THE SABIN-ASPEN
VACCINE SCIENCE & POLICY GROUP

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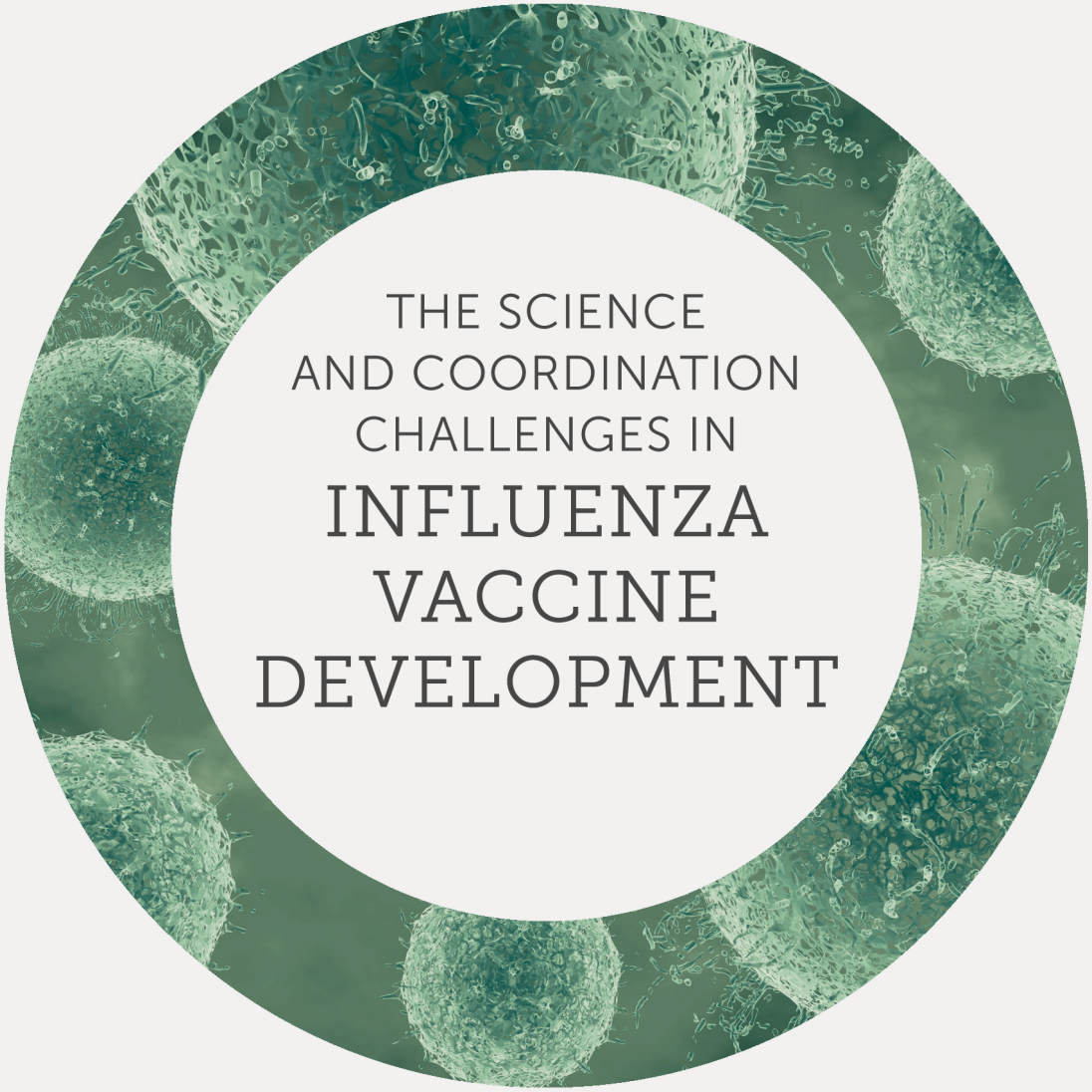

THE SCIENCE AND COORDINATION CHALLENGES IN INFLUENZA VACCINE DEVELOPMENT

Heather Youngs, Ph.D.

An excerpt from
Accelerating the Development of a Universal Influenza Vaccine

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FOREWORD

Vaccines are among the greatest global health achievements of all time. The World Health Organization estimates that immunizing children against diphtheria, tetanus, pertussis, and measles saves 2 million to 3 million lives every year. In the United States alone, these vaccines have prevented more than 21 million hospitalizations and 732,000 deaths among children born in the last 20 years, according to the Centers for Disease Control and Prevention.

One of our most urgent needs is a vaccine that will protect the world's people against influenza — a vaccine that is safe and highly effective, a vaccine that works in the young and the old and everyone between, a vaccine that is protective against any viral strain that might arise, and a vaccine that confers lifelong immunity. The launch of the Sabin-Aspen Vaccine Science & Policy Group (the Group) in 2018 coincided with the 100th anniversary of the worldwide Spanish influenza epidemic, which infected an estimated 500 million people and led to as many as 50 million deaths. In a more typical year, when the impact of the circulating strain of influenza is not so extraordinary, the virus still causes an estimated 290,000 to 650,000 deaths worldwide, mostly in adults age 65 or older.

As co-chairs of the Group, we are convinced that the goal of attaining a universal influenza vaccine is a highly worthy pursuit. The bold, actionable recommendations we put forward in this inaugural report are designed to communicate the urgent need, invigorate the necessary research, and overcome admittedly daunting scientific and operational obstacles.

The Group was formed to advance innovative ideas for harnessing the life-saving power of vaccines in the U.S. and around the globe. Collectively, the leaders, thinkers, and practitioners among this membership bring in-depth knowledge of vaccine-related scientific, medical, and political challenges. To encourage cross-disciplinary dialogue, these experts are joined by trailblazers in public health, regulatory science, philanthropy, venture capital, biotechnology, genetics, ecology, ethics, and journalism. We owe them our deepest thanks.

