacts of cases, as a preventive measure in high-risk individuals, and to protect geographically adjacent areas at risk for spread. This vaccination campaign, which has been credited with reducing case counts, has been made possible by the availability of a vaccine in sufficient quantities to permit such activities.^{4,5}

Despite their manifold benefits to both public and individual health, the development of vaccines against emerging infectious diseases is fraught with unique challenges, including a limited market size, long development timelines, high rates of clinical trial failure, a unique legal environment, and a challenging regulatory environment (as vaccines are given to healthy individuals).

While the “one bug, one drug” approach has dominated MCM R&D, many policymakers and technical experts have advocated for the prioritization and development of platform technologies that would offer the potential for far greater speed and flexibility in vaccine development. Regardless of the technical approach employed, platform vaccine technologies can use a common system to generate multiple separate antigens to serve as potential vaccine candidates.^{6,7} This process itself is already an important potential means of improving vaccine development.

Juxtaposing the urgent need for vaccines to combat emerging infectious disease outbreaks—including those with the potential to become global catastrophic biological risks (GCBRs)—with the oft-cited potential of vaccine platforms has prompted many stakeholders and funding agencies to prioritize the development of vaccines derived from platform vaccine technology. However, there has been little in-depth analysis of platform vaccine technologies as a distinct class of technologies and approaches, with the aim of understanding their proposed role, their financial attractiveness, and the regulatory structure with which they will interface.

Purpose, Methods, and Analysis



Purpose

The Johns Hopkins Center for Health Security conducted this study to develop an expert assessment of the promise of and challenges posed by vaccine platform technologies. A major aim of this study is to inform vaccine preparedness activities and national and international policies that may seek to rely on vaccine platform technologies in ways that contribute to the development of new vaccines with epidemic and pandemic potential.

Methods and Analysis

Review of Published Literature and Previous Reports

The Center project team surveyed current biomedical literature on the topic of vaccine platform technologies. The literature review encompassed all classes of platform vaccine technologies, including viral-vectored platforms, cell line platforms, and nucleic acid–based platforms. The literature review was accomplished with extensive PubMed searches on these subjects. Relevant US government policy and strategy documents were also reviewed.

Informational Interviews

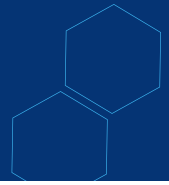
The Center project team conducted a number of informational interviews of leading experts in the field to receive feedback regarding the scope of the project and preliminary assessments made by the project team, and to gauge interest in attending a workshop on the topic.

Vaccine Platforms Workshop

The Center project team completed a preliminary analysis that synthesized the results of our literature review. Those findings were used to design and facilitate a meeting held on December 11, 2018, at the Johns Hopkins Center for Health Security in Baltimore, MD. The purpose of the meeting was to gain additional insight and input into the project analysis, examine assumptions, and test possible recommendations. Participants included representatives of domestic and international companies, industry trade groups, and the federal government; consultants; and other independent subject matter experts. Attendees are listed in Appendix A.

Conclusions

This final report presents the Center's assessment of the promise and challenges of vaccine platform technologies, informed by our literature review and the views of workshop participants or sponsors who met on December 11, 2018, at the Center. The findings and recommendations in this report are those of the Center and do not necessarily reflect the views of those who were interviewed or who attended the workshop at the Center.



Finding 1: Definitions of Vaccine Platform Technologies Vary

The term *platform* has become a buzzword that is applied to many different vaccines that may be derived from widely divergent technological approaches. Use of the term *platform* in reference to a vaccine can create cachet for potential investors and policymakers. This is because platforms have been associated with breakthrough technologies, innovation, and the potential for accelerated development timelines. Indeed, some funders automatically prioritize funding of vaccines that are made using platforms.

The concept of a platform, when applied to vaccine technologies, does refer to specific types of vaccines and cannot be objectively applied to all vaccines. If one conceives of a platform as simply a “plan” or “design,” any vaccine, or indeed any product, is a platform, rendering the term useless.

