

THE SABIN-ASPEN  
**VACCINE SCIENCE  
& POLICY GROUP**



Accelerating the  
Development of a

**UNIVERSAL  
INFLUENZA  
VACCINE**



Foreword by Harvey V. Fineberg and Shirley M. Tilghman

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# THE SABIN-ASPEN VACCINE SCIENCE & POLICY GROUP



## ABOUT THE SABIN-ASPEN VACCINE SCIENCE & POLICY GROUP

The Sabin-Aspen Vaccine Science & Policy Group brings together senior leaders across many disciplines to examine some of the most challenging vaccine-related issues and drive impactful change. Members are influential, creative, out-of-the-box thinkers who vigorously probe a single topic each year and develop actionable recommendations to advance innovative ideas for the development, distribution, and use of vaccines, as well as evidence-based and cost-effective approaches to immunization.



# THE SABIN-ASPEN VACCINE SCIENCE & POLICY GROUP



July 2019

It is with great pleasure that we present the first annual report of the Sabin-Aspen Vaccine Science & Policy Group, which explores challenges and opportunities to develop a universal influenza vaccine. Here you will find a package of Big Ideas and supporting work, designed to overcome the scientific, financial, and organizational barriers to developing a vaccine that confers lifelong immunity against even the most catastrophic strains of influenza.

The scope of that ambitious goal is matched only by the exceptional talent of the Vaccine Science & Policy Group, which convened for the first time in October 2018. Harvey V. Fineberg, president of the Gordon and Betty Moore Foundation, and Shirley M. Tilghman, president emerita of the university and professor of molecular biology and public affairs at Princeton University, serve as co-chairs. The 22 other accomplished members include science and policy experts and disruptors with experience in government, industry, philanthropy, and advocacy on both the domestic and global front. We are fortunate to have the benefit of their collective wisdom and are grateful for the time and creative energy they have all dedicated to this work.

We are also proud of the partnership between our two organizations, which has made this effort possible. The Sabin Vaccine Institute is a leading advocate for supporting vaccine research and development, enabling access to vaccines and advancing knowledge and innovation in the field. The Aspen Institute, through its Health, Medicine and Society Program, builds on core principles of rigorous non-partisanship and respect for evidence to tackle some of the nation's most complex health problems.

Recognizing the imperative of advancing vaccine science and policy, we saw that synergy was possible by pairing Sabin's scientific expertise and Aspen's convening power. It only made sense to reinvigorate ties that actually go back some 4 decades, when Dr. Albert B. Sabin, who brought the oral polio vaccine to the world, participated in Aspen Institute-sponsored programs. Both of our organizations have track records of bringing together the sharpest minds across multiple disciplines to help society move in bold new directions, and we are fully committed to continued collaboration.

This inaugural report is the beginning of an undertaking that we believe can transform the development, distribution, and use of vaccines, and ultimately save millions of lives every year. We are honored to have launched this initiative.

A handwritten signature in black ink that reads 'Dan Porterfield'.

Dan Porterfield  
President and Chief Executive Officer  
The Aspen Institute

A handwritten signature in black ink that reads 'Amy Finan'.

Amy Finan  
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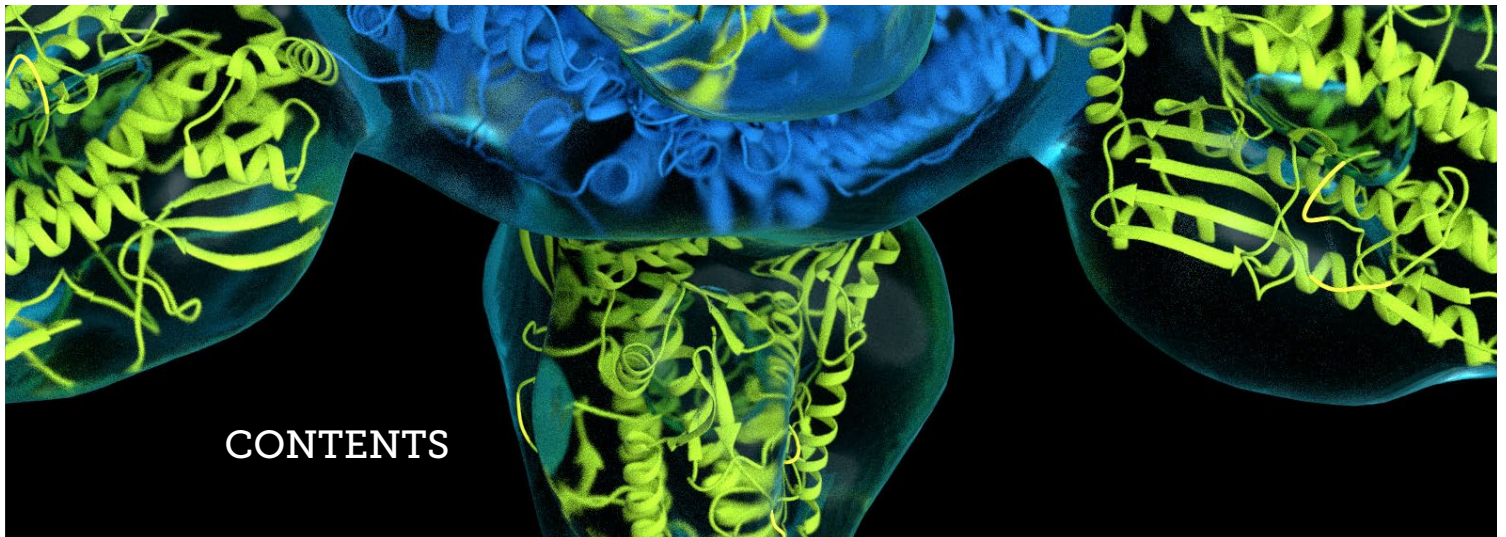
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**Harvey V. Fineberg, M.D., Ph.D.**  
Co-Chair



**Shirley M. Tilghman, Ph.D.**  
Co-Chair

## 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.



# Part 1

## SABIN-ASPEN VACCINE SCIENCE & POLICY GROUP REPORT

Accelerating the Development of a Universal Influenza Vaccine

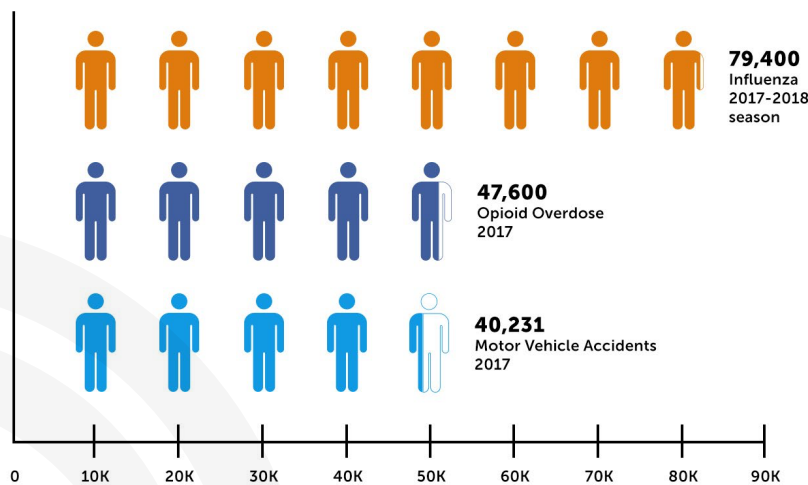
## CALL TO ACTION

Influenza is a serious infectious disease, but there is considerable complacency about the threat posed by this illness. What we casually refer to as “seasonal flu” is a recurrent epidemic. Every year influenza is transmitted from person to person, resulting in significant illness, hospitalizations, and death. Annual seasonal influenza is responsible for an estimated 3 million to 5 million cases of mild to severe illness and between 300,000 and 650,000 deaths – with the true impact in low- and middle-income countries not fully appreciated because systems and infrastructure are not in place to accurately identify and track the disease (Iuliano et al., 2018).

In Europe, influenza results in 4 million to 50 million symptomatic cases each year, and 15,000 to 70,000 European citizens die every year as a consequence of influenza infection (European Centre for Disease Prevention and Control [ECDC], 2015).

While there is considerable variability in the severity of influenza and the impacts on populations worldwide, in the U.S. during the 2017-2018 season, the more than 79,000 deaths from influenza were greater than deaths from opioids and almost double the number of deaths due to automobile accidents in 2017 (National Safety Council, 2018; Scholl, Seth, Kariisa, Wilson, & Baldwin, 2019; see Figure 1). The Centers for Disease Control and Prevention (CDC) reported that in the United States alone during the 2017-2018 influenza season, there were more than 48.8 million cases of influenza, more than 22.7 million medical visits, and 959,000 hospitalizations (CDC, 2018a).

Figure 1: Number of deaths in the U.S. from influenza, opioid overdose, and motor vehicle accidents



Source: Based on data from the Centers for Disease Control and Prevention (2018a); National Safety Council (2018); and Scholl et al. (2019)



The primary means of preventing influenza infection and the morbidity and mortality it causes is through an influenza vaccination, which is recommended annually. In many countries that have influenza vaccination programs, complacency by the public and even by health care professionals may result in failure to recognize the true nature of the threat from influenza and low rates of vaccination coverage. Others are deterred by vaccine costs and the difficulties of incorporating seasonal influenza vaccination targeting a wide age range into already fragile immunization systems that are built for childhood vaccination schedules.

In the U.S., despite the recommendation that everyone 6 months of age or older without medical contraindications be vaccinated annually, vaccination rates are typically low. The CDC estimates that during the 2017-2018 season, influenza vaccination coverage among adults was about 37 percent, although coverage varied considerably by age and state. This low coverage rate also reflects a decrease in overall coverage of about six percentage points from the previous year (CDC, 2018b). Uptake of seasonal influenza vaccine in high-risk groups in the World Health Organization (WHO) European Region is low and declining in several European Union (EU) countries (Navarro-Torné, Hanrahan, Kerstiëns, Aguar, & Matthiessen, 2019).

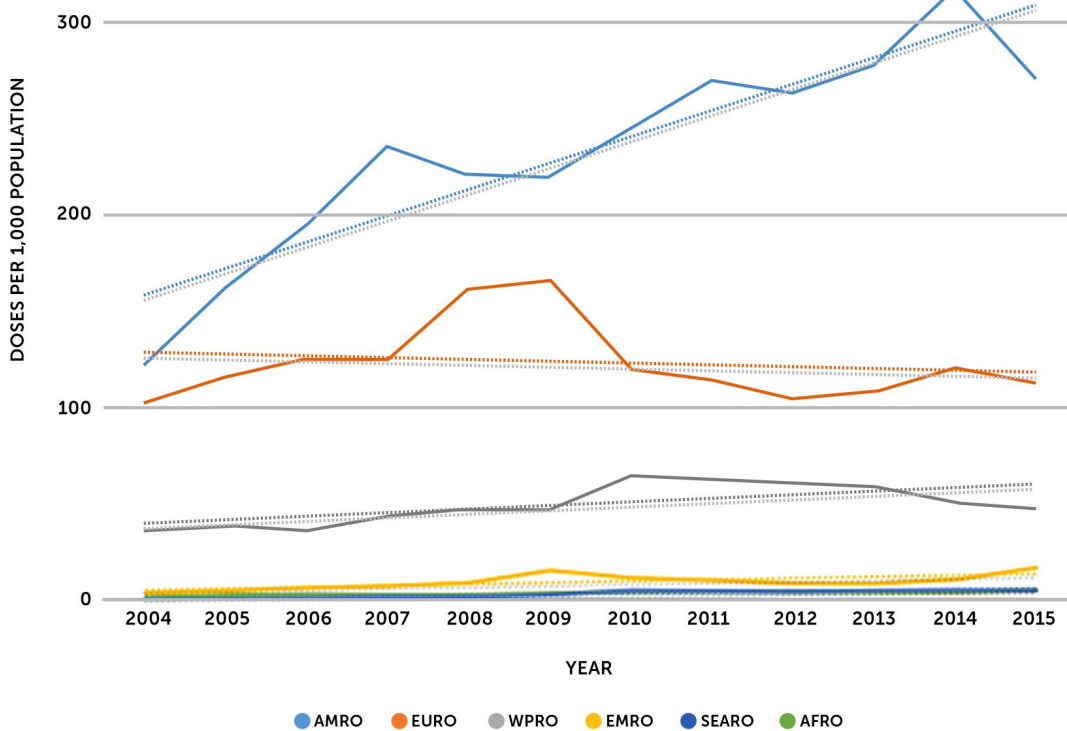
In addition to the inconvenience of getting vaccinated, people forgo influenza vaccines due to the belief that influenza is a mild illness, the false perception of risks of severe side effects or acquiring influenza from the vaccine, and the failure to recognize the benefits of immunization often overshadowed by varying and suboptimal vaccine effectiveness. Each of these issues has been highlighted as a barrier affecting influenza vaccine acceptance and demand (Paules, Sullivan, Subbarao, & Fauci, 2018; Schmid, Rauber, Betsch, Lidolt, & Denker, 2017). Despite the recommendation by the World Health Assembly for all countries to have influenza vaccination policies and programs, there are wide disparities in influenza vaccine use (Global Burden of Disease, 2018; Ortiz et al., 2016; World Health Assembly, 2003). Only three of the six global WHO regions<sup>1</sup> accounted for about 95 percent of all influenza vaccine doses distributed in 2017 (Palache et al., 2017; see Figure 2).