In October 2018, members convened for the first time at the Aspen Institute campus in Aspen, Colorado, to participate in two and a half days of thought-provoking conversation about how best to speed the quest toward a universal influenza vaccine. Their deliberations were informed by the four commissioned white papers included in this compendium, written by some of the most knowledgeable people in the field.

The bold, actionable recommendations we put forward in this inaugural report are designed to communicate the urgent need, invigorate the necessary research, and overcome admittedly daunting scientific and operational obstacles.

Armed with those and other rich resources, members looked for transformative Big Ideas. The package of ideas contained in this report is the result of that process. We expect to disseminate the report widely through the networks of the members of the Group as well as those of both Aspen and Sabin.

The Sabin-Aspen partnership behind this initiative is powerful and synergistic. Sabin is committed to advancing vaccine research and extending the full benefits of vaccines to all people, regardless of who they are or where they live. Sabin carries on the legacy of Dr. Albert B. Sabin, best known for creating the oral polio vaccine, which contributed to dramatic reductions in the burden of polio. The Health, Medicine and Society Program has a stellar reputation as a trusted, non-partisan player in the field of health care and health policy, and the Aspen Institute, where it is housed, is widely known for its capacity to convene people from many disciplines and perspectives.

In addition to the Group's members and the authors who participated in our inaugural meeting, we are most grateful to Flu Lab — the Launch Funder of the Group — which provided support for this report and the research and other meetings that informed it. This important work simply would not have been possible without Flu Lab's strong commitment to efforts designed to accelerate the development of a universal influenza vaccine through new innovative ideas and cross-sector collaborations, in addition to and including this prestigious Group.

We also want to acknowledge the many contributions of staff from the Sabin and Aspen organizations. Bruce Gellin, Stacey Knobler, and Jamie Minchin from Sabin and Ruth Katz and Katya Wanzer from Aspen all worked tirelessly together to help develop and manage this new initiative and our inaugural meeting. Finally, we want to recognize Margaret K. Saunders, deputy editor with Health Affairs, for her editorial work on the four commissioned papers and this final report.

It is tremendously rewarding for us to work with all of those so dedicated to driving vaccine development forward, and we eagerly anticipate our continued progress.

THE SCIENCE AND COORDINATION CHALLENGES IN INFLUENZA VACCINE DEVELOPMENT

Heather Youngs, Ph.D.

INTRODUCTION AND CONTEXT

The current state-of-play for influenza research and vaccine development is fairly robust in terms of funding and the breadth of activity, yet we still do not have effective seasonal vaccines and no unified approach toward a universal flu vaccine.

The U.S. spends between $250 million and $300 million annually on influenza research (in addition to spending on related programs, such as biodefense and biotechnology; National Institutes of Health [NIH], 2019). This is roughly equivalent to spending on each of these other areas:[1] brain cancer, arthritis, gene therapy, and genetic testing, and is roughly double the median program funding for all areas.[1] Despite recent progress in fields such as structural biology and synthetic biology, influenza vaccines remain inadequate in terms of efficacy, availability, or potential to scale during a pandemic. The 2011-12 influenza vaccine was 74 to 94 percent effective in children under 15 years of age, but only 50 to 60 percent effective in adults, with lower efficacy in pregnant women (Centers for Disease Control and Prevention [CDC], 2017). The 2015 influenza vaccine was about 60 percent effective (CDC, 2016); the 2017 vaccine was only about 40 percent effective against both influenza A and B (CDC, 2018).

There are several possible explanations for the lack of progress, including:

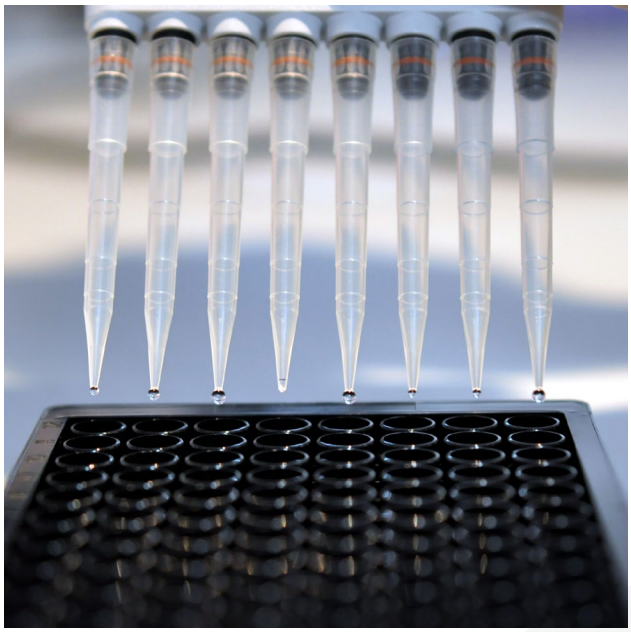
- The science is not good enough; we still need basic immunology research.
- There are technical challenges in leveraging the science fully.
- There is not enough investment (financially or intellectually) in translating that science into use.
- There are regulatory or infrastructure challenges in fully leveraging the science.

[1] The median value was calculated from data in 285 "Research/Disease Areas" from Fiscal Year 2014 to Fiscal Year 2018 (NIH, 2019).

To better understand the issue, our team conducted a review of the state of research and development (R&D). We reviewed the literature and conducted interviews with researchers and funders, both public and private. We found that all of the above are true. There is definitely room for more funding in basic immunology and vaccine development — in general and specifically for influenza. There are also many opportunities to increase coordination of activities to better direct efforts to translate discoveries into use.