However, when applied to vaccines or other medical products, the Webster’s definition is particularly applicable: “a vehicle used for a particular purpose or to carry a usually specified type of equipment.”⁸ The first uses of the term *platform* with respect to vaccines related to a viral vector carrying the antigen of choice (“equipment”). The first PubMed listing using the term *platforms* refers to the use of polymer delivery systems for vaccines, reflecting the original understanding of platforms as referring to delivery vehicles.⁹ The World Health Organization (WHO) definition of a platform is consistent with this usage:

a production technology with which different viral vectored vaccines are produced by incorporating heterologous genes for different proteins into an identical viral vector backbone.¹⁰

Jargon terms such as *plug-and-play* and *cartridges* reflect that general understanding of the concept.

As vaccine development continued, platforms that are not based on a viral vector began to emerge. Nucleic acid vaccines (DNA and RNA), which are recipe-like platforms, as well as cell lines that can be coupled to viral expression systems can also be thought of as platforms because the technology involved can be used in an almost similar fashion for multiple targets.

While definitional wrangling might seem irrelevant, it is an important consideration, because labeling a vaccine “platform-based” may predispose it for greater attention and funding. While using the term loosely might facilitate vaccine development, it is also important to recall that the application of the adjective *platform* to vaccines originated to distinguish certain vaccines from traditional vaccines, including even from multivalent vaccines such as pneumococcal conjugate vaccines, in which a carrier protein is used to enhance immunogenicity.

Similarly, molecular “clamps” to stabilize viral protein targets are more akin to adjuvants that can be used in multiple vaccines than true platforms.¹¹ Adjuvants and other immunogenicity-enhancing agents are best thought of as supplemental ingredients to a vaccine and not the true delivery vehicle for the vaccine. The belief that all novel vaccines are derived from “platforms” vitiates the entire purpose of developing such terminology. Vaccine technologies such as the pneumococcal conjugate vaccine carrier protein or traditional multivalent vaccines are powerful and crucial for public health, but they do not meet the definition of platforms.

Finding 2: A Spectrum of Platforms

Aside from definitional issues, it is important and clarifying to view platforms as lying on a spectrum. The spectrum can be thought of as moving from viral vectored vaccines on one end to nucleic acid vaccines on the other. In essence, the spectrum moves from delivery vehicle–focused vaccines, such as viral-vectored vaccines, to more recipe-like vaccines with nucleic acid vaccines. To label a vaccine platform “recipe-like” refers to the fact that a similar process can be used to make varied vaccines using a common technology (eg, nucleic acid synthesis machinery or printers) that requires little alteration in process or components when changing among targets. Figures 1 and 2 illustrate a conceptual map of various existing platform technologies.