**In many countries that have influenza vaccination programs, complacency by the public and even by health care professionals may result in failure to recognize the true nature of the threat from influenza and low rates of vaccination coverage.**

Beyond its significant annual toll as a recurring seasonal epidemic, influenza poses a unique and graver threat — the ability of the influenza virus to rapidly mutate and spark a pandemic.

<sup>1</sup> WHO Regional Office for the Americas/Pan American Health Organization (AMRO), WHO Regional Office for Europe (EURO), and WHO Regional Office for the Western Pacific (WPRO).

Figure 2: Regional trends of seasonal influenza dose distribution per 1,000 population (by WHO region)



Source: Palache (2018)

Influenza poses a looming threat unlike almost any other natural disaster. Without warning, an entirely new strain of the virus may emerge to threaten an immunologically unprotected human population and challenge our ability to design effective vaccines *before* they are needed. The impacts of widespread illness and efforts to contain a pandemic could overwhelm health care systems, curtail and restrict global trade and travel, disrupt global supply chains of essential goods and local social services, and greatly increase school and work absenteeism. A large-scale pandemic has the potential to cost the global economy up to \$6 trillion (National Academy of Medicine, 2016), and simulations show that an estimated 33 million people could die in the first 6 months of an outbreak (Institute for Disease Modeling & Bill & Melinda Gates Foundation, 2018).

The year 2018 marked the centenary of the 1918 influenza pandemic estimated to have infected 500 million people and killed from 50 million to as many as 100 million people worldwide (Taubenberger & Morens, 2006). The ever-present threat of influenza — heightened by reminders of the epic toll of the 1918 pandemic — propelled the Sabin-Aspen Vaccine Science & Policy Group (the Group) to examine the broad vaccine research and development (R&D) enterprise and to identify current opportunities, challenges, and barriers for the development and delivery of a universal influenza vaccine (UIV). To inform recommendations designed to drive impactful change, the Group probed the current state of discovery and translational science, the structures and organization of R&D related to vaccines, and how funding and financing underwrite existing vaccines and promote the development of new vaccines.



## FRAMING THE CHALLENGE

The goal of developing and delivering a UIV — capable of eliminating the current threats to the health and well-being of populations worldwide — is the driver behind the ideas and recommendations included in this report. These proposed next steps — the Group’s Big Ideas — were informed by the extensive work to date led by governments, academic researchers, global industry and biotech firms, and philanthropists; these ideas seek to reinforce and extend this ongoing work and catalyze new work to achieve the breakthroughs that thus far have been elusive.

Selected recent advances reviewed by the Group and supported by governments, academia, and the private sector include:

- The National Institutes of Health’s National Institute of Allergy and Infectious Diseases (NIAID) 2018 strategic plan highlights its commitment to support the research needed to advance the development of a UIV that provides long-lasting protection against multiple strains of the virus for seasonal and potentially pandemic influenza (Erbelding et al., 2018). The strategy notes that “advances in influenza virology, immunology, and vaccinology make the development of a ‘universal’ influenza vaccine more feasible than a decade ago” (Erbelding et al., 2018, p. 347) due to efficiencies and insights in deep gene sequencing and advances in structural biology, among other scientific innovations.
- Through the Programme for Research and Technological Development and Horizon 2020, the EU is supporting major initiatives to develop novel influenza vaccines through improving understanding of immunity against the influenza virus and immune response to influenza vaccines; identifying genetic biomarkers that characterize highly pathogenic influenza strains; and using new immunization technologies, adjuvants, vectors and delivery systems, formulations, and vaccination methods (Navarro-Torné et al., 2019).

Philanthropic efforts are also taking an active role in catalyzing new thinking and approaches:

- Last year, the Bill & Melinda Gates Foundation launched a “Universal Influenza Vaccine Development Grand Challenge” with the goal of identifying “novel, transformative concepts that will lead to the development of universal influenza vaccines offering protection from morbidity and mortality caused by all subtypes of circulating and emerging (drifted and shifted) Influenza A subtype viruses and Influenza B lineage viruses for at least three to five years.” The \$12 million Grand Challenge is seeking bold and innovative ideas, interdisciplinary collaboration outside of traditional influenza

communities, and transformative approaches. Later this year, pilot grants of \$250,000 to \$2 million will be awarded by the Foundation and Flu Lab, a new influenza-focused charitable organization, with the aim of starting clinical trials by 2021. Importantly, the Grand Challenge is intended for a vaccine that can be used in all age groups around the world and especially in developing countries (Bill & Melinda Gates Foundation, 2018).

- The Wellcome Trust recently announced its support of the development of an influenza vaccines R&D roadmap to accelerate progress toward development of universal or broadly protective influenza vaccines. The roadmap includes several objectives: document gaps and barriers in influenza vaccine R&D; identify achievable, realistic goals and associated milestones with clearly defined timelines aimed at addressing gaps and barriers; build consensus among a wide range of international stakeholders on key priorities and strategies in influenza vaccine R&D; balance transformative and pragmatic changes in vaccine technology to improve breadth and durability of protection from influenza infection and/or severe disease; stimulate informed investments in influenza vaccine R&D; and create a framework to enable tracking and monitoring of progress over time (Plain, 2019).




Beyond the important expansion of scientific understanding and increased funding to support the discovery and development of a UIV product, significant progress in expanding vaccine coverage and providing increased levels of vaccination assistance to low- and middle-income countries (LMICs) for new vaccine introduction and immunization system development has been achieved over the past 15 years (Haakenstad et al., 2016). These investments (from national governments and multilateral organizations) and the health systems they support provide increasing opportunity to consider effective approaches for introducing and expanding influenza vaccination in LMICs (WHO, 2019b). Additionally, WHO's recently released global influenza strategy for 2019-30 includes a focus on strengthening pandemic preparedness and response, including vaccination (WHO, 2019a). In many LMICs, a UIV — that is more broadly protective and provides a longer duration of immunity — would be expected to be more cost-effective and logistically feasible for introduction into these immunization systems.

To systematically review these existing activities and the potential of these combined efforts, the Group commissioned four white papers to illuminate the vaccine R&D landscape and examine how these elements apply more specifically to influenza vaccines. The papers were designed to be complementary: to present the complexities and scope of the problem in terms of the dangers of influenza; to analyze the scientific and structural challenges to and opportunities for innovation in reforming or reshaping the current research, development, and production system for influenza vaccines; and to consider potential solutions to create a more rapidly available and effective influenza vaccine. These papers are compiled in Parts 2 and 3 of this report.



## PRINCIPAL FINDINGS

The world has arrived at a pivotal moment when innovative research using emerging tools and technologies, together with a strategic approach toward development of a UIV, could lead to a real breakthrough that has to date eluded past efforts. The convergence of new and rapidly progressing advances in the life sciences, manufacturing platform technologies, and computational sciences, applied to everything from protein structure to predictive algorithms of vaccine efficacy, make the current moment a more promising time than ever to marshal resources toward the goal of dramatically reducing the threat of influenza. Nonetheless, many technical, scientific, and organizational challenges remain. Appreciating these challenges, the Group's deliberations were shaped by the following principal findings:

 **The threat of human disaster from influenza is great — yet this threat is underappreciated and its timing unpredictable. We can no longer afford to delay in solving this urgent problem.**

The Group agreed that influenza poses a unique disease threat because it extracts a high toll on human life year after year and also raises the specter of a truly catastrophic global pandemic. Complacency about influenza is seriously misplaced — it is a worldwide problem that requires a worldwide solution. At the same time, current approaches to R&D of influenza vaccines, while significant, do not respond effectively or adequately to this danger. Annual seasonal epidemics of influenza are far more serious than is widely recognized, and the risk of a global pandemic — although infrequent — poses an ominous threat.

As revealed in our background papers and discussions, the pace of innovation in vaccine development generally has slowed over the past 5 years, with a flattening in the development pipeline, higher attrition for vaccines programs, and limited progress in meeting the vaccine needs of many countries. Although there are substantial investments in basic research and vaccine development, R&D programs for influenza vaccines do not measure up to the scale of the problem. Current development of an annual vaccine based on tracking viruses and predicting which strains will prevail, then drawing on a predominantly egg-based manufacturing system, is utterly outdated. The persistence of outmoded technologies and reliance on often ineffective approaches (and the markets they sustain) have tended to deter focused investment in a UIV. We need to adopt a new mindset that elevates development of a UIV to the fast track.

**> A universal influenza vaccine is a critical tool to eliminate influenza disease and ensure lifelong protection from illness.**

Protecting the world's population against influenza will require a transformational shift in concept and execution, from reactive vaccine development and immunization against annual influenza to a UIV that provides lifelong or multi-year protection against a broad spectrum of influenza strains. A successful universal vaccine would be safe and effective across all populations, it would dramatically improve upon the current influenza vaccines in terms of the breadth of protective efficacy and duration of protection, and most importantly, it would solve the problem of vaccine delay and lack of availability in the early stages of a global pandemic.

Apart from a long-lasting, broad-spectrum, safe, and effective vaccine, two other critical tools are wanting to cope with influenza. The first is more effective anti-viral drugs effective at all stages of acute illness. And the second is a field-ready and user-friendly diagnostic test to ascertain whether a patient actually has the disease; the goal is to improve our global understanding of disease burden and efforts to prevent it.

**> The process to develop a universal influenza vaccine should promote transformational innovation.**

The current system for development and production of new influenza vaccines has not been broadly innovative. Change has been slow to come: vaccines have been manufactured the same way for decades, and the science of immune protection remains uncertain and awaits discovery informed by advancing progress and technology in the life sciences. A shift in emphasis from seasonal protection to lifelong protection will be disruptive, but it is the best way to reduce the influenza threat. New scientific innovations show potential for opening new lines of experimentation in vaccine development. Novel science comes with uncertainty, but the inadequacy of current influenza vaccines represents an assured risk. A new approach should draw on lessons from innovation experiences in both health and non-health sectors to inform strategies for achieving a UIV.



**> A focused and accelerated effort involving collaboration among all stakeholders is most likely to lead to a vaccine that will provide an effective defense against the domestic and global threat of influenza.**

To meet the global threat of influenza, we need a targeted, coordinated effort that examines the entire vaccine and immunization ecosystem and brings together all parties engaged in the development of a UIV — policymakers, funders, producers, innovators, implementers, regulators, procuring entities (usually governments), scientists, and vaccinologists. Indeed, as we have learned from the rollout of vaccines for diseases such as measles, HPV, and Ebola, efforts should also include the perspective of individuals, families, and communities, as they stand to be impacted most by a transformative UIV. Such an approach should start with improved cooperation that complements existing R&D activities and also moves toward higher levels of coordination among all stakeholders. This should be followed by open collaboration and convergence in achieving the goal of eliminating the threat of influenza.



Although there are many groups pursuing different aspects of influenza research and vaccine development, there are critical gaps in scientific understanding and research that impede progress. The NIAID 2018 strategic plan lays out a template for the scientific gaps to be filled, with the overarching goal of providing long-lasting protection against multiple strains of the virus for seasonal and potentially pandemic influenza (Erbelding et al., 2018). A strategic convergence of efforts is most likely to foster the kind of robust, synergistic ecosystem that can lead

to innovations that ultimately achieve a UIV. There must be more effective coordination among key players in the fields of basic science and vaccine R&D with a common goal in mind: a UIV. The problem is so important, so complex, and so urgent that it deserves its own dedicated effort, and to give it the greatest chance of success, that effort must be more than

an aggregation of business as usual. Despite the scientific challenges to the development of a UIV, the Group emphasizes that the most powerful force constraining progress is the current system's fragmentation and lack of goal-oriented coordination.



The limited application of existing knowledge from new discoveries and technologies — with the potential to significantly, or even radically, change vaccine effectiveness, production, and coverage — may well be the most limiting feature of R&D for influenza vaccines. The persistence of coordination problems in “hand-offs” among academia, industry, and government discourage more rapid breakthroughs from emerging. For influenza vaccine development specifically, emerging science and technology should be targeted at improving vaccine efficacy; shortening production timelines; enabling the acceleration of testing and clinical trials of products to replace existing vaccines; and improving distribution, global access, and uptake. Overcoming systemic bottlenecks, improving coordination, and promoting continuous learning among the various actors in the ecosystem to reliably test, adapt, and implement new discoveries are essential. These feats can only be accomplished through a focused and concerted effort.