IN GENERAL, MAKING A VACCINE IS EASY, BUT MAKING A "GOOD" VACCINE IS HARD

A good vaccine is one that produces robust and long-lasting immunization against a particular pathogen and, ideally, its close evolutionary variants. Recent progress in fields such as structural biology and synthetic biology offer a variety of potential new routes to vaccine development. Table 1 details the advantages and disadvantages of different vaccine approaches. It appears that few, if any, of the new technologies (so far) produce the same immunogenicity as a live, attenuated pathogen in terms of initial response and sustained immunological memory. Vaccines made with recombinant technologies are safer than using whole, attenuated or inactivated virus, but the process of identifying the best antigens[2] is typically slow and is not always successful. Although proteins can be expressed easily in cultured cell systems or cell-free systems, they do not always fold properly and may not present the same three-dimensional structure to immune cells as they do when they are isolated and not part of the whole virus. Viruses like influenza, with quickly mutating surface proteins, are particularly challenging because the antigen set is variable.



[2] Antigens are the parts of a virus that activate immune responses (e.g., antibody amplification). Typically, they are short protein sequences on the virus surface with specific three-dimensional geometry.

Table 1: Advantages and disadvantages of various vaccine types

	Advantages	Disadvantages
Traditional, whole pathogen vaccines The virus is made less virulent or inactivated/killed through chemical or biological manipulation.		
Live, attenuated	- Good immunogenicity - Long-lived immune response - T and B cell activated - Additional heterologous effects (poorly understood) - Can sometimes achieve cross-protection to related strains - Can have good effect with oral dosing (easy to administer)	- Slow timeline - Possible reversion to highly antigenic type - Depends on the mutation rate of the pathogen - Hard to tell what mutations were important in attenuating virulence - Poor stability and difficult maintenance
Inactivated, killed	- Good immunogenicity - Safer than live attenuated (low probability of disease) - Good stability and easy maintenance	- Can lose effectiveness over time (boosters needed) - Immunogenicity typically less than live attenuated - Cross protection rarer but still possible - No or poor immunity in oral dosing
Modern, recombinant vaccines Specific parts of the virus (antigens) with the potential to initiate an immune response are used instead of the whole virus.		
Protein/ subunit	- Safe because they cannot cause disease they prevent and there is no possibility of reversion to virulence - Cannot spread to unimmunized individuals - Stable and long-lasting (less susceptible to light, temperature, humidity) - Can distinguish vaccinated people from infected people	- Requires multiple doses - Immunogenicity typically less than whole organism - Can create local inflammation
DNA	- No risk of infection - Antigen presentation by both MHC class I and class II molecules - Polarize T-cell response toward type 1 or type 2 - Immune response focused on antigen of interest - Ease of development and production - Stability for storage and shipping - Cost-effectiveness - Obviates need for peptide synthesis, expression and purification of recombinant proteins - In vivo expression ensures protein more closely resembles normal eukaryotic structure, with accompanying post-translational modifications	- Limited to protein immunogens (not useful for non-protein-based antigens, such as bacterial polysaccharides) - Possibility of inducing autoimmunity - Possibility of tolerance to the antigen (protein) produced - Potential for atypical processing of bacterial and parasite protein (limited effect) - Risk of integration into genome or other damage - Limited memory cell induction
RNA	- No risk of infection - Ease of development and production - Obviates need for peptide synthesis, expression, and purification of recombinant proteins - In vivo expression ensures protein more closely resembles normal eukaryotic structure, with accompanying post-translational modifications - Room temperature storage for at least 18 months	- Fairly low immunogenicity (requires more work on delivery and adjuvants)

SCIENCE PROGRESS IN STAGES OF INFLUENZA VACCINE DEVELOPMENT

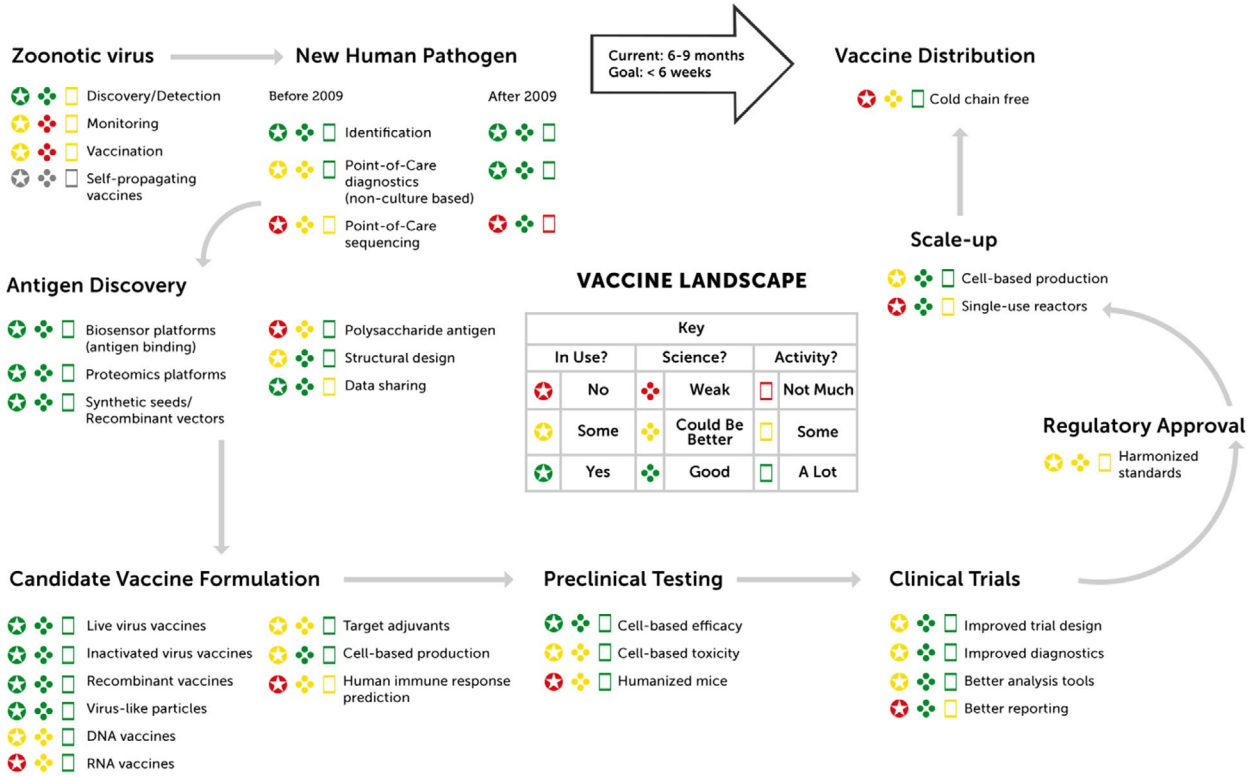
There appear to be many open science questions in general vaccine development, including:

- Why do some vaccines that seem to stimulate robust antibody production still not provide complete or long-lasting immunization?
- Why does the effectiveness of some vaccines decline rapidly, while others provide long-lasting protection?
- Are there better measures to predict effectiveness?
- How can we avoid adverse effects? Are there better predictors for people at risk?
- How do we avoid antibody-dependent enhancement[3] for closely related serotypes or pathogen families?
- How do carbohydrate antigens stimulate immune responses, and how can we predict and mimic this?
- How do we make useful vaccines for protective antigens that are known but are too variable or in the wrong conformation?
- How can we identify animal pathogens destined to become significant infectious agents within the human population?
- Why do some people not mount an adequate response to vaccination?

To better understand the issues specific to influenza vaccines, our team evaluated the R&D landscape. As shown in Figure 1, we identified some areas that need additional scientific progress, but we saw many more instances where scientific advances had been made but were not yet in use.

[3] Antibody-dependent enhancement occurs when non-neutralizing antiviral proteins facilitate virus entry into host cells, leading to increased infectivity in the cells (Tirado & Yoon, 2003).

Figure 1: Example of the scientific landscape in influenza vaccine development. The items listed are considered state-of-the-art technologies to either improve vaccine efficacy or shorten the timeline of production.



Source: Open Philanthropy Project, unpublished analysis

Starting at the upper left corner with a new pathogen, we can track the process of vaccine development through several stages that include identification of new strains, antigen discovery, candidate vaccine formulation, pre-clinical testing, clinical trials, regulatory approval, scale-up, and distribution. Currently, this cycle takes 6 to 9 months for a few seasonal strains. Improved technologies could theoretically shorten the cycle to less than 6 weeks, which is crucial for averting potential pandemics. A universal vaccine would replace the cycle entirely, providing long-lasting protection against all but the most divergent strains.

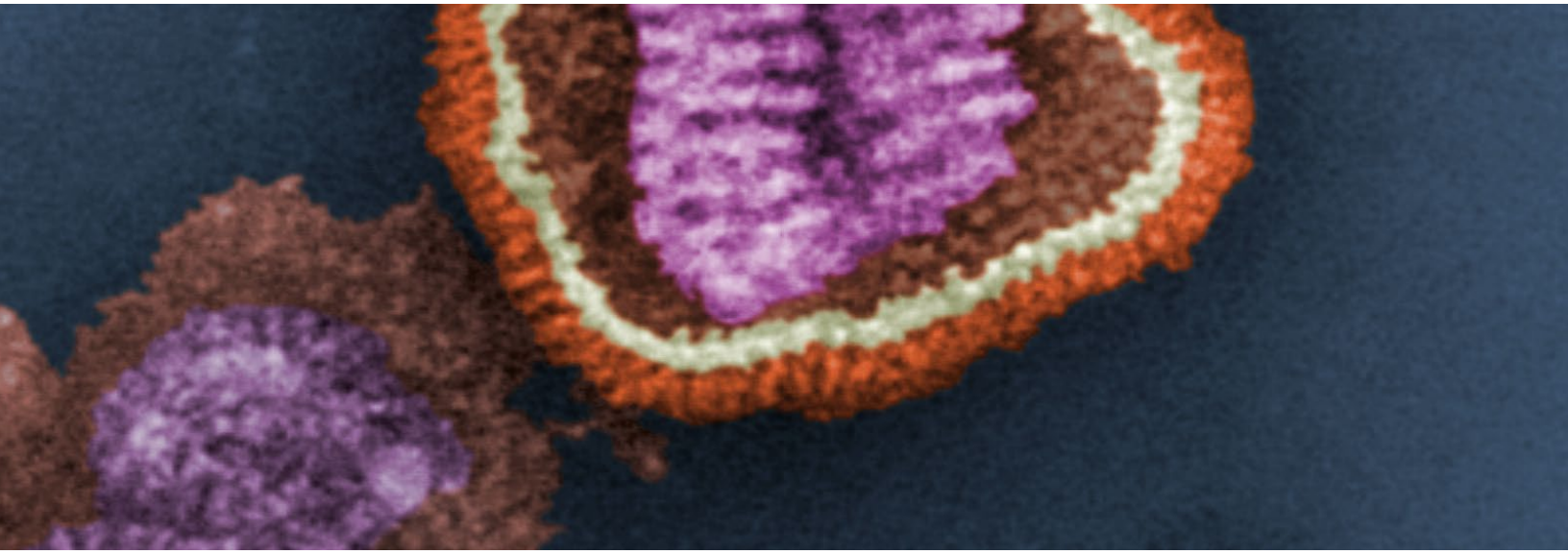
1. **Tracking Infectious Disease and Identifying New Pathogens.** There is a substantial ongoing effort to better understand the various pathways by which new influenza strains arise through host jumping. The FLURISK project, started in December 2011 through funding from the European Food Safety Authority, aims to develop an epidemiological and virological evidence-based influenza risk assessment framework to assess influenza A virus strains. The U.S. has been monitoring H5N1 since 1998. However, monitoring and surveillance have been heavily criticized as being sporadic, outdated, and having poor geographic representation (Butler, 2012). "At least 119 countries conducted avian influenza virus surveillance in wild birds during 2008–2013, but coordination and standardization was lacking among surveillance efforts, and most focused on limited subsets of influenza viruses" (Machalaba et al., 2015, p. e1). Monitoring of influenza in swine is much less developed, with small, on-again, off-again monitoring programs in the U.S. and EU and sporadic inspection in China.