Figure 1: A spectrum of platform technologies

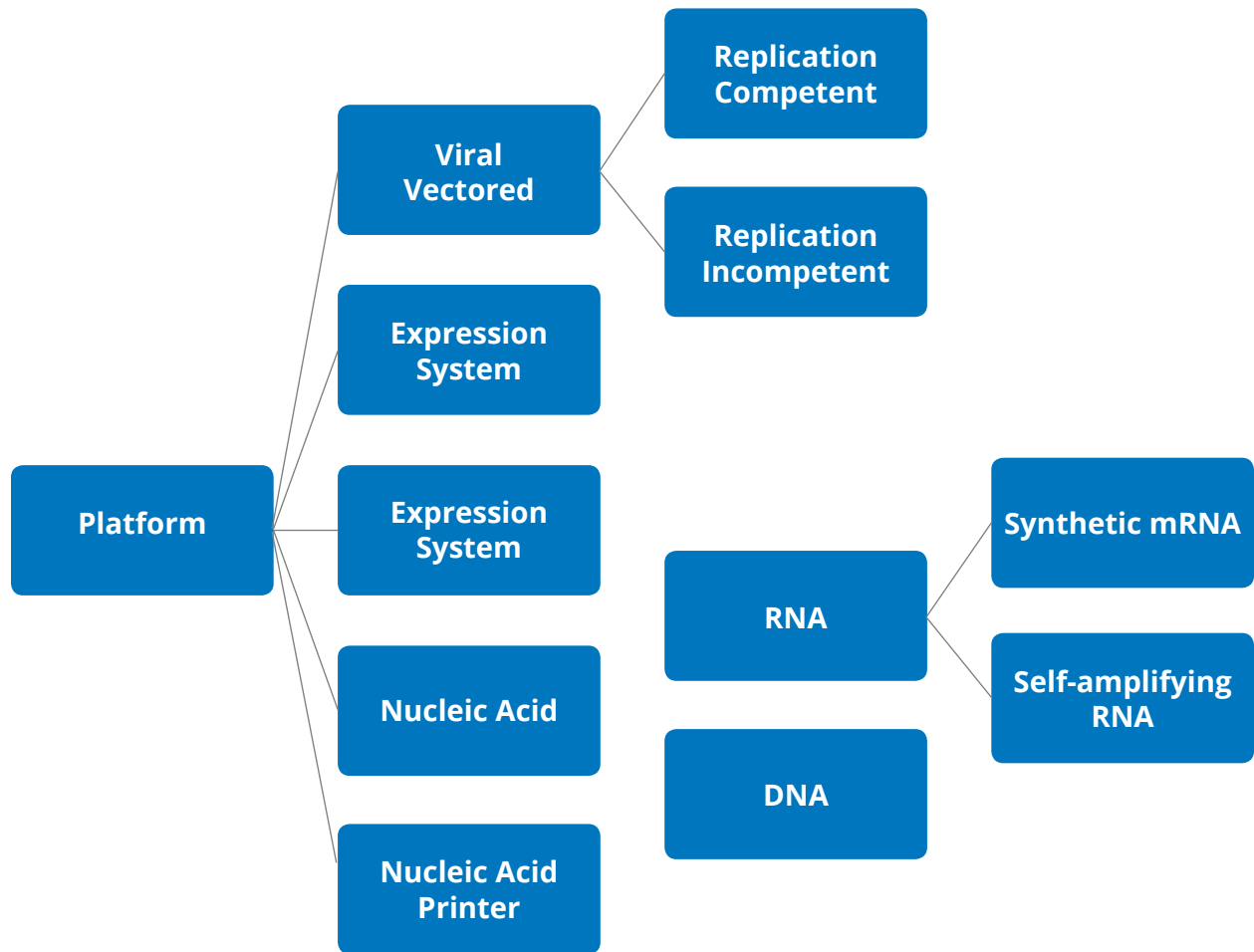


Figure 2: Examples of how existing platforms can be classified

Viral Vector	Expression Platform	Nucleic Acid	Other
VSV (RC)	Baculovirus Expression System	Synthetic mRNA	Nucleic Acid Printer
ChAd (RI)	Tobacco Plant Cells	DNA	
17D (RC)		Self-amplifying RNA	
MVA (RI)			

ChAd – Chimp Adenovirus, RC – Replication Competent, RI – Replication Incompetent

The spectrum can also be seen to include disparate approaches such as protein-based vaccines and nucleic acid vaccines.