## THREE BIG IDEAS TO ACCELERATE THE DEVELOPMENT OF A UNIVERSAL INFLUENZA VACCINE

Based on these framing principles, the Group proposes the following three Big Ideas to accelerate the development of a UIV. The aim is to achieve lifelong protection against the disease, with the goal of creating a UIV to protect everyone. To accomplish this ambitious goal, we propose:

- The creation of an entity to spearhead this initiative.
- The advancement of an R&D agenda that actively seeks to broaden the range of scientific perspectives contributing to transformational changes in the pursuit of a UIV.
- The development and implementation of a communications strategy explicitly designed to reinforce the true impact of influenza and the urgency of the global need for a UIV.



**Move swiftly to create a single-mission entity focused on accelerating the development of a universal influenza vaccine to achieve global protection.**

The scale and severity of the threat posed by influenza requires a focused, accelerated, and collaborative effort to achieve the goal of a UIV — with multiple forces converging to build momentum for the development of a UIV that would be transformational for public health:

- Recognition by key leaders that the development of a UIV is a global good, for which there is a pressing need.
- Increased global focus on pandemic preparedness and security.
- Recent advances in science and technology that can be leveraged toward a UIV.

Fragmentation is our foe. With the recognition that government, industry, or philanthropy alone is unlikely to achieve the desired impact, a new, independent entity should be established to maintain dedicated focus on UIV, in partnership with multiple sectors and key stakeholders.

Given the urgency, the entity would operate within the guiding design principles that are the basis for this Big Idea:

- Maintain dedicated focus on the goal of UIV development informed by end-stage goals of global access and demand.
- Complement activities of existing stakeholders in the UIV ecosystem, as a UIV can only be achieved through partnership.
- Provide catalytic funding to unlock challenges that impede progress.
- Embed the concept of transformational change into the DNA of the entity, as there is a need to take risks commensurate with the potential benefit of a UIV.
- Evolve in an agile way alongside progress toward a UIV, functioning with flexibility and speed and processes for continuous learning.

In effect, the new entity would pursue efforts that are both cooperative and collaborative among academia, government, and industry and synergistic with current public health and research activities. It would be able to convene stakeholders across science, product development, regulation, public policy, program design and implementation, and end users — and welcome relevant expertise so that UIV development draws upon best practices of all component elements. Industry, regulatory, policy, and program leaders would be encouraged to get involved early, with a transparent, openly accessible process.



The new entity should include and leverage existing investments from public, philanthropic, and industry sources and build on a full understanding of ongoing work and resources to augment and complement endeavors already underway rather than replace or compete with them. Indeed, new resources for this entity would commence with activities to identify and fill critical gaps and more effectively leverage and supplement existing R&D activities on a UIV.

The new entity should have dedicated funding matched to identified needs and strategic goals, with an initial minimum timeline of 5 years. Even with adequate resources in hand, leaders of the new entity would have to prioritize the work and phase in critical operations

over time. Given the current state of readiness, the entity would likely start by attending to gaps in upstream innovation and translation, learning quickly from what works and what does not. It should draw on lessons from the best of other models with similarly bold approaches to realizing critical health, scientific, or industrial interventions and outcomes — the International AIDS Vaccine Initiative, the Cystic Fibrosis Foundation, and Medicines for Malaria Venture health initiatives, for example, as well as those outside the health field, such as the Center for Automotive Research and the Deep Decarbonization Pathways Project. This vision urges experts to identify the best way to make progress quickly, identify gaps, and fill them. A total systems approach would be employed to achieve the desired goal — it must be audacious by design, envisioning an ambitious solution that is truly transformational, scalable, and accessible.



More specifically, the entity would add value by carrying out the following core functions:

- *Enabling collaboration:* Inter- and intra-disciplinary collaboration among scientists and vaccinologists, experts who are traditional and non-traditional to UIV, researchers and product developers, and UIV policy and programmatic stakeholders.
- *Product-focused support:* Enable progression of candidates or platforms to create a UIV, with the end goal of achieving global access and broad program implementation.
- *Data- and asset-sharing:* Provide shared resources, both as incentives for collaboration and to decrease barriers to entry for any single player or new players.
- *Ecosystem visibility:* Track activity throughout the UIV ecosystem to surface potential opportunities and accelerate progress; provide lateral and external visibility.

- *Catalytic funding*: Allocate funding as an incentive for novel collaboration and research, to enable data- and asset-sharing, and to drive product-focused support; ensure that funding is flexible, rapidly deployed, and appropriately targeted to drive catalytic impact.
- *Championing the cause*: Rally support for the “moonshot” end goal both within the UIV ecosystem and to the broader public; provide thought leadership to surpass incrementalism; ensure sustained commitment, public demand, and readiness for a UIV.

## Develop and implement a universal influenza vaccine innovation agenda.

To develop a UIV, there must be a comprehensive scientific understanding of the challenge, from the biology of the virus and our immune response to it, through development, licensure, policy development, and introduction and delivery of the vaccine. Critical to achieving success will be a directed agenda to bring new science and technology to generate creative problem-solving and to meet this challenge. This “all hands on deck” approach is expected to catalyze innovation in influenza vaccine development, direct current capacity to move in groundbreaking ways, and accelerate the pace toward realizing the goal of a UIV.

Such an agenda would stimulate and welcome novel, bold ideas. It would pursue transformative concepts, and promote — even incentivize — the convergence of science from multiple sectors to achieve the goal of a UIV. Indeed, the agenda should include researchers from disciplines who may not currently have UIV in their sights but possess innovative approaches, key scientific understanding, or technological capacity that may be transformative in reaching this goal. Ideally, with an eye on the total system, a single-mission entity would be well situated to ensure that creative thinking and an innovative plan are integral at every stage in the process.

**A single-mission entity would be well situated to ensure that creative thinking and an innovative plan are integral at every stage in the process.**

An initial framework for shaping various research activities within the agenda should build upon the strategy recently developed by NIAID (Erbelding et al., 2018) and engage current and new scientific partners. Targeted efforts would aim to improve the scientific understanding of:

- Influenza natural history and transmission.
- Immune response and protection, including robust correlates of protection, inclusive of an understanding of correlates based on natural infection and vaccine exposure.

- Validated models to better predict and attain higher vaccine efficacy.
- Best practices in the vaccine development process to identify what works well and how it can be better supported and scaled up or extended.
- Standardized analytical immunological assays to establish benchmarks for individual vaccines and cross-vaccine comparisons as a “fundamental building block” based on the premise that it is important to share assays and transfer assays to low-income countries.
- Clinical trial design and implementation, including the representation of special populations (e.g., pregnant women) and hard-to-reach populations (e.g., low-income or displaced persons) in basic, translational, and operational research efforts.

In addition, to further support the vaccine R&D efforts, key research is needed to improve the tools used to identify and monitor influenza, including:

- Effective diagnostics that are inexpensive and can be used in real time and can be made widely available.
- Surveillance systems to better understand virus evolution as well as disease burden to inform policy decisions and contribute to the evidence base for UIV investments and distribution.

### **Design a new communications strategy to propel a movement for a universal influenza vaccine.**

Complacency undermines the opportunity to eliminate the looming threat of influenza. A fresh communications strategy to counteract complacency, therefore, is also urgently needed. A strategy should be designed to compel action toward the development of a UIV.

Shifting the paradigm of how the public, health professionals, and policymakers talk and think about influenza requires a re-framing of the issue to convey the pressing need for defenses against influenza — including use of a UIV. Influenza is *sui generis*; that is, it is unique: Influenza simultaneously costs lives and economic prosperity every year and also threatens catastrophic potential that has been demonstrated historically — no other threats to human health and security fit this category. It is essential to articulate to multiple audiences why influenza is different and distinctive and thus warrants a special approach. We need to build widespread awareness of the threat of influenza and provide momentum and demand for a solution.

A targeted, creative, and comprehensive communications strategy would aim to:

- Inform policy makers, donors, and the public about
  - Influenza disease — including its health and economic costs.
  - Influenza vaccines and the continued need for current vaccines despite limitations.
- Educate practitioners and the public alike about influenza disease and immunization — including how to recognize it and how it is best prevented and treated — distinguishing its seriousness from the myriad maladies often referred to as “flu.”



- Emphasize the transformative change made possible by a UIV to generate political will and resources at the global and national level among policymakers and philanthropists to drive efforts toward a UIV and strengthen the argument for a new approach to influenza.
- Establish the importance of partnerships and strategies that engage a global set of stakeholders, including governments, multinational agencies, nongovernmental organizations, the public, and the vaccine industry, to effectively develop and deliver a UIV.
- Use the social communities of the digital world to make the story of influenza personal to engage the public in tracking and diagnosing influenza and methods for mapping influenza in their geographic regions; support community forums and other information-sharing platforms to amplify information that conveys the threat to not only human health but also economic and social stability.



- Target messages to specific audiences (such as policymakers, providers, and the public) with sensitivity and understanding of their various viewpoints and knowledge of the issue.
- Develop messages that are data-driven — that is, messages that use evidence that has been gathered and tested for this purpose — to ensure scientific rigor and avoid common mistakes of earlier public health communication campaigns.
- Incorporate insights from behavioral and decision science research on vaccine acceptance and demand messaging strategies to encourage uptake of a UIV.

A focused and accelerated effort to build an effective defense against the global influenza threat is needed and must be powered by demand for solutions from domestic and global policymakers and from the broader public. Executing an effective communications strategy around influenza requires roles for policymakers and regulators as leaders in re-framing influenza as a serious global issue. The Group calls upon public health authorities around the world to participate in such an effort.



## MOVING FORWARD

Based on the principle that the world cannot afford to delay in meeting this urgent challenge, members of the Group are in unison in urging the creation of a single entity — mobilizing the efforts of government, philanthropy, and industry — whose sole purpose is to develop and produce a UIV. The Group understands this Big Idea to be intentionally disruptive, yet potentially transformative. In the Group's view, that is exactly the kind of action required to get the job of developing a UIV done.

The Group appreciates the need for incremental steps (including a multi-faceted communications strategy) in achieving this overall goal, and supports them as well. To that end, the Group is committed to continuing the work begun here, especially by disseminating this report to those best in a position to act on the Big Ideas put forth and, where appropriate, by championing their adoption.

Now is the time to organize and move forward to reduce the threat of influenza, ensure the security of individuals, and protect countries from the burden of annual influenza and the constant threat of an influenza pandemic. We have already waited too long. But it is not too late to begin.

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## Part 2

### FRAMING THE ISSUE

Influenza Vaccines and Scientific Priorities in the United States

## INFLUENZA VACCINES AND SCIENTIFIC PRIORITIES IN THE UNITED STATES

Michael Specter

As a continuing threat to public health, there is probably no greater danger than the possibility of an influenza pandemic. Other viruses are more consistently deadly — human immunodeficiency virus (HIV) is more mutable, for example, and others, such as measles, are more contagious. No virus currently in the wild is capable of killing vast numbers of people as rapidly or with greater efficiency than influenza.

This paper attempts to gauge the current state of vaccine preparedness, as well as the economic and scientific obstacles to change. I also outline some of the more promising approaches that could lead to a more comprehensive prevention strategy and an effective universal vaccine.

I spoke with nearly three dozen epidemiologists, virologists, molecular biologists, and public health officials; not one told me that the vaccines currently available are adequate. Nor did any argue that the current approach to influenza protection and preparedness is the best — or even close to the best — we can do. Their general view, and mine, is that the current system of discovery, research, and production of new vaccines might as well have been designed to stymie innovation rather than to foster it.

Some of this has to do with the nature of influenza itself. Flu comes in two basic patterns: annual seasonal epidemics during winter months (in the tropics they can last all year) and pandemics. The effects of seasonal influenza are far more consequential than even most physicians recognize. Each year in the United States, influenza infects about 10 percent of the population. For the past decade, annual hospitalization costs related to influenza have been about \$10 billion. As many as 5 million severe illnesses caused by influenza are reported throughout the world each year, and about 250,000 to 500,000 people die. (These are official World Health Organization [WHO] figures; most experts consider those numbers to be serious underestimates.) In the United States, according to data recently released by the Centers for Disease Control and Prevention (CDC), influenza killed and hospitalized many more people in 2017-2018 than any seasonal epidemic in decades.

**The current system of discovery, research, and production of new vaccines might as well have been designed to stymie innovation rather than to foster it.**





A global pandemic is the viral equivalent of a perfect storm. They are rare, but they pose a much greater threat than those of annual outbreaks. To succeed, pandemics require three essential conditions, which rarely converge, but are impossible to anticipate. First, a new flu virus must emerge from the animal reservoirs that have always produced and harbored such viruses — one that has never infected human beings and, therefore, one to which no person would have antibodies.

Second, the virus has to actually make humans sick (most don't). Finally, it must be able to spread efficiently — through coughing, sneezing, or a handshake.