   Fast and accurate point-of-care diagnostics and point-of-care sequencing will have a big impact on improving outcomes for infectious disease, accelerating pandemic response and helping us to understand how viruses are evolving so we can make effective vaccines and improve responses to highly pathogenic strains with pandemic potential. Sensitivities of current tests are not equivalent for all influenza types. For example, one analysis of seven point-of-care tests revealed severe limitations for H3N2, H7N9 (about 40 to 60 percent in-use clinical sensitivity; Chan et al., 2013) and H1N1 (10 to 70 percent; Vemula et al. 2016). Uptake of the newest technologies, which are more accurate for some strains, is slowed by higher cost, the need for technically skilled operators, and facility requirements. Getting these technologies into common clinical settings (not just larger hospitals and research facilities) requires funding and regulatory support structures. For example, there are only a handful of diagnostics for influenza available in the U.S. that do not require certification under the Clinical Laboratory Improvement Amendments.[4]

   Harmonizing data standards and expansion of shared, secure databases are essential to this process. The World Health Organization (WHO) has established FluID, a global data sharing platform for influenza epidemiology, and FluNet, a global web-based tool for influenza surveillance first launched in 1997 that tracks virological data provided remotely by National Influenza Centres (NICs) of the Global Influenza Surveillance and Response

[4] In 1988, Congress enacted the Clinical Laboratory Improvement Amendments (CLIA, 1988) to modernize the 1967 Clinical Laboratory Improvement Act (CLIA, 1967). The objective of the CLIA program is to ensure quality laboratory testing, although all clinical laboratories must be properly certified to receive Medicare and Medicaid payments. CLIA covers approximately 260,000 laboratory entities. A provision added to the Balanced Budget Act of 1997 (Balanced Budget Act, 1997) to exempt physician office labs was deleted. Many physicians avoid doing laboratory work in an effort to escape entanglement with CLIA (Association of American Physicians and Surgeons, n.d.).

System (GISRS) and other national influenza reference laboratories collaborating actively with GISRS or uploaded from WHO regional databases. The data at country level are publicly available and updated weekly. The platform accommodates both qualitative and quantitative data, which facilitates the tracking of global trends, spread, intensity, and impact of influenza. These data are made freely available to health policymakers in order to assist them in making informed decisions regarding the management of influenza.



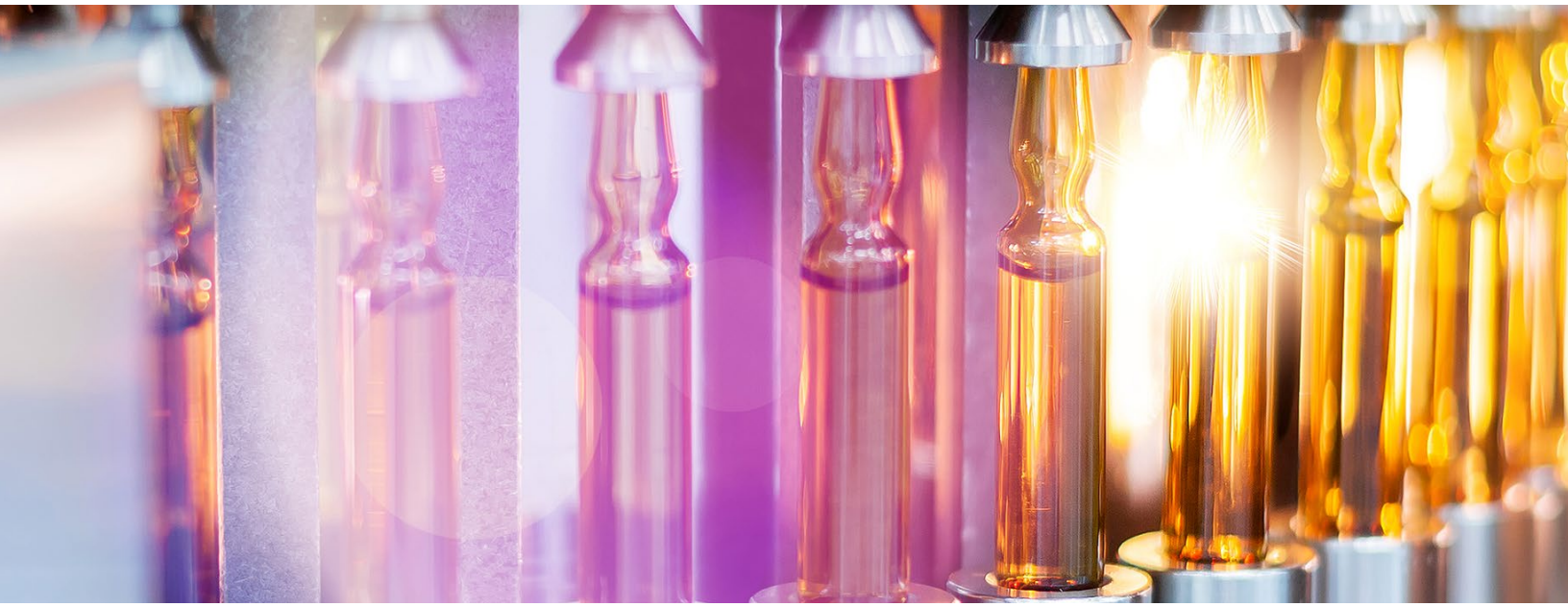
2. **Antigen Discovery.** Antigen discovery is perhaps the most critical area for decisions in vaccine design and the most active area for vaccine science R&D. Scientists have made amazing progress in recombinant systems, structural biology, proteomic platforms, and biosensors that can measure, design, and predict protein structures, which is important for vaccine design. Even so, only a handful of conserved antigenic regions (epitopes) are being pursued for a universal influenza vaccine (UIV). We need better tools to evaluate conserved regions, better ways to model variable regions and chimeric structures in viral particles, better tools to predict protein structures from amino acid sequences, better tools for assembling predicted structures from synthesized peptides in vitro, better methods to properly present antigens to the immune system in order to achieve a robust memory response, and better ways to quickly assess immunological response in pre-clinical testing. Open-access databases, such as National Center for Biotechnology Information's (NCBI) Influenza Virus Resource, Influenza Research Database, and EpiFlu, facilitate sharing of viral genome sequences and encourage collaborative research.
3. **Candidate Vaccine Formulation.** Since the pandemic in 2009 and the associated increase in funding from agencies such as the U.S. National Institute for Allergy and Infectious