It might be argued that traditional vaccines such as the standard quadrivalent inactivated influenza vaccine should be termed a platform since the manufacturing process changes little from year to year. However, this is a misapplication of the term. With standard influenza vaccines, there is no identical delivery vehicle employed with different seasonal iterations, but a novel construction of a subunit vaccine using a similar manufacturing process. By contrast, influenza vaccines manufactured using the baculovirus expression vector system (BEVS) and modified vaccine Ankara (MVA) are true platforms.^{12,13}

In the realm of viral-vectored vaccine platforms, there are important distinctions between approaches. The chief distinction is whether the viral vector delivered to the vaccinee is replication-competent or replication-incompetent in humans. Replication-competent viruses, because of their need to fully replicate in order to express the protein antigen of interest, are best understood as true infections akin to live-attenuated vaccinations. For example, the vesicular stomatitis virus (VSV)–vectored Ebola vaccine involves the expression of the Ebola glycoprotein after replication of the VSV *in vivo* post-injection. As such, a productive infection is initiated and can precipitate adverse effects related to the infection. In contrast, a replication-incompetent vaccine does not have this requirement and is replication-defective in humans; it does not establish productive infections. Such a division is important biologically and consequently becomes relevant to the product's safety and efficacy, and hence to regulatory actions as well.¹⁴

Nucleic acid vaccines can be subdivided into DNA and mRNA categories. While their synthesis methods may be very similar, DNA vaccines have become less favored because their efficacy requires passage across 2 compartments, the cell membrane and the nuclear membrane, which is challenging from a delivery perspective.¹⁵

mRNA vaccines do not require such a complicated journey and must merely make it to the cytoplasm of the target cell. mRNA vaccines can be further subdivided into self-amplifying mRNA (sa-mRNA, SAM) and synthetic mRNA vaccines. sa-mRNA vaccines have the advantage of lower administration dose.^{16,17}

Some platforms for vaccine do not involve delivery of a viral vector itself into humans but a cell line expression system that makes protein antigens. One such example is that used to manufacture the recombinant influenza vaccine. This system employs an insect cell line that is infected with a baculovirus containing the influenza hemagglutinin protein (and can be adapted to other antigens as well). In this situation both the cell line—which remains the same—and the baculovirus vector are the platform.¹⁸ A similar analysis can be applied to vaccines developed using tobacco plant cell lines.

It is important to recognize that there are many disparate vaccine platform approaches, because the overall goal is to develop new vaccines against the myriad infectious disease threats we face. Each platform, as well as traditional approaches, has its own merits, and which vaccine ultimately will be successful cannot be preordained.

Finding 3: Regulatory Agencies License Products, not Platforms

One of the potential advantages of platform vaccines is that because of their ability to be used for multiple targets, they are often deemed to be candidates for unique approaches to regulation. The argument is that because platforms have a common backbone on which only the candidate target is varied, the platform itself might be something that is largely accepted by regulatory agencies, with limited evaluation needed for the new target.

Such a view was embodied in the World Health Organization (WHO) proposed guidance for Ebola vaccines, in which it was stated that both immunogenicity and toxicity studies could be omitted and phase I trials commenced if robust data were available from prior use of the same platform against another viral antigen.¹⁰ Concerns exist, however, as to whether such an approach is feasible, given that immunogenicity and autoimmune considerations are antigen-specific.

However, regulatory agencies approve products, not platforms. Such agencies evaluate submissions as whole products intended for human use, rather than as components. Each product submission, irrespective of whether it was made using a platform, is viewed as a whole. But with increased use of a specific technology, regulatory agencies may become more comfortable with how such technology works, its overall safety, and its history, allowing more rapid approval and less onerous approval decisions with each subsequent submission. Use of such techniques as “master files,” whereby one manufacturer might reference a prior approval, is one such approach that provides a pathway that might be useful for fostering platform technology.

Additionally, regulatory agencies are likely to recognize the inherent differences between replicating and nonreplicating viral vectors and will likely require more robust safety data for replication-competent viral vectors. In fact, such a distinction is recognized currently by the US Department of Agriculture (USDA), which will allow conditional approval of nonreplication-competent viral vector animal vaccines based on prior approval of the platform.¹⁹

Currently, in the United States, there are several approved vaccines that are true platforms (eg, yellow fever, recombinant influenza vaccine), but no secondary or predicate products are approved based on those platforms. However, at least 2 17D yellow fever platform-based vaccines have been approved in other countries: Sanofi Pasteur’s dengue vaccine Dengvaxia and

Sanofi Pasteur’s Japanese encephalitis vaccine, Imojev.²⁰ Regulatory filings likely referenced the 17D yellow fever vaccine data, but approval of predicate 17D-based products proceeded in the usual fashion. This fact may reflect the lack of a special pathway recognizing the unique category of platform-based vaccines.