There have been four global pandemics in the last century: 1918, 1957, 1968, and 2009. They have varied widely in severity. In 1918, an estimated 50 million to 100 million people died. The 1957 and 1968 pandemics are estimated to have killed 1.5 million and 750,000 people, respectively. Although definitive data are elusive, the 2009 pandemic was less deadly than any other; there were fewer than 500,000 deaths throughout the world and not nearly as many people died in the United States as usually die from seasonal strains.

That was a biological fluke, and as others have pointed out, the mildness of the 2009 pandemic in the United States probably did more to increase complacency with officials and the public — and more to expose the world to the risk of a devastating new pandemic — than anything that has happened in decades. Most people I interviewed for this report (and for previous stories) believe the WHO acted with admirable speed to declare a pandemic in 2009; nonetheless, timely access to vaccines in the developing world was more the exception than the rule. By the time the vaccine was widely available, more than a billion people had been infected. That should surprise no one. Even in America, it takes weeks to distribute enough influenza vaccines to meet demand; once approved, the vaccine needs to be shipped to thousands of doctors' offices, hospitals, pharmacies, and other health providers. After being administered, the vaccine then takes at least a week to stimulate antibodies.

There are no absolutes in the physical world, and there might not be another pandemic for 2 years, or 40, or a century. But I have never spoken to a person in the field who doubts that there will be one. In 2009, only the mildness of the strain — which nobody could have

anticipated or even hoped for — saved the world from millions, perhaps even tens of millions of deaths. And that was in a year in which the system — according to most accounts — functioned the way it was supposed to function. “Once it got out there, that thing burned right through the forest,” one virologist told me a few years later. “We caught an amazingly lucky break, but let’s not kid ourselves. Luck like that never lasts.”



The U.S. federal government estimates that, in most years, seasonal influenza kills between 3,000 and 49,000 Americans. At least 80,000 people died in the winter of 2017-2018. The previous high, based on analyses dating back more than 30 years, was 56,000 deaths. The estimates, which are always necessarily vague, point to one of the many fundamental problems associated with treating influenza: We have no decent rapid or accurate diagnostic tools, so in most cases neither the people who are sick nor the doctors who treat them are sure whether they actually have influenza. Both the incidence of the disease and the rate of protection are based on poorly defined criteria, including the presence of “influenza-like illnesses in the community,” and there are many similar illnesses. Nobody confuses measles with whooping cough or polio. If you get measles, you know it’s measles. When you get influenza, it could be para influenza, adenovirus, coronavirus, rhinovirus, or other respiratory infections.

**The U.S. federal government estimates that, in most years, seasonal influenza kills between 3,000 and 49,000 Americans.**

The term “I have the flu” means little to most people; it has become a generic shorthand for saying “I am sick” with a bad cold or a norovirus or any of a number of other seasonal maladies. New genomic solutions hold great promise to alter this equation. Researchers from the Broad Institute of MIT and Harvard, as well as the Innovative Genomics Institute, a collaboration between researchers at the University of California, Berkeley, and the University of California, San Francisco, have each started diagnostic companies that deploy versions of the gene editing tool CRISPR, which acts like a molecular GPS system to detect viral and bacterial infections. The tools work like pregnancy tests. They can detect influenza viruses — even specific strains — with uncanny accuracy. The tests, which are currently in development, are cheap and, in most cases, will be simple enough to use at home.

Influenza presents both an individual and a potential public health crisis. Nonetheless, people rarely react to a public health threat unless they believe it will affect them or their families. Because the potential risks posed by influenza are rarely understood, and because nearly every winter illness is considered the “flu,” few people take influenza pandemics seriously.

That is due partly to the curse of successful public health measures: When a pandemic is mild or an outbreak never materializes, nobody rejoices. People don't generally celebrate the absence of a theoretical disaster. A potential risk averted is considered no risk at all.



In the past, the perception that current vaccines are already highly effective in preventing influenza presented a true barrier to developing new technologies. Officials remain reluctant, however, to focus publicly on the vaccine's true mediocrity. At times, the influenza vaccine is appallingly ineffective. In 2015, the vaccine protected fewer than a quarter of those who received it. In the winter of 2017-2018, the effectiveness figure was a bit better: 36 percent.

Why then don't we do a better job of protecting people from such a reliable cause of sickness and death? It is not that leaders don't care, nor do they fail to see the implications of continuing with a mediocre vaccine. Rather, the flu virus is the beneficiary of a strange convergence: The federal research establishment is not focused on influenza. Testing, developing, and manufacturing new products is not normally what the government does. Academic researchers are largely dependent on government grants — and despite a constant stream of urgent rhetoric and an excellent strategy paper published this year in *The Journal of Infectious Diseases* by senior public health officials, influenza is at the top of no National Institutes of Health (NIH) list when it comes to doling out research funds. Two bills to increase funding for influenza research have recently been introduced in Congress. Neither made it to the floor for a vote. Perhaps most importantly, pharmaceutical companies have little incentive for significant investment. This creates a vacuum of leadership, innovation, and commitment to change.

The status quo is powerful, and when taken as a block, the biomedical establishment has been simply unwilling — or to be charitable — unable to move in any meaningful way. Some of that is legitimate ball-bobbling among the NIH, industry, and researchers. But more of it is a result of short-sighted leaders who guard their turf rather than concede that we need to change course. Whenever people try to alter the current system, the old guard rises up in outrage.



There is little incentive for any company to try and break the paradigm. In part that is because the CDC and its Advisory Committee on Immunization Practices (ACIP) are reluctant to encourage competition. The federal government needs a diverse supply of vaccine manufacturers, so public health officials are hesitant to say one vaccine is better than another.

**To make a better vaccine and one that is rapidly available would require changing the infrastructure, and there has been a huge investment in the present establishment.**

“You almost don’t even have a chance to test a new vaccine,” one of the nation’s senior government scientists told me. “Because what are you going to test it against? Each year you have six companies rolling out these vaccines, all of which are suboptimal, and all of which are highly recommended by the CDC. So how do you come in and say, ‘Guess what, I think I have one that’s better than all of yours,’ and you do a clinical trial. We are all aware that the overall efficacy of the influenza vaccine is modest at best — but usually poor. And we all know the danger that poses. But we think of any number of reasons to close our eyes.”

The failures are obvious to anyone who takes a cursory look at the economics of manufacturing influenza vaccines in the United States. To make a better vaccine and one that is rapidly available would require changing the infrastructure, and there has been a huge investment in the present establishment. It is a bit like trying to get the world to stop burning fossil fuels. We know we need to, and we know we can, but industrial societies have invested so heavily in a carbon economy that, without proper incentives, it is almost impossible to make people walk away from it.

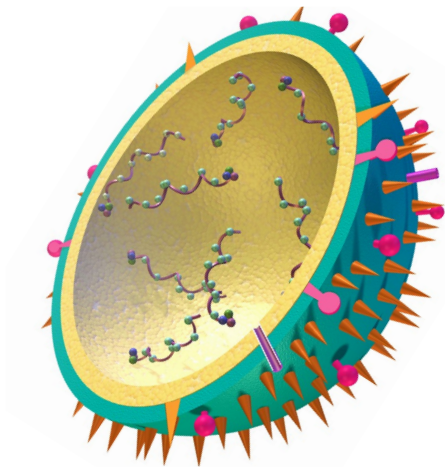
It takes years to develop a concept for a new medical product, carry out pre-clinical research, test a candidate, and turn it into a drug or vaccine. Historically, the NIH created the intellectual property and industry took it from there. But industrial production is driven by markets, and markets do not always serve the interest of public health. It doesn’t take a genius, of course, for a pharmaceutical executive to embrace NIH research, and invest in it heavily, when federal scientists develop a drug like Lipitor or Viagra. But for less profitable products, the risks for companies are almost always greater than the possible benefits.

“When you have something that industry perceives as high-risk,” one federal research scientist told me, “people in our field refer to that as ‘the valley of death’. And that means that researchers have a concept and maybe some pre-clinical data, but industry is almost never going to pay to move it to the next level, so somebody’s got to enter and deal with the valley of death. And that somebody ends up being the NIH. If it’s a public health matter like influenza or Ebola, the NIH will not only develop the concept, but also do all the testing. At some point a company will have the opportunity to obtain a fully developed product at essentially no risk and with remarkably little cost. You know where this happened? Ebola. Concept, NIH, pre-clinical work, NIH, phase 1 trials, NIH, phase 2, NIH. Same with phase three. GSK appeared at the end and what is the risk to them? None.”

**Shareholder value and public value are almost always at cross purposes. What maximizes the public health value of a vaccine — a single dose that works for the rest of your life — is bad for business.**

Shareholder value and public value are almost always at cross purposes. What maximizes the public health value of a vaccine — a single dose that works for the rest of your life — is bad for business. Once you vaccinate people and they are protected, you won’t see them or their money again. That’s not an attractive business model. Furthermore, vaccines are often so effective that they permit people to forget that a disease exists. The relationship between measles and the spurious fear of autism offers the most obvious illustration. In the United States, few parents, or at this point, pediatricians, have ever encountered a case of measles, and it is hard to convince people there is danger associated with a virus they have never seen. Before 1962, the year the measles vaccine was introduced, hundreds of thousands of children were infected each year, many would become severely ill, and several hundred would die. In 2017, there were 117 infections and no deaths.

It is getting much harder to obtain federal funds for the type of basic research necessary to make major advances — particularly with a disease like influenza, for which there is already a treatment. There is no serious constituency advocating for new flu vaccines or antivirals. Most rich donors want to make specific grants: \$160 million dollars for Alzheimer’s or \$50 million dollars for HIV or breast cancer or Parkinson’s disease. Philanthropists often lay down very particular rules for spending their money. That is not how science works best, but it is how federal science works today.



Moreover, brilliant researchers are often savvy enough to select topics that get funded: HIV, cancer research, autism, neurology, and genomics. It takes a brave recent Ph.D. or postdoc to say, “I want to focus on a disease that, while everyone agrees it is a terrible danger and scientifically challenging, nobody really wants to think about or fund.”

Our anemic response to the threat of influenza ought to remind us that, as a society, we are poor at balancing risks. How prepared should we

be for various low probability, high consequence events like a meteor or a pandemic? Those are questions we rarely ask, let alone attempt to answer.



Most of our vaccines (for all diseases) have been manufactured the same way for years — even decades. One might ask, why are they not improved? There are any number of reasons, each of which may seem trivial, but they add up to a series of overwhelming obstacles. First, as soon as you make a substantial change in the way a vaccine is made, you have to again demonstrate that it’s safe and effective, and that costs hundreds of millions of dollars. Then, if the current vaccine basically works, there is no theoretical argument that you can make to say the new vaccine is going to be safer than one that has been used for decades. If you want to reestablish the safety of a tetanus or rabies vaccine (or a new kind of influenza vaccine), how would you do it? You’re not going to withhold the vaccine and do a controlled experiment. It would be unethical. And the existing vaccines, antiquated and mediocre as many of them are, still work. So the status quo is rarely challenged because once a vaccine is seen as safe it is very difficult to replace. (This is not true only of influenza. Most researchers argue that it should be possible to produce a more effective pertussis vaccine as well. And yet, there are no meaningful incentives to spur innovation.)

Among those people with whom I spoke, there was unanimous agreement that we badly need a universal influenza vaccine (UIV). It has been nearly a decade since the President’s Council of Advisors on Science and Technology (PCAST) argued, in a 2010 report on influenza, that the National Institute of Allergy and Infectious Diseases (NIAID) should

expand and emphasize programs of support for the basic science. The same report urged the creation of an X Prize-like competition to encourage scientists to pursue a UIV. The suggestion went nowhere.

Certainly, making the switch to a universal vaccine will be difficult scientifically, economically, and ethically. There has been a lot of influenza research in the past 15 years, some of it highly promising; essentially all that money stems from three events: 9/11, the H5N1 scare of 2004, and the 2009 pandemic. The federal government has an organization almost expressly devoted to dealing with these issues: the Biomedical Advanced Research and Development Authority (BARDA), and everyone who mentioned BARDA to me did so in a complimentary way. BARDA has been instrumental in calling for a universal flu vaccine and in arguing that the government should fund innovative approaches to preventing influenza because there wasn't the economic incentive without government intervention.

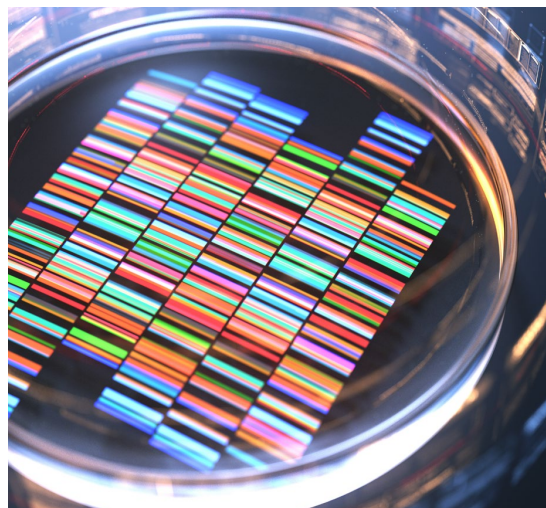
Largely out of a fear that somebody will use a virus as a weapon against the people of the United States, Congress has appropriated more than \$8 billion for influenza research in the past 15 years. But those supplemental funds are dwindling rapidly, and when the government needs money for new public health crises — Zika, for instance, or Ebola — invariably that money is siphoned from existing BARDA programs.