Diseases (NIAID) and WHO, there has been a renewed effort at improving the pipeline for candidate influenza vaccines. The progress in the academic space has been steady; however, uptake of advances into use has been slow. As shown in Table 1, there are many different types of vaccines. One of the biggest challenges in vaccinology is the historical tradeoff between safety and efficacy (strength and persistence of the immune response) with artificially constructed vaccines. Many new technologies for candidate vaccines, including virus-like particles, self-amplifying vaccines, and nucleic acid vaccines, are all being actively explored in academic labs and startup companies with some uptake into larger companies. DNA and RNA vaccines have the best potential for speed and fewer storage issues than protein-based vaccines. The researcher can quickly sequence a new viral strain and synthesize the vaccine in a matter of hours, but delivering these genetic elements to the right tissues at the right concentrations is still a challenge. Novel, more targeted adjuvants (chemical or biochemical vaccine additives that boost an immune response) are needed for these novel vaccine types. Work on adjuvants, a previously ignored area, has been spurred by funding by the NIH and disappointing clinical results for the first wave of DNA vaccines. Many companies are using faster cell-based production platforms, which will likely contribute to standardization and improved timelines for new vaccine development, though at higher cost.

4. **Pre-clinical Testing.** Overall, insufficient knowledge of the human immune response is still hampering accurate pre-clinical testing protocols. New approaches to activate T cell and innate immune responses to augment antibody or B cell responses are promising, but there is little consensus on the appropriate measures and metrics for protection in animal models. Many startups and academic labs are trying to develop human cell-based assays to improve and accelerate pre-clinical testing. These technologies have not yet been adopted widely, but the science is improving. Efforts to improve animal models are limited, but there are some efforts to humanize mice[5] to make them more accurate proxies to investigate vaccine strategies (Graham et al., 2016; Sasaki et al., 2018; Shultz, Brehm, Garcia-Martinez, & Greiner, 2012; Yu et al., 2008).
5. **Clinical Trials.** There are still a lot of unknowns with regard to variations in immune response, formation of long-term immunity, and antigenicity in humans. Research to better understand the effects of previous pathogen exposure on vaccine performance and the drivers of antibody repertoire through B cell clonal selection and maturation are still needed. This information is important in developing a UIV amid the backdrop of lifetime exposures to many different seasonal flu strains and previous immunizations.

[5] "Humanized mice" are mouse strains with severe immunodeficiency (e.g., Prkcdscid or SCID) that have xenografted human cells such as peripheral blood lymphocytes (PBLs) and fetal bone marrow, liver, and thymus (BLT).

Efforts to improve clinical trial designs and implement new measures of immunity are much discussed, but it is unclear when and how new tools and metrics will be used in practice (Blohmke, O'Connor, & Pollard, 2015). The testing requirements for evaluating UIVs are still in flux, and there is a need for new tools to compare biomarker data from recent clinical trials with data collected in the past on both licensed and failed vaccine candidates. This requires improved reporting requirements.



6. **Scale-Up of Vaccine Production.** Technologies to enable cheaper and faster vaccine production are slowly beginning to make their way into commercial use. With traditional egg-based manufacturing, the virus is altered via a series of adaptations that have the goal of increasing productivity. It appears that for the 2012-2013 influenza vaccine campaign, these process improvements resulted in mutations in the HA protein and a loss of vaccine effectiveness. This problem is not encountered in cell-based recombinant systems, in which the natural HA sequence of the virus can be used without the need for mutation. Yet cell-based production has not been widely adopted, mainly due to increased cost and higher technical proficiency requirements compared to egg-based production. Stricter regulatory constraints could catalyze the shift toward cell-based production.

   A scarcity of providers constricts vaccine supplies, as well as the ability to ramp up production during pandemics. In 2009, there were just a few vaccine producers, including large pharmaceutical companies whose main focus is on other drugs. In 2017, four companies accounted for 89 percent of the vaccine market.