In contrast to the viral-vector–based products, when the platform is a cell line that facilitates the expression of viral proteins such as the insect cell line baculovirus expression system, the cell line platform can be prequalified by regulatory agencies. Prequalification can remove costly and time-consuming steps that would be required for future use of the cell line.

Finding 4: Rate-limiting Elements of Vaccine Development Can Be Diminished with Platforms

Vaccine development is usually an arduous and expensive process whose progress is measured in decades.^{21,22} During emerging infectious disease outbreaks—and even during seasonal influenza—long lead times for development are the norm. During an infectious disease emergency, any lag in vaccine availability or any supply constraints could be highly consequential. For example, in the 2009 H1N1 pandemic, in which a traditional egg-based vaccine was developed, the bulk of delivery occurred after the peak of viral activity, limiting the vaccine’s positive impact and magnifying the negative effect of the pandemic virus.²³

By contrast, a platform-based approach can be much more rapidly scaled up and the delivery of vaccines expedited. This rapidity of manufacture can also be consequential for replenishing vaccine stockpiles during outbreaks. Such replenishment of stockpiles became a real concern with the 2018-19 Ebola outbreak in the DRC in which the VSV platform–based Ebola vaccine has been deployed.²⁴

A platform-based approach is akin to a biological warm-base for vaccine manufacture—a sustainable infrastructure that is always at the ready for use with new products. This warm-base is even more evident when multiple candidates, especially those for routine childhood or adult vaccines, are also developed in parallel using the same platform.

Much discussion of platforms often centers disproportionately on potential regulatory streamlining that may or may not occur. However, even without any specific regulatory considerations being given to platform-based vaccines, the speed of the general platform-based approach—even if restricted to the pre-IND phase—will likely have a measurable impact on vaccine availability.

Finding 5: Platform Vaccine Technologies Have the Potential to Minimize Risks Associated with Emerging Infectious Diseases

Vaccine development is fraught with financial risk and opportunity cost for the pharmaceutical industry. Development costs of vaccines traditionally can exceed \$1 billion, and only vaccines that are routinely administered to large swaths of the population (eg, shingles, human papillomavirus, pneumococcus) have the potential for a return on investment comparable to other pharmaceutical products.^{21,22}

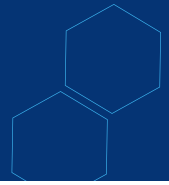
Additionally, vaccines, even when approved and with substantial market potential, face considerable risk, as long-term adverse effect reporting, negative publicity, and the anti-vaccine movement disproportionately involve this class of pharmaceutical products.

Emerging infectious disease vaccines, critical for regional epidemic and pandemic preparedness, are the riskiest class of vaccines because they have little to no market and uncertain need for use. When companies develop such vaccines, they can be subject to negative publicity, as evidenced by the reaction to Sanofi Pasteur's development of a Zika vaccine.²⁵

Because a platform vaccine technology can be leveraged for multiple uses—both for emerging infectious diseases and routine infectious diseases—it is a means of achieving economies of scale and lowering the risk of ventures in emerging infectious diseases. Platform vaccine technologies are a sustainable pluripotent infrastructure that can be applied to emerging infectious disease vaccines with minimal added financial risk.

Engagement with emerging infectious diseases has often been relegated exclusively to the domain of corporate social responsibility because of the lack of financial return. Indeed, multiple programs have been created to incentivize corporate investment in MCMs for these infections. Because of the manifold nature of vaccine platform technologies, which are equally adaptable to both commercially attractive and emerging infectious disease products, what was often deemed to be the exclusive purview of corporate social responsibility can become part of a standard product portfolio.