Before describing some of the prospects for new vaccines, I thought it best to include a cursory primer on viral genetics. If you are reading this paper, you may consider the information wholly unnecessary. If so, skip it. But I thought it would be better to provide extra context than to leave out something essential.

*Influenza comes in three types, designated A, B, and C. The B and C forms can infect people and make them sick, but they're not common, and they're rarely serious. Type A is the virus we worry about. Every influenza virus has hundreds of microscopic spikes rising from its surface. Most are made of a viral protein called hemagglutinin, which can latch onto cells that the virus seeks to enter. The other spikes are called neuraminidase, an enzyme that helps the virus spread. These two proteins are the reason that flu viruses are labeled with the letters "H" and "N." One can think of an influenza virus like a stalk of cauliflower, and Type A influenza has been so successful for so long because the head keeps changing. It is among the most mutable of viruses and is capable of swapping or altering one or more of its eight genes with those from other strains. (Much of the stalk, however, remains stable as the virus mutates.)*

*Because this virus evolves so quickly, an annual flu shot is at best a highly educated bet on which strain is most likely to infect you. The vaccine stimulates antibodies that should provide protection from the particular strain of the virus that epidemiologists think will predominate each year. But if you are infected with a flu virus whose surface proteins have changed, your antibodies won't recognize them fully. That new strain could edge its way past the human immune system's complicated defenses and establish a new infection, and though you might have some resistance, depending on how the strain had changed, you would need an entirely new set of antibodies to fight it. This goes on throughout our lives, and these small changes on the surface of the virus — the antigen — are called "antigenic drift."*

*The eight viral flu genes are put together in segments a bit like a line of connected Lego blocks, and they are easily dismantled, changed, and reassembled. When animal strains of influenza mix with human strains, there is always the possibility that the result will be an entirely new virus. That is called "antigenic shift." When large fragments of genetic material are replaced with genes from other influenza subtypes or with genes from other animals, like pigs or chickens, the outcome is something that the human immune system will be unable to recognize. And even with the sophisticated tools of molecular genetics, we cannot predict how a virus will change or when or whether it will become more or less dangerous. We don't even know if survival of the fittest, when it comes to viruses, means survival of the most virulent — a virus so powerful that it kills all its hosts couldn't last long.*



The current vaccine system is based on an old concept of immune protection: Essentially, the vaccine attempts to block the top viral envelope protein from attaching itself to receptor cells in our immune system. Effectively, the vaccine provides a plug — which often doesn't fit well, but it fits well enough to keep out the viral acid. And that's usually good enough. The problem is that the plug binds to a region that is totally malleable. But the hemagglutinin



protein keeps mutating, which often makes the plug useless. So every year it's sort of a crapshoot to determine how to configure the annual vaccine. Teams of epidemiologists look at outbreaks in the southern hemisphere at the end of their winter and make a guess about which strains are most likely to come our way.

The selection process is uncertain at best. Nor is the system scientific. Influenza is not even a human virus; it's a bird virus. But it constantly mutates away from birdiness toward humans. The process we use to produce hundreds of millions of doses of flu vaccine each year is almost unimaginably out of date.

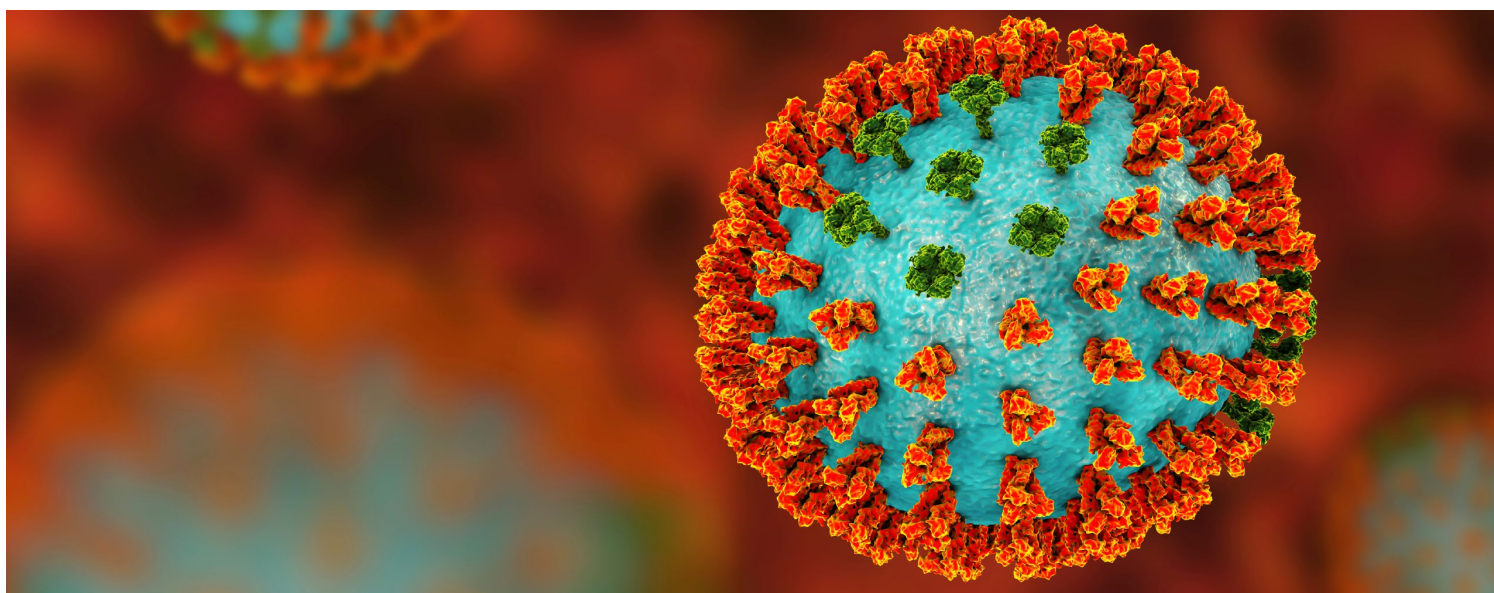
Today we can download most of the world's recorded music on our phones. If you are walking on a street in Bulgaria or Indonesia or Iowa, you can summon a map showing where you are standing and where the nearest coffee bar or jazz club is located. And yet most of our influenza vaccines are produced in eggs as they were in 1947. It's labor intensive, time-consuming, expensive, and imprecise. But before shifting from egg manufacture to a system where vaccines are produced in yeast or cells and grown in vats, there would have to be a costly transition period during which we made both types of vaccine. The U.S. would have no choice; otherwise, if the new method didn't work, 300 million people would be left with no viable vaccine. That is one reason (of many) that nobody has been willing to make the kind of large investment that will be required to begin a new era for influenza vaccines.



A universal vaccine would permit companies to design antibodies long before the first wave of infection. People would be protected from childhood, ideally with one shot, then one or two boosters later in life. Influenza would then become like polio or whooping cough or measles: a serial killer rendered powerless by the use of preventive medicine. But "if you propose any of this stuff at NIH, the reviewers are people who don't think big," a brilliant young geneticist told me. "I hate to say it, and I hate to speak poorly of them, and there are some excellent reviewers who take their job seriously, but there are a lot of people who look at it and are just like, 'Yeah, I can't do this, so there's no way you could do that.' And the comments I get back are just stuff like 'this is impossible,' 'this will never work,' 'you can't do this,' 'you can't do that.'"

**Influenza would then become like polio or whooping cough or measles: a serial killer rendered powerless by the use of preventive medicine.**

I cannot stress too strongly how reluctant scientific and public health leaders are to try radically new approaches to influenza vaccines (even when those approaches have worked in other contexts or if the research is conducted by well-established scientists with long track records of success).



What all universal flu vaccine candidates have in common is that, although some of the parts of the flu virus change rapidly, other parts of the virus are relatively stable. Universal vaccines target these stable parts of the virus. Some of the new vaccines being studied stimulate a type of cell called T cells, which recognize key proteins from within the flu virus and kill them. It is not a perfect solution — at least not yet. T cells, to some extent, will decrease more rapidly over time than the antibodies stimulated by more conventional vaccines. Some vaccine candidates are designed to protect against different strains within influenza A, but there is also an influenza B. So a truly universal vaccine will need to cross both of those strains, which may be difficult. Some researchers suggested to me there might have to be two vaccines, one for A and one for B. Other scientists thought that would not be necessary, but without clinical trials it will be impossible to know. And there are very few such trials underway. Even two vaccines, though, if they were each administered once and provided strong protection, would be infinitely better than what we have today.

Frustrated scientists argue that if we treated influenza the way we respond to emerging diseases like SARS or Zika, there would be fewer roadblocks. David Baltimore's group at Caltech has published research not only on stimulating immune cell responses to HIV but

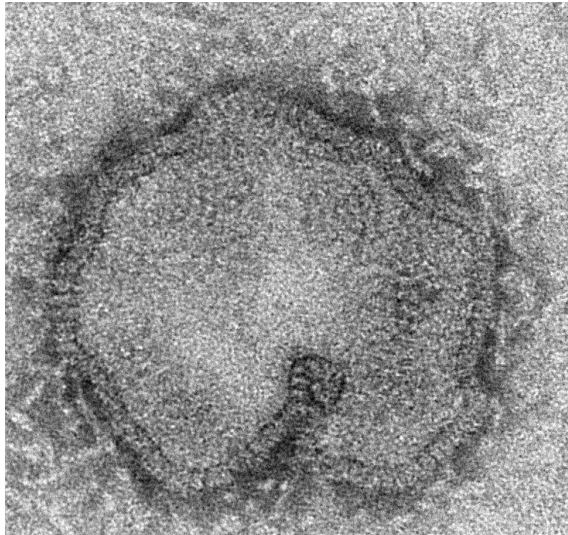
also to influenza, hepatitis C, and malaria. (Several other research teams are now taking similar approaches.) The scientists began by searching for a protein they could administer like a drug that would generate an effective immune response. They soon discovered a class of antibodies that bind to the stalk of the flu virus (whereas most bind to the head).

“They [the stalks of the flu virus] are regions which have to remain stable because they carry out essential viral function,” one member of Baltimore’s team said. “So once you find such an antibody it’s actually very powerful. And it’s more or less independent of what’s going on around the viral head. We simply encode the antibody that we already know to be protective in a form that can be delivered systemically to naïve people [those who have never been exposed to the virus]. So essentially it’s a drop-in replacement for the standard vaccine, whereas instead of giving a bunch of killed viruses and letting the immune system do the work, you administer the vaccine in a recombinant viral vector that encodes the genes for one of these antibodies. It is then injected into the muscle after which the animal will make as much of the antibody as you want, and it does so, in mice at least, for the life of the animal.”

That makes the protein much more like a universal solution than a seasonal antibody. And in fact, the team at Caltech found one antibody that seems to cover all influenza viruses. This approach, viral immunoprophylaxis, is now being tested. The delivery vehicle is an adeno-associated virus vector that carries the genes of the antibody. The solution, though, even if it works in mice, is far from perfect.

Scientists have yet to figure out how to direct the body to make a specific antibody. This is a problem with HIV vaccine research as well. The ability to generate a group of antibodies is promising, but successful vaccines make highly specific antibodies. (Think of antibodies as fences that keep out invaders. A chain-link fence might protect your chickens from a local fox, but it won’t do much to fend off a hawk or stop a flood.)

Nobody has previously stimulated the manufacture of specific antibodies for vaccines. So there is no history, even in mice, of understanding rules that will help researchers to find a pathway. Several groups — at Caltech, Scripps, and University of Washington, among others — are working on that problem. All are trying to figure out how to coax the body to make this particular antibody. But money is required for such fundamental research, and money is scarce.



Another promising, and allied, area of research is being led by David Baker, a structural biologist at the University of Washington's Institute for Protein Design. On computers, he and his team design proteins that will bind to the virus to keep it from entering a healthy cell. Baker has successfully made proteins that bind to all types of a variety of hemagglutinins, including H1, or swine flu; H5, or avian flu; and H2, or Asian flu. He has begun to create a database of proteins that would fight potential mutations of various influenza strains. This would save scientists

valuable time because they would no longer have to grow protein samples or sort through hundreds of potential compounds and then find a live virus to test them against. Instead, these designed proteins could be tested with advanced computer modeling and stored in a database accessible to drug manufacturers.