   The ability to produce large amounts of vaccine in the event of a pandemic emergency is also limited by the availability of production platforms. To take advantage of the fast

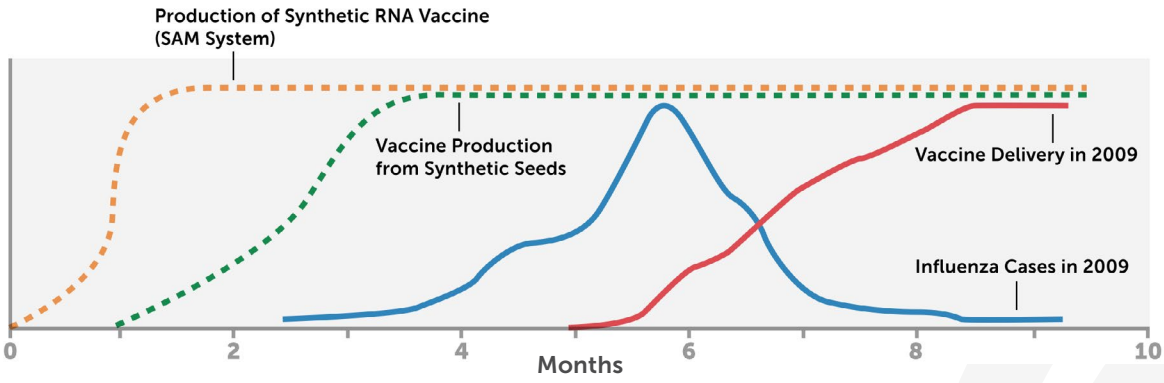
turnaround of cell-based systems, access to appropriate culture facilities that meet safety standards is required. While developed nations have some capacity for converting cell culture systems normally used to produce biomaterials or pharmaceuticals to emergency vaccine production, this conversion can be time-consuming and costly. The most plausible new technology to meet this demand are disposal units (e.g., plug-and-play plastic vessels for growing cells and purifying proteins). Inertia from existing capital investments in steel vessels and dedicated production lines disadvantages large pharmaceuticals in this area.

7. **Vaccine Distribution.** There is a lot of ongoing research and improved techniques to avoid cold-chain (refrigeration) requirements and enhance vaccine shelf life, but uptake has been lacking. It is unclear if this simply reflects residual industrial and clinical inertia, or if these newer approaches are too expensive or do not meet performance needs or regulatory hurdles.

CONVENTIONAL TECHNOLOGY IS SLOW

Speed is a critical factor for seasonal and pandemic influenza vaccine development. Although vaccines are one of the foundations of modern medicine, the traditional approaches to vaccine development are not very agile. The average vaccine takes 10.71 years to develop and has a six percent chance of making it to market (Lagerwij, Suman, Hintlian, Chen, & Scott, 2015). In 2009, it took nearly 3 months from the first case of influenza to the start of vaccine manufacturing (Figure 2).

Figure 2: Timeline of the 2009 influenza virus pandemic showing that, by using the conventional technologies at that time, large quantities of vaccines became available only after the peak of the viral infection. The dashed lines indicate the hypothetical time course for vaccine production from synthetic seeds and the synthetic self-amplifying mRNA system (Table 1), which might help to produce large quantities of vaccine in the future before the peak of influenza infection.



Source: De Gregorio & Rappuoli (2014)

In most cases, until recently, vaccine development was based on a slow empirical approach rather than rational design based on detailed mechanistic understanding of the immune system functions and the structural properties of antigens. Today, once the sequence of the virus is available, we can synthesize the genes and make a synthetic virus to seed vaccine manufacture in less than a week (Dormitzer, 2015). Cell-based production systems could be ramped up quickly, shortening production time to less than 30 days (Figure 1). Ensuring these rapid production methods produce highly effective vaccines for the widest demographic possible is still a grand challenge. Rappuoli and Dormitzer (2012) cogently outline how this and other new tools, such as improved assays for immune titer, can greatly accelerate the deployment of vaccines. More generally, they identify a series of organizational and operational changes that could build upon the recent technical advances. These include sequencing at NICs; widely accessible databases for genomic, metagenomic, and antigenic datasets; improved surveillance of routine respiratory infections; use of mammalian cell cultures in place of eggs; integrated interagency analysis of new flu strains (e.g., the CDC and the U.S. Department of Agriculture working together); and reclassification of attenuated versions of highly pathogenic viruses. Although Rappuoli and Dormitzer's scenario is optimistic, it is within the realm of possibility. We anticipate even more opportunities to improve surveillance and genetic data through point-of-care testing, on-site sequencing and modern data platforms.

LACK OF COORDINATION SLOWS PROGRESS

Vaccine development, like many other areas of technological progress, requires the coordinated action of three ecosystems — academia, industry, and government — not to mention support and acceptance by consumers. These large socioeconomic ecosystems each have their own sets of rules — different drivers, restrictions, and modes of operating — that affect which activities they choose to prioritize and how they interact with each other. To further complicate matters, none of these enterprises is static or entirely self-contained. They continually morph over time, overlapping and separating their agents and activities. It is not surprising that gaps in manpower, financial support, and intellectual effort toward any one goal (e.g., vaccine development) appear and disappear. When the gaps are sustained, progress is curtailed.

In the current R&D climate, one can generalize vaccine development as a hand-off among these three ecosystems (Table 2). Much of the basic science and early candidate development happens in academia. This research transitions to the industrial sector for further applied research and clinical testing, although some of these activities can be shared with academia and government support.