Recommendations



Recommendation 1:

Vaccine technology proliferation, platform or non-platform, should be the goal.

When a vaccine technology can be labeled a platform, it is often given heightened attention by the media, investors, funders, and public health leaders. Such a scenario has created a multiplicity of uses of the concept of “platform” that, in many instances, see it stretched beyond its intended use.

Such disputes over the clarity of the concept detract from the primary objective of developing myriad vaccines against infectious disease threats. To achieve that with high likelihood will require multiple vaccine candidates against prioritized pathogens. The more varied the candidates are in terms of vaccine technology, the more likely a successful vaccine is to emerge.

When new epidemic agents are identified, it will be most valuable to support multiple vaccine approaches. Development and investment in various technology classes and approaches, whether they employ platforms or not, will be the most rapid likely means to success.

Recommendation 2:

The assessment of how a given platform-based vaccine will accelerate development timelines should not be primarily focused on the expectation for new regulatory streamlining but more on the basis of acceleration of manufacturing.

The rapidity with which a candidate vaccine can be developed can be substantially accelerated with the use of vaccine platform technologies. This speed of scale-up can potentially bring a vaccine to the pre-IND stage of development within weeks of threat identification.

Though much discussion on vaccine platforms focuses on easing regulatory filings and expediting regulatory approval timelines, there is no convincing evidence that human health regulatory agencies are equipped statutorily to expedite the process in this way. While animal health agencies may have been able to accommodate platforms as such and public health agencies have developed aspirational guidance, human regulatory agencies in the foreseeable future will focus on complete products rather than vaccine platforms.

The increased use of master files and additional regulatory comfort with new technology will, over time, likely have important positive effects on regulatory filings for human vaccine platform technologies. However, the primary speed advantage conferred by platform technologies—in both routine and emergency contexts—will likely arise in the pre-IND stage. Expert judgment suggests that overall development time could possibly be cut by months.

Recommendation 3:

Traditional vaccine development should and will continue to play a critical role in vaccinology alongside platform-based approaches.

While vaccine platform technologies offer tremendous promise for conquering infectious disease threats in a more rapid, cost-effective, and technologically elegant manner, traditional vaccinology will continue to be a major driver of vaccine development and will never be wholly abandoned.

Traditional vaccinology includes inactivation of vaccines with formalin, serial passage for attenuation, use of adjuvants, use of viral-like particles, and many other techniques that were used to make vaccines whose diversity stretches from tuberculosis to human papillomavirus. When new threats emerge, it is important to not prejudice the quest for a vaccine by a priori declarations of what the candidate vaccine's development pedigree should be.

Recent events have shown a successful investigational Zika vaccine being developed using traditional attenuation techniques, and interest in a traditionally made HIV vaccine has increased. Furthermore, the infrastructure and knowledge base used to develop and manufacture routine childhood and adult vaccines using traditional approaches is sizable.

Recommendation 4:

Place a high priority on mRNA-based vaccine techniques that appear particularly promising in terms of ease of manufacture, adaptability to various targets, and biological delivery.

Of the various vaccine platform technologies on the horizon, mRNA-based techniques appear to be particularly promising. Though no mRNA (or nucleic acid) vaccines are in commercial use, their proliferation appears imminent. mRNA vaccines have several attributes that are particularly effective against emerging infectious disease threats.

When viewed as a platform, mRNA vaccines are somewhat different in attributes from viral-vectored vaccines and, for this reason, are simpler and can be thought of as more recipe-like.