By placing amino acids into the grooves of the binding site of the influenza virus, Baker's team has managed to block the virus from entering the body. (Think of a climber on a rock face: First, he would need to find a place to put his hands and feet to get a grip. Then he would need to fit his body properly against the mountain.) Baker designs amino acids to fit into the viral cavity. Then he designs proteins that hold them in place — a kind of molecular version of a Velcro strap. The amino acids fill the pockets of the virus like expanding glue, which would then prevent viral particles from attaching themselves to the usual binding sites. Groups at Scripps have done similar work. Not every protein binds properly, but those that do work with exceptional regularity. In fact, early studies have shown that mice given injections of these proteins within 24 hours of infection are completely protected — even from lethal strains of flu.

Preliminary success in mice is exciting, but it raises another problem, one identified by PCAST in its 2010 influenza report: "Although there is much to be learned yet from model organisms such as the mouse, there is insufficient research effort focused on understanding the human immune system. In particular, there should be a targeted focus and a better understanding of antibody production in human beings."



The ultimate solution, of course, will be digital. At some point, routine clinical diagnostics will move from our current systems to sequencing. And those sequences would simply be posted, then downloaded by a company that can drop them into a vaccine.

The genomic entrepreneur Craig Venter, among others, believes we can, and will, go further. His goal is to make a vaccine that can be produced in the time it takes for a plane to fly across the world. "There is no reason that we couldn't do that," one synthetic biologist told me. "We would have to rethink everything we do and it's hard because the dogma is all around us. But we have the tools and it has to happen."

Venter hates decorum and rank, which irritates a lot of his colleagues, but his research is hard to dismiss. "We have two different parts of the vaccine construction process," he has said. "We have the sending unit, that can actually be the genetic code of something, send it up to the cloud and in the second part is the receiving unit." He calls this a "digital biological converter — A teleportation at the speed of light." If this seems like science fiction, it is perhaps important to recall Arthur C. Clarke's famous maxim: "Any sufficiently advanced technology is indistinguishable from magic."

That has never been as true as it is when Venter talks about rewriting genetic codes digitally and then moving them around like the data points they could become. It wouldn't be hard to move the sequences of a virus around the internet. "One day everybody will have one of these little devices on their home computer and we can stop pandemics before they start because in areas where these outbreaks occur you just download the vaccine and vaccinate people very quickly [and] it stops the spread," he has written. Venter has already built prototypes that can send and receive data; they are a long way from working on a vast scale, but there are no scientific reasons anyone has cited to think they couldn't.



The 2011 movie “Contagion” portrayed a world in which nearly every person on earth was killed by a flu pandemic while awaiting the vaccine. It was perfectly plausible. But why should we allow that to happen? Instead of having to deal with a major pandemic where you can’t leave your home or your city, imagine that you had a little box next to your computer, like a 3D printer, and you got an e-mail and that gave you a chance to actually make a vaccine instantly. What we routinely do with information now, we will soon be doing with information and biology together.

Obviously, there are profound risks: Instead of giving your partner a genetic disease or an infection, you could e-mail it. People could use this technique to cause harm, which happens every day with computer viruses. The development of CRISPR and its combination with gene-drive technology has forced scientists and ethicists to begin to discuss these possibilities more seriously. Those discussions will need to take on even more urgency as the science improves. Risks almost always grow in proportion to the possible benefits, but that shouldn’t prevent us from trying harder to solve one of our biggest health problems. The risks of doing nothing are infinitely greater.



**Michael Specter** is a staff writer at The New Yorker. Since joining the magazine in 1998, he has written about agricultural biotechnology, the global AIDS epidemic, avian influenza, malaria, the world’s diminishing freshwater resources, synthetic biology, geoengineering, new ways to edit DNA with CRISPR, and the implications of using gene-drive technology to alter the genes of various species. His profile subjects include: PETA founder Ingrid Newkirk, Dr. Oz, Peter Singer, Vandana Shiva, Miuccia Prada, and Richard Branson. Specter came to The New Yorker from the New York Times, where he had been senior foreign correspondent, based in Rome. From 1995-98, Specter served as co-chief of The Times Moscow bureau.

Specter has received the Overseas Press Club’s Citation for Excellence, the Global Health Council’s annual Excellence in Media Award, AAAS Science Journalism Award, the Mirror Award, and the James Beard Award. His 2009 book, “Denialism: How Irrational Thinking Hinders Scientific Progress, Harms the Planet, and Threatens Our Lives,” received the Robert P. Balles Annual Prize in Critical Thinking, presented by The Committee for Skeptical Inquiry.

# Part 3

## BACKGROUND PAPERS

# REFUELING THE INNOVATION ENGINE IN VACCINES

Michael Conway, J.D.; Adam Sabow, M.B.A.; Jennifer Heller, Ph.D.; Gila Vadnai-Tolub, M.B.A.; and Tara Azimi, M.P.P.

## INTRODUCTION

From a global public health standpoint, vaccines are considered one of the most important inventions in human history. Some notable achievements of vaccines include the eradication of smallpox and the near eradication of polio viruses. Approximately 300 million people died of smallpox between 1900 and 1979 — millions more were disfigured; however, by 1979, vaccination programs had completely wiped out the disease (Fenner, Henderson, Arita, Jezek, & Ladnyi, 1988). In 1988, at the onset of a global campaign to end polio, there were 350,000 new cases per year; nearly 30 years later, only 22 cases were reported in war-stricken areas where immunization was not possible (World Health Organization [WHO], 2018).

The past 20 years have seen a rejuvenation of innovation in vaccines, including pneumococcal, rotavirus, HPV, and varicella. Indeed, in its 2017 annual letter, the Bill & Melinda Gates Foundation reported that 122 million children's lives had been saved since 1990 — and that vaccines were the biggest reason for this decline in childhood deaths (Gates & Gates, 2017).

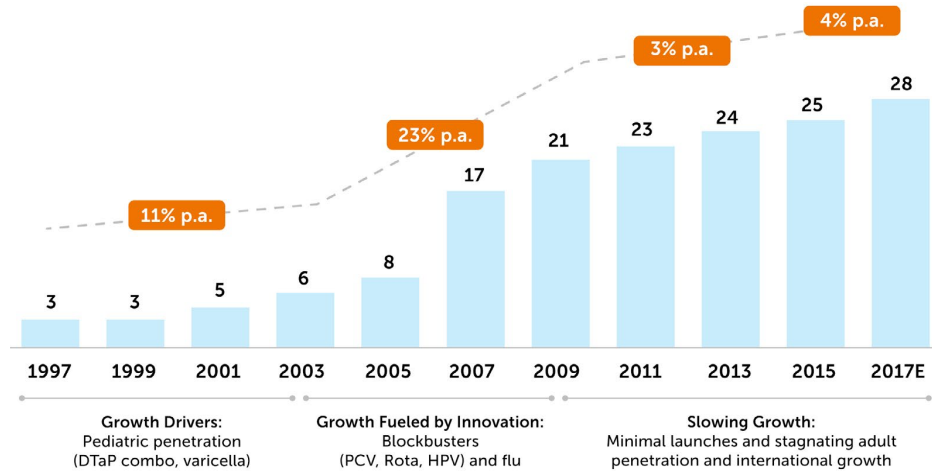
These statistics are in line with the historically high growth rate of the vaccine industry — 12 to 15 percent year on year over the past 2 decades — double the rate of the rest of the pharmaceutical industry (Figure 1). In the past 10 years, the number of vaccines in the pipeline has also doubled to 336 vaccines in 2017 (Figure 2). And while, to date, vaccines have mostly focused on disease prevention, we expect them to increasingly play a role in treatment (for example, therapeutic vaccines for cancer) and thus have even greater impact in the future.



Figure 1: After a period of rapid growth, vaccines sales have slowed in recent years

**Global Vaccines Sales, 1997 - 2017**

US \$, Billions

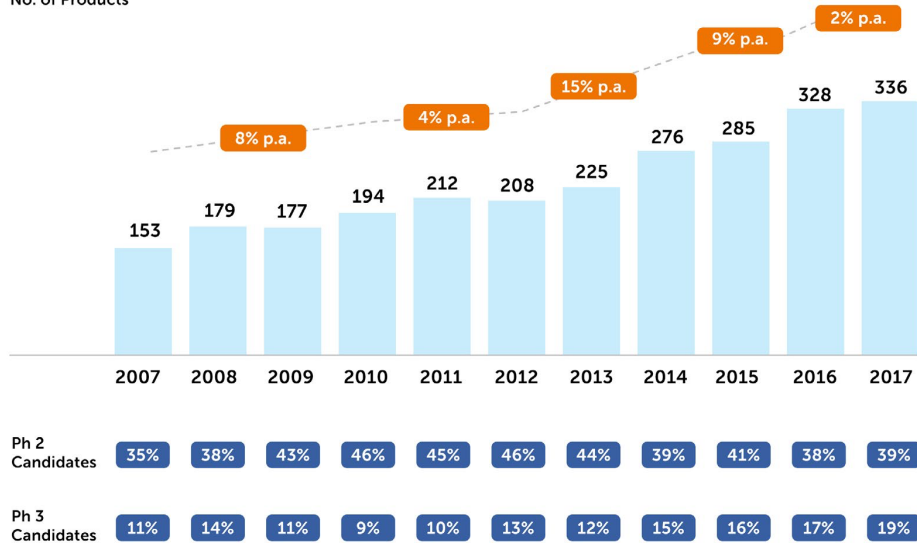


Source: EvaluatePharma, September 2018; McKinsey & Company internal analysis of data

Figure 2: The number of vaccine programs in development has flattened over the past 2 years

**Vaccines in Development Globally (Phase I to Pre-Registration), 2007 - 2017**

No. of Products

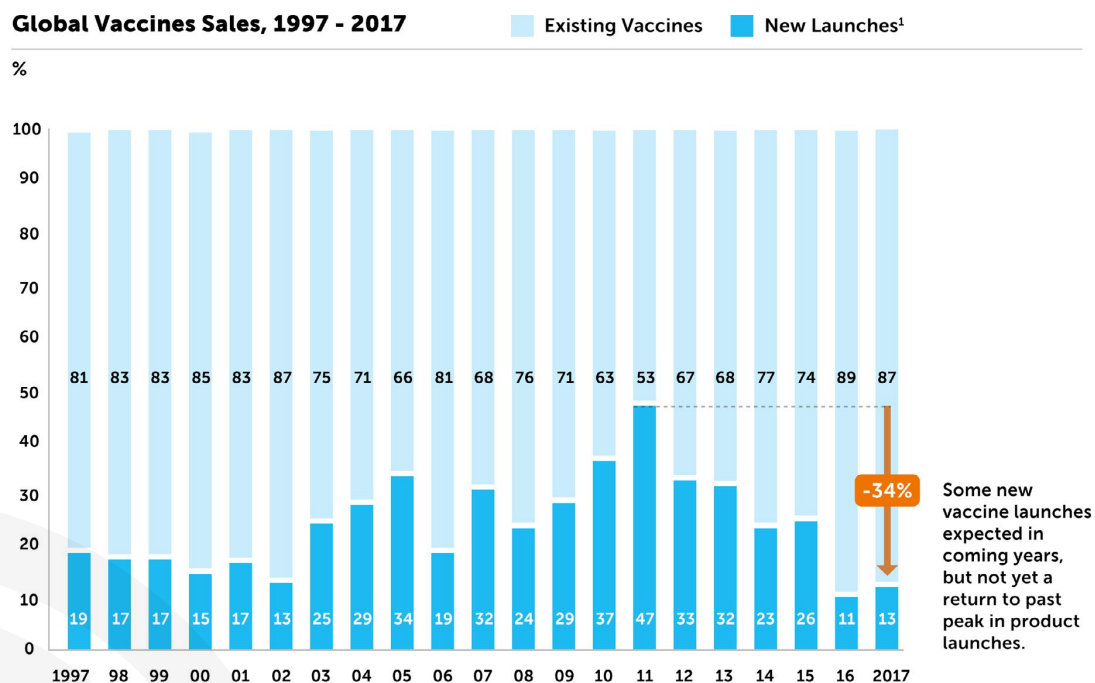


Source: Pharmaprojects, September 2018; McKinsey & Company internal analysis of data

However, we have seen four signs of slowing innovation in vaccine development over the past 5 years:

- Revenue growth has slowed to below five percent in the past 5 years (Figure 1).
- We are now seeing a flattening development pipeline (Figure 2), with the share of growth from new vaccines launched down from almost 50 percent in 2011 to less than 15 percent in 2017 — the lowest level in 20 years (Figure 3).
- We are recording higher attrition rates for vaccine development programs relative to other biologics (that is, pharmaceutical drug products manufactured in, extracted from, or semi-synthesized from biological sources), with fewer shots on goal, meaning fewer vaccine candidates are advanced to clinical studies (Figure 4).
- There are remaining unmet needs cutting across multiple categories of vaccines, including high-income endemic diseases (such as HIV and norovirus) and those endemic to low-income regions (for instance, tuberculosis and malaria).