Table 2: Map of the activities, agents, barriers, and business-as-usual incentives in vaccine R&D. Misalignment creates gaps across the landscape from basic science to implementation that slows progress.

Basic Science	Finding Candidates	Development	Production	Distribution	Monitoring
Activities					
ï Understanding basic immunology ï Understanding population effects in humans and reservoir species ï Virus evolution	ï Screening ï In vitro studies ï Animal studies	ï Kinetics ï Toxicology ï Formulation/ production protocols ï Clinical trials	ï Scale-up ï Quality control ï Regulatory approval	ï Marketing ï Sales ï Clinical use	ï Sampling ï Data processing ï Information sharing
Main Barriers					
ï Opportunity costs – other research topics better suited to achieving academic goals	ï Opportunity costs – other research topics better suited to achieving academic goals ï Lack of funding for translational work	ï Lack of investment ï Failure of candidates ï Economic risk	ï Costs ï Opportunity costs for resource use ï Technical barriers ï Regulatory hurdles	ï Low consumer confidence ï Low price point drives down profits ï Competition	ï Opportunity costs for resource use ï Non-standardized practices ï Lack of coordination
Consequences					
ï Research is not focused on goal	ï Research is not focused on goal ï Information generated is insufficient to move forward	ï Research is not focused on goal ï Information generated is insufficient to move forward	ï Good candidates may be abandoned ï Other products prioritized	ï Other products take priority ï Supply does not meet demand	ï Weak information ï Reduced efficacy
Agents					
Mainly Academia Some Industry/Govt.	Academia Some Industry	Mainly Industry Some Government	Mainly Industry Some Government	Industry, Government, NGOs	Mainly Government Some NGOs/ Academia

Business-As-Usual Incentives		
Academia	Industry	Government/NGOs
ï Funding ï Publish high-profile papers (innovative new approaches) ï Make progress in 3 to 5 years (student/postdoc project)	ï Convert leads to products (path to sizable market) ï Integrate activities (efficient use of resources) ï Optimize financial/pipeline models (path to profitability)	ï Address large unmet needs ï Integrate activities (efficient use of resources) ï Optimize political and financial capabilities

Surviving technologies progress to commercial production, an industry activity that is influenced by distribution, and market uptake, an activity that relies on consumers and is often supported by government. Outcome monitoring largely falls to government but may be assisted by academic and industrial partners. Lack of alignment and coordination occurs across the R&D spectrum.

The range of choices and optimization factors creates a complex landscape for vaccine development that could be considered non-ideal by different stakeholders. For example, there may be conflicting goals between industry and governments regarding prioritization of capital. In an ideal case for pandemic preparedness from a government point of view, vaccine platforms would be fast, effective, efficient, cheap, standardized, and interchangeable. From an industry point of view, the platforms would be fast, effective, efficient, profitable, and proprietary. Filling these gaps and reconciling disparate drivers is a continually evolving challenge in vaccine development.

CONCLUSION

Building on the work of others (Koff, Gust, & Plotkin, 2014; Oyston & Robinson, 2012; Wiedermann, Garner-Spitzer, & Wagner, 2016), we identified several systemic issues in general vaccine development that require additional research support, better implementation strategies, or infrastructure support. They include:

- **Inadequate understanding of the nuances of the human immune system impedes rational approaches to generate specific, potent, broad, and durable immune responses in humans.** This was the problem most cited in the literature. Although the subject of excellent and prolonged scientific research, there is still so much that is poorly understood about the nuances of the human immune system. Additional research support is still needed.
- **Insufficient pre-clinical data leads to failures in clinical trials.** Biomarkers for effective protection (sufficient and long-lasting immunization) are particularly lacking. "The ability to predict the immunogenicity and efficacy of a vaccine by innate signatures may offer great opportunities for streamlining future clinical development" (Koff et al., 2014, p. 590). Scientific research in this area is robust, but few advances have reached implementation.

- **Variable and insufficient information on the previous history of infectious exposures of intended vaccine recipients hobbles our ability to determine the best vaccine regimens.** We must improve our understanding of how to optimize vaccines for all patients, including pregnant women, newborns, and the elderly, regardless of previous exposure to the same or similar viruses. This area could benefit from additional basic research support but also needs infrastructure support including data management.
- **Some vaccines do not work well for all people.** Many intended vaccine recipients have relatively weakly responsive immune systems (the elderly, young, or immunocompromised). We need a better understanding of how to optimize for these weak responders. This area has received more recent attention but would benefit from additional research support.
- **Genetic variation presents considerable challenges for some vaccines.** Viruses mutate their antigens, requiring constant surveillance and quick adaptive response in the vaccine production chain. There are many areas where support for additional research, policy, and infrastructure is needed.
- **Development is expensive.** Costs affect decision-making and prioritization of efforts. This means that sometimes important infectious disease needs are not addressed. There is some activity in science and engineering that could reduce costs; however, regulatory hurdles continue to be an issue in deployment.
- **Access is limited for poor populations.** Limited access to the best vaccine technology contributes to global health costs and disparity. This continues to be an important political, economic, and regulatory issue.

While some solutions are emerging, many areas still need additional research support, better implementation strategies, and, most importantly, improved coordination among stakeholders to reliably test, adapt, and implement new discoveries. In general, we found delayed uptake to be most pronounced where a "hand-off" was required between institutions. For example, when an approach moved from the academic or government laboratory to a company or when a developed product moved through regulatory hurdles into the health system, there were almost always additional activities required during these transitions, which slowed or jeopardized the translation of discovery to use. Often it was unclear who would take ownership of and pay for those additional activities. This lack of coordination, exacerbated by gaps in leadership and risk ownership across the R&D landscape, is a major barrier to progress. It is possible that philanthropies and private institutions can fill these gaps.

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