Using the same technology for synthesis—the RNA printer—mRNA transcripts corresponding to genetic elements of target pathogens can be relatively easily synthesized once the genomic sequence of the target protein is known.²⁶ The rate-limiting steps for many mRNA vaccines may be pathogen isolation and manufacturing capacity. The proliferation of genetic pathogen sequencing power is increasing daily and could be immediately applied to new targets once the microbial identity of a target is known.

mRNA vaccines, which share many attributes with DNA vaccines, have one salient advantage: ease of delivery. For a DNA vaccine to be viable, it must traverse not only the host cell membrane but also the nuclear membrane. This passage may prove cumbersome to engineer. An mRNA vaccine, by contrast, has no such requirement, as its translation is cytoplasmic.

Self-amplifying mRNA vaccines (sa-mRNA, SAM) offer an additional advantage in that they require lower dosages than traditional mRNA vaccines. Dosage considerations have become paramount, given vaccine supply issues in recent years, and lower dose dilution studies have been performed in order to stretch supplies.

Lastly, mRNA vaccines and mRNA vaccine technology are being pursued not just for infectious disease uses; they are also highly prized in oncology. Oncology, when juxtaposed with infectious diseases, is a lucrative, robust field that possesses none of the market uncertainties that uniquely characterize the infectious disease field of medicine. Harnessing and leveraging the technology, expertise, and economies of scale that will be engendered by oncological applications of mRNA vaccines may prove very fruitful for infectious disease–targeted mRNA vaccines.

Recommendation 5:

Platform vaccine technologies for emerging infectious disease medical countermeasures require special considerations, given market conditions.

Although platform vaccine technologies offer much promise in achieving a rapid, sustainable, and cost-effective mechanism to develop vaccines against emerging infectious disease threats, they will still be situated in a unique market that requires special considerations and incentives.

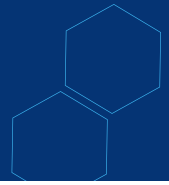
The emerging infectious disease market is one that is characterized by countless challenges and uncertainties, which have been well described. Among these challenges is the fact that market size is unknown and can increase from zero to tens of thousands or millions in a matter of months. Also, emerging infectious diseases disproportionately affect resource-poor regions of the world who have little to no ability to purchase vaccines for childhood diseases, let alone novel emerging infectious disease vaccines. Market purchases are often made by governments, nongovernment organizations, public health agencies, and philanthropic agencies—often at deep

discount. Thus, financial opportunities and return on investment are strictly delimited in this area, while opportunity costs abound.

Clinical trial design, legal liabilities, and public relations considerations are also important factors that vaccine manufacturers must consider when entering emerging infectious disease markets.

It is not surprising that this field is seen to be almost exclusively part of corporate social responsibility activities and has been kept divorced from ordinary operations in many companies. Vaccine platform technologies may allow development processes for emerging infectious diseases to be more in keeping with regular business operations, but there will likely still be funding and priority challenges that will need to be bridged by support and investment from government and philanthropic and international organizations.

Conclusion



As pandemic preparedness matures, the integration of nascent vaccine platform technologies into emerging infectious disease medical countermeasure development has the potential to have a significant impact on human resilience to both GCBR-level and other scales of epidemic threats. As vaccine platform technologies move through successive developmental stages, it will be important to track their progress, measure their speed of development, and catalog their successes and failures.

Employing these technologies, while not supplanting traditional vaccines entirely, has the promise to deliver rapid vaccine solutions in a streamlined, cost-effective manner.

It is important to emphasize that platform vaccine technologies are not a panacea for the threat of pandemics and emerging infectious diseases. While these technologies have important capacities for shortening development times, the magnitude is more likely to be in months not years. Vaccine platforms will, despite their unique attributes, be situated in a context of clinical safety and efficacy trials and regulatory agency compliance.

This report is an expert assessment of vaccine platform technologies. We found that there is great promise in these technologies, irrespective of any regulatory ease that may or may not be feasible. We hope that this report will provide important context to evaluate, discuss, and further these technologies in the quest to systematically remove the danger of infectious diseases and increase human resilience to these threats that span from regional outbreaks to GCBR-level events.

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Appendix A: Meeting Participants, December 11, 2018

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