Figure 3: The proportion of sales from new vaccines has declined in recent years

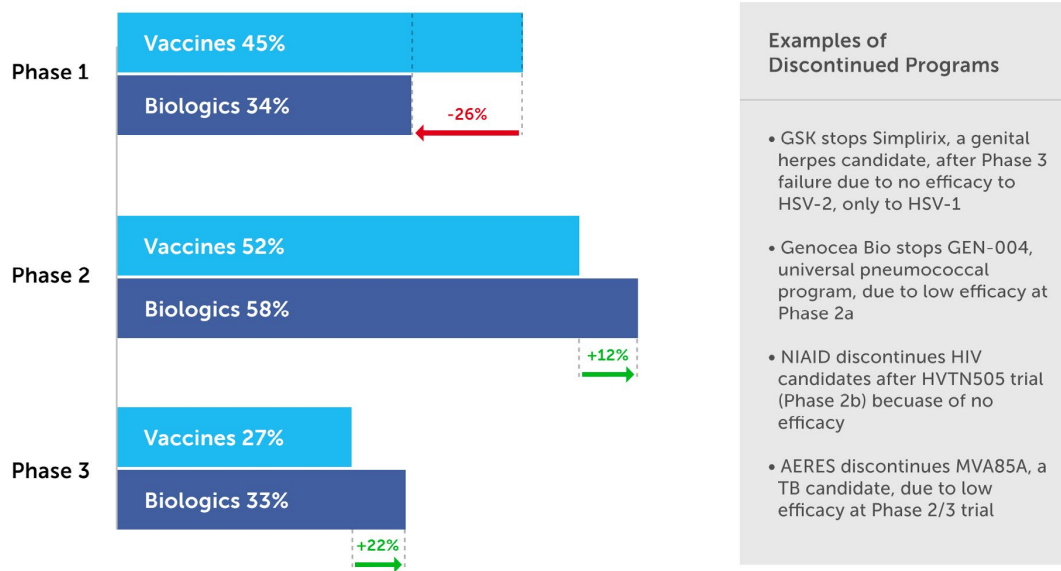


<sup>1</sup> Defined as any vaccine that received FDA approval in the preceding 5 years.  
 Source: EvaluatePharma, September 2018; McKinsey & Company internal analysis of data

Figure 4: Vaccine candidates receive fewer “shots on goal” relative to other biologics

**Attrition Rate of Programs**

% from 2007 - 2017



Attrition in Phase 1 driven by 3 factors: (1) limited funding, especially for Phase 2, (2) biologic complexity of candidates, and (3) evidence that identifies unviable candidates earlier than for biologics

Source: *Pharmaprojects*, September 2018; McKinsey & Company internal analysis of data

Historically, the “Big 4” global vaccine manufacturers (i.e., Merck, GSK, Pfizer, and Sanofi) have driven most innovation. However, in the past 5 years, their pipeline growth has been flat, and the majority of new programs in the pipeline have been driven by emerging market players with “me too” vaccines (that is, vaccines undifferentiated from those already on market) and by smaller biotechs (Figure 5). While there is potential for significant innovation from biotechs, there is an open question around whether sufficient absorptive capacity exists in the system to bring these programs through development. Indeed, our observations on the pharmaceutical industry suggest that manufacturers vary broadly in their ability to identify, acquire, and gain from external innovation.

Figure 5: The market is starting to see an increase in the number of overall new programs, largely driven by small biotechs and emerging market players

**Vaccine Development Programs Globally<sup>1</sup>**

Number of Programs



<sup>1</sup> Includes only infectious disease vaccines, both prophylactic and therapeutic; excludes all cancer vaccines.

<sup>2</sup> Refers to top 20 players with vaccines pipelines, including in-licensed products.

<sup>3</sup> Including Japan.

Source: Pharmaprojects, September 2018; McKinsey & Company internal analysis of data

The external market expects a return to growth, with analysts forecasting six percent to nine percent growth in the global vaccine market over the next 5 years (EvaluatePharma, 2018). In addition, there is considerable potential for new antigens as well as novel synthetic modalities (i.e., mRNA-based products). Inherent in these market assumptions is the successful Phase 3 completion of several vaccines in development as well as further advancements in innovation. The key question is whether the vaccine industry can overcome several challenges that are currently impacting innovation.

## CHALLENGES TO INNOVATION IN VACCINES

Our research on industry trends suggests reinvigorating vaccine innovation will require addressing three underlying issues:

- Increased investment requirements for research and development (R&D) and manufacturing.
- Increased opportunity cost as relative investment economics converge with biologics.
- Higher technical complexity and commercial uncertainty compared to recent innovations.

These challenges have the potential to impact different categories of vaccine manufacturers in different ways: On the one side, they could create opportunities for innovation by new players; on the other side, they may create structural barriers that offer an advantage to existing players.

### **Increased Investment Requirements for R&D and Manufacturing**

One emerging trend contributing to a progressively challenging environment for innovation is an increase in investment requirements for R&D and manufacturing. These shifts in the broader infrastructure impact the overall economic equation of the vaccine industry by increasing the length of time and costs associated with innovation.

On the R&D side, regulatory scrutiny overall is on the rise across more complex products (e.g., biologics, vaccines, and other sterile injectables), with longer timelines for vaccine approvals (Figure 6). Given the preventive nature of these drugs, vaccines also face a heightened bar for quality and safety, thereby adding both complexity and additional costs throughout the development process.

**Figure 6: Time to regulatory approval for vaccines is consistently higher than other drug categories**

**Time to FDA Approval by Drug Technology**

Median Number of Days



<sup>1</sup> Data not available due to no FDA approvals recorded in this year.

Source: EvaluatePharma, February 2018; McKinsey & Company internal analysis of data

In addition, many of the pipeline programs have lower incidence rates than prior vaccine innovations and thus face evolving clinical trial requirements. Clinical trials need to elicit a strong and lasting immune response and require a natural incidence of the disease where the trial is being conducted. Developing a vaccine for diseases with a lower incidence requires many more participants and sites to demonstrate efficacy, increasing both the cost and the duration of the trials.

On the manufacturing side, we have seen shortages, recalls, and other manufacturing challenges in recent years — recent examples include typhoid and varicella recalls due to efficacy concerns, as well as shortages and prequalification removals for pediatric combination vaccines due to manufacturing reliability issues. These issues have resulted in lost sales and significant investment requirements to transform vaccine manufacturing networks.

### **Increased Opportunity Cost as Relative Investment Economics Converge with Biologics**

Increased technical challenges are resulting in the convergence of success rates for bringing vaccines to market with those of biologics. However, given the higher revenues derived from blockbuster biologics compared to vaccines — for example, the largest biologic's revenues are more than two to three times greater than those for the largest vaccine, pneumococcal conjugate, with peak revenues of \$6 billion (EvaluatePharma, 2018) — this convergence of success rates reduces the relative attractiveness for investment in vaccines compared with the past, especially as the largest global vaccine manufacturers all have competing priorities. As pharmaceutical companies allocate capital to opportunities with the highest return on investment, this change in the relative investment economics will be a consideration in future decision-making for vaccine innovation.

### **Higher Technical Complexity and Commercial Uncertainty Compared to Recent Innovations**

Many vaccine industry leaders consider the recent major innovations (such as pneumococcal, rotavirus, and HPV) to be lower-hanging fruit in immunization — these vaccines had high commercial potential and higher relative technical feasibility. The remaining potential innovations face increased commercial uncertainty and technical complexity in an environment of increasing R&D and manufacturing investments, as described above.

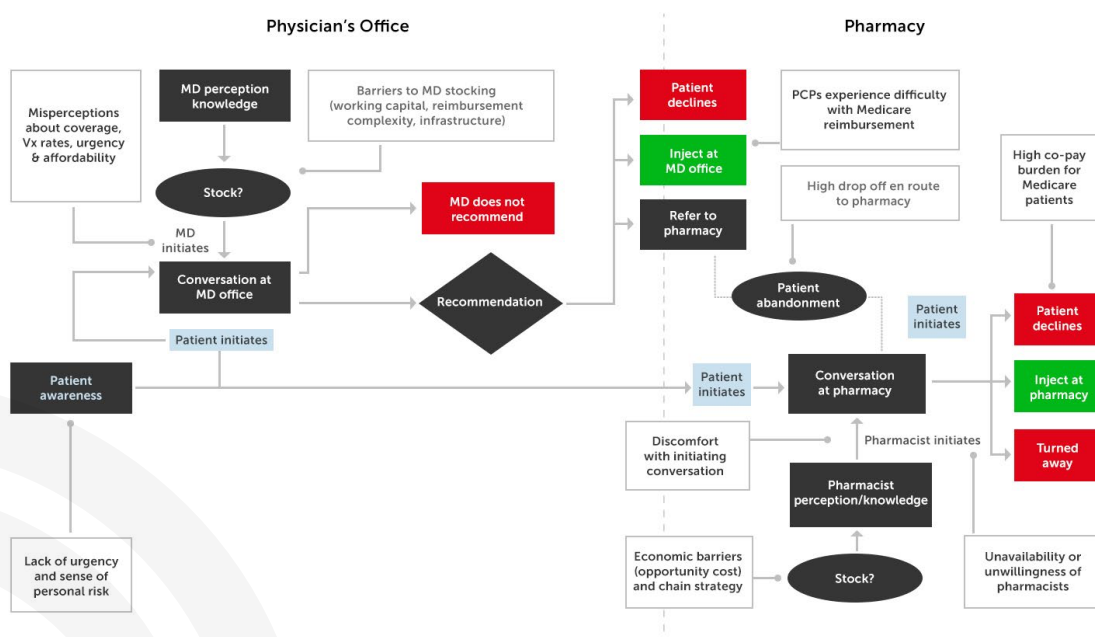
From a commercial perspective, the pipeline of remaining innovations has a different commercial profile (Figure 7) — the absolute size of relevant populations is smaller, and the programs have less established pathways compared to pediatric or adolescent vaccines, which have recommended immunization schedules. In this context, capturing the full market potential still requires navigating a complex vaccine care flow with many influences and inputs (Figure 8). Obtaining the recommendation for inclusion in immunization schedules is the most uncertain step, as vaccine manufacturers typically have limited visibility on what recommendations to expect. This step is critical to secure reimbursement and access to markets and builds additional uncertainty in relation to return on investment for vaccine manufacturers. Additionally, once a vaccine is on the market, capturing market share requires navigating a broad set of stakeholders (physicians, retailers, payers, and patients), often with uncertain pricing and market demand contributing to additional commercial risk. In terms of technical feasibility, the remaining pipeline innovations are challenging; in particular, the potential blockbusters are often long sought-after vaccines that have been tried (and failed) multiple times in the past (e.g., HIV and universal flu).

Figure 7: Drivers of commercial attractiveness and technical feasibility

	Commercial Attractiveness		Technical Feasibility	
	<b>Assessment of Commercial Attractiveness</b>		<b>Assessment of Technical Feasibility</b>	<b>Example of Challenging Vaccine</b>
<b>Volume</b>	<ul style="list-style-type: none"> <li>Is there a large population at risk? Does the disease have a high incidence?</li> </ul>	<b>Natural Immunity</b>	<ul style="list-style-type: none"> <li>Does the pathogen trigger antibody response and confer immunity post-infection?</li> </ul>	<ul style="list-style-type: none"> <li>HIV</li> </ul>
<b>Price</b>	<ul style="list-style-type: none"> <li>Are people or payers willing to pay for the vaccine?</li> <li>Are there other vaccines or treatments on the market?</li> </ul>	<b>Adaptability of Pathogen</b>	<ul style="list-style-type: none"> <li>Is there high antigenic variability or does the pathogen mutate/evolve quickly?</li> </ul>	<ul style="list-style-type: none"> <li>Universal flu</li> </ul>
<b>Ability to Access Market</b>	<ul style="list-style-type: none"> <li>Are there existing commercial channels?</li> <li>If not, is there a way to make the commercial access work?</li> </ul>	<b>Strength of Immune Response</b>	<ul style="list-style-type: none"> <li>Can an adequate immune response be achieved? Are adjuvants necessary and do they work?</li> </ul>	<ul style="list-style-type: none"> <li>Pertussis</li> </ul>
		<b>Clinical Trials</b>	<ul style="list-style-type: none"> <li>How easy are clinical trials (i.e., finding population at risk, diagnosing, prevalence of disease)? Is there a correlate of protection?</li> </ul>	<ul style="list-style-type: none"> <li>Clostridium difficile</li> </ul>

Source: McKinsey & Company internal analysis (2018)

Figure 8: Capturing share requires navigating a complex vaccine care flow with many influences and inputs



Source: McKinsey & Company internal analysis (2018)



Stepping back, as the sources of growth shift from relatively low-hanging fruit to new opportunities for innovation, we see six vaccine archetypes emerging with varying levels of technical complexity and commercial opportunity (Figure 9).

- 1. High Income:** Vaccines targeting diseases in high-income markets including health care-acquired infections (e.g., *Clostridium difficile* and *Staphylococcus*) as well as other disease areas (e.g., norovirus). These programs have moderate technical feasibility but vary in commercial potential. For example, nosocomial vaccines have high market potential but unclear commercial models and indications (i.e., they may not have a clear immunization schedule), whereas other high-income vaccines have moderate commercial potential and a mix of potential commercial models.
- 2. Potential Blockbusters:** Vaccines targeting high-burden diseases with large potential patient pools (such as HIV and respiratory syncytial virus), thus carrying a high commercial potential. Challenging technical complexity results in low-to-moderate technical feasibility for these innovations.
- 3. Therapeutic Vaccines:** Vaccines used as a method of treatment to fight an existing disease or condition, rather than as a preventive measure. Potential applications include oncology, smoking cessation, and addiction. High unmet need results in a high commercial potential for these programs, but technical feasibility is low to moderate.
- 4. Incremental Improvements:** Improvements to existing vaccines to address unmet needs (i.e., improvements in efficacy, duration of protection, and ease of use). While technical feasibility is moderate to high, the commercial value is uncertain, particularly in assessing the price these incremental innovations can command.
- 5. Emerging Threats:** Vaccines targeting emerging epidemiology threats and future priorities for innovation (e.g., Ebola and Chagas disease). These programs have an uncertain commercial demand profile given lack of clarity on the willingness of governments and agencies to stockpile significant amounts or pay more than “costs” to maintain supply options. The technical feasibility is moderate and varies by disease.
- 6. Low Income:** Vaccines targeting diseases with a higher burden in low-income markets (e.g., tuberculosis and malaria) with moderate commercial potential and low-to-moderate technical feasibility. The evolution of supply and demand for vaccines in emerging markets creates significant ambiguity, compounded by the entrance of new local players. In addition, as Gavi, the Vaccine Alliance (Gavi), countries (developing countries that receive support from the Gavi public-private partnership to increase access to vaccines) transition to take over responsibility for financing vaccine programs, growth in those emerging markets may slow — as experienced in Angola and the Republic of the

Congo, where the governments have struggled to meet their co-financing requirements in recent years (Kallenberg et al., 2016).

**Figure 9: We have identified six archetypes of vaccine innovation**

ARCHETYPE	DESCRIPTION	PROFILE	EXAMPLES
<b>1 High Income &amp; Nosocomial</b>	<ul style="list-style-type: none"> <li>Vaccines targeting healthcare-acquired infections with larger burden in high-income markets</li> </ul>	<ul style="list-style-type: none"> <li>Moderate technical feasibility</li> <li>Nosocomial: market potential high, but commercial model/indication unclear</li> <li>Others: moderate commercial potential &amp; mix of commercial models</li> </ul>	<ul style="list-style-type: none"> <li>Clostridium difficile</li> <li>Staphylococcus</li> <li>Norovirus</li> </ul>
<b>2 Potential Blockbusters</b>	<ul style="list-style-type: none"> <li>Vaccines targeting high-burden diseases with large potential patient pools</li> </ul>	<ul style="list-style-type: none"> <li>High commercial potential - large burden of disease and large potential patient pools</li> <li>Low-moderate technical feasibility</li> </ul>	<ul style="list-style-type: none"> <li>HIV</li> <li>Universal influenza</li> <li>Respiratory syncytial virus</li> <li>Hepatitis C</li> </ul>
<b>3 Therapeutic Vaccines</b>	<ul style="list-style-type: none"> <li>Vaccines used as a method of treatment to fight an existing disease/condition, rather than a preventative measure</li> </ul>	<ul style="list-style-type: none"> <li>Commercial potential high</li> <li>Low-moderate technical feasibility</li> </ul>	<ul style="list-style-type: none"> <li>Oncology</li> <li>Smoking cessation</li> <li>Addiction</li> </ul>
<b>4 Incremental Improvements</b>	<ul style="list-style-type: none"> <li>Improvement to existing vaccines to address unmet needs (e.g., in efficacy, duration of protection, ease of use)</li> </ul>	<ul style="list-style-type: none"> <li>Uncertain commercial value for incremental improvements, especially on price</li> <li>Moderate-high technical feasibility</li> </ul>	<ul style="list-style-type: none"> <li>Pertussis</li> <li>Typhoid</li> <li>Measles</li> </ul>
<b>5 Emerging Threats</b>	<ul style="list-style-type: none"> <li>Vaccines targeting emerging epidemiology threats and future priorities for innovation</li> </ul>	<ul style="list-style-type: none"> <li>Limited reliable and large-scale commercial potential e.g., vaccine only stockpiles</li> <li>Moderate technical feasibility</li> </ul>	<ul style="list-style-type: none"> <li>Ebola</li> <li>Zika</li> <li>Middle East Respiratory Syndrome</li> </ul>
<b>6 Low Income</b>	<ul style="list-style-type: none"> <li>Vaccines targeting diseases with higher burden in low-income markets</li> </ul>	<ul style="list-style-type: none"> <li>Moderate commercial potential and mix of commercial models</li> <li>Low-moderate technical feasibility</li> </ul>	<ul style="list-style-type: none"> <li>Malaria</li> <li>Tuberculosis</li> </ul>

Source: McKinsey & Company internal analysis (2018)

## WHERE DO WE GO FROM HERE?

Given these commercial and technical challenges and the criticality of vaccines in advancing public health, continued innovation in the vaccine industry can best be supported via a comprehensive and shared agenda across key stakeholders: researchers, manufacturers, government and policy makers, and payers. Several potential solutions might contribute to refueling the vaccines innovation engine.

- Demand Clarity:** Earlier clarity on market demand would provide increased commercial certainty for vaccine manufacturers by helping to identify the priority innovations to address unmet market need. One potential method might be to publish target product profiles (TPPs) on the desired innovations. In addition, this could include advance

recommendations that would clarify likely recommendation and/or use given a specific profile and would be particularly relevant for high-income, nosocomial vaccines (Archetype 1), as well as innovation in therapeutic vaccines (Archetype 3).

- **Value Communication:** Stakeholders could also consider becoming more active in articulating priorities and value associated with material improvements to an existing standard of care (e.g., addressing whether an improved *Haemophilus influenzae* type B (Hib) vaccine would achieve market premium or whether universal flu vaccines are adequately valued). This improved transparency would be particularly relevant for innovation addressing incremental improvements in vaccines (Archetype 4).
- **Economic Incentives:** One potential approach to creating incentives for innovation is to facilitate funding for new models of industry partnership for both emerging threats (Archetype 5) and low-income unmet needs (Archetype 6). The Coalition for Epidemic Preparedness Innovations (CEPI) has made significant progress in building alliances to finance and coordinate the development of new vaccines to prevent and contain infectious disease epidemics. However, as CEPI primarily focuses on early-stage development (through Phase 2 clinical trials), additional solutions are still needed to address the challenge of funding the high-cost, late-stage development.
- **Collaboration and Data Sharing:** Improving transparency and data sharing could be valuable in overcoming technical challenges and achieving breakthroughs where they are most needed. Private-public partnerships may be particularly relevant for Archetype 4 innovations, such as HIV, tuberculosis, and respiratory syncytial virus (RSV) — in such cases significant need remains, but there are critical technical challenges and the expected economics do not currently warrant industry leadership. A second form of collaboration could be to develop new technology platforms that enable shared production across antigens; this would be particularly valuable for emergency response innovations (Archetype 5) to enable rapid scale-up. A third option could be to generate more data regarding the burden of disease for pathogens that may be emerging or simply poorly understood. Finally, enhanced clarity on the public end-to-end vaccines and immunization agenda — from funding early research to trial design and preferred clinical trial site networks and ultimately through approval and market access — could boost innovation.
- **Early Consultation on Innovation Design:** Meanwhile, manufacturers could seek early and active engagement with regulatory and recommendation agencies throughout the development lifecycle of new vaccines to obtain timely input to key decisions, including trial design, thereby helping to de-risk the commercial uncertainty of innovation.

## CONCLUSION

After a period of significant growth over the past 2 decades, vaccine innovation faces several challenges going forward — namely increased investment requirements for R&D and manufacturing, higher opportunity cost as relative economics converge with biologics, and greater technical complexity and commercial uncertainty compared to recent innovations. However, we believe there remains significant opportunity for vaccine manufacturers and other stakeholders (regulators, policy makers, and payers) to facilitate the next wave of vaccine innovation.



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# INFLUENZA VACCINATION AND THE VACCINATION ECOSYSTEM

Michael Watson, M.B.Ch.B., M.R.C.P., A.F.P.M.

## INTRODUCTION AND CONTEXT

Influenza is a global viral infectious disease. It infects 10 to 20 percent of us annually, causing an estimated 3 million to 5 million influenza cases (Peasah, Azziz-Baumgartner, Breese, Meltzer, & Widdowson, 2013) and 300,000 to 645,000 influenza-associated respiratory deaths (Iuliano et al., 2018). Seasonal influenza is caused by continuously mutating (drifting) strains of influenza A that are naturally selected by their ability to evade the immune response induced by preceding strains. The continuous arms race between our immune system and the virus means we will all experience many influenza infections in our lifetimes.

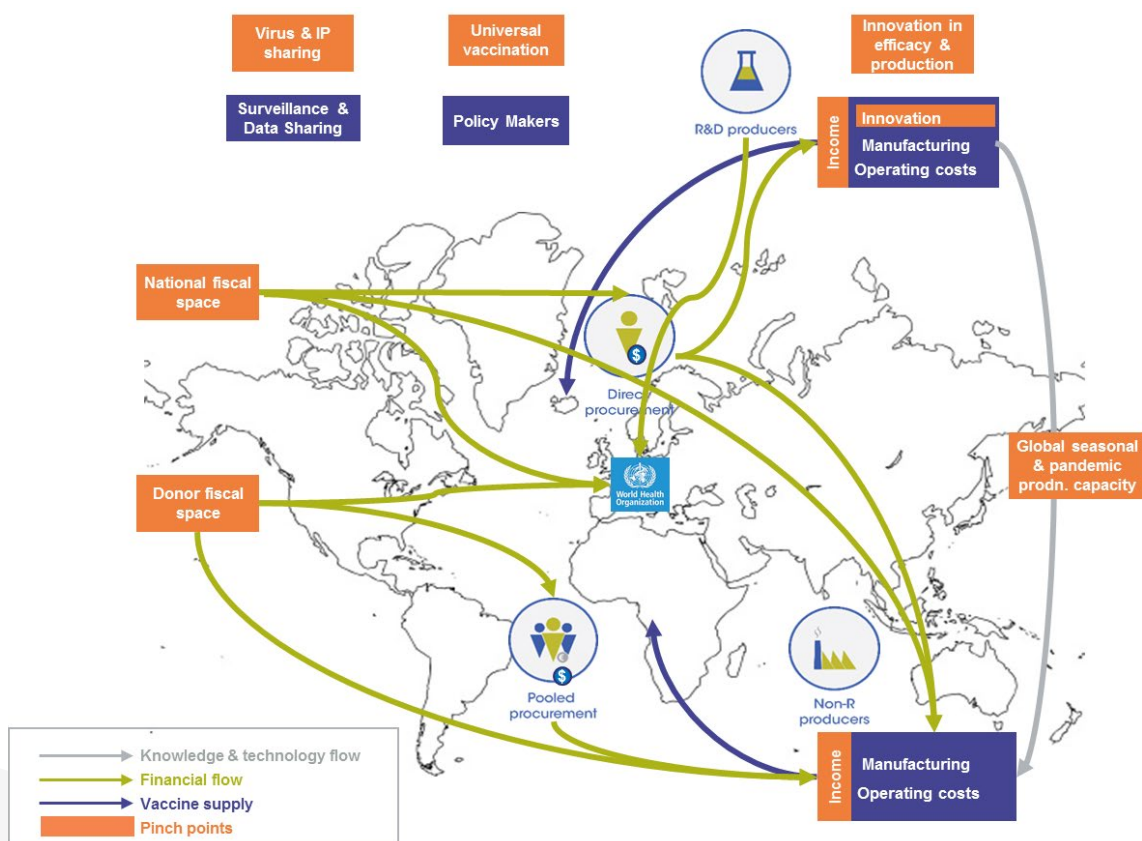
Every 10 to 40 years, a more significant shift in the influenza strain results from wholesale swapping of human influenza genetic segments (Hemagglutinin [H] and/or Neuraminidase [N]) with segments from bird or pig strains. Our immunity to these shifted strains ranges from partial to usually non-existent, resulting in global pandemics that kill between 120,000 and more than 50 million people.

Protection against influenza relies on personal hygiene measures, antivirals, and vaccines. However, hand hygiene; sneezing into arms instead of hands; and avoiding hand shaking, hugging and kissing, crowds, and young children are unreliable or simply unavoidable. Antiviral drugs may reduce the duration of illness, but late diagnosis, restricted access, and potential for resistance limit their use and usefulness (Lehnert, Pletz, Reuss, & Schaberg, 2016). Prevention through vaccination, therefore, remains our best medical strategy. However, we need to improve on the unpredictable and often low effectiveness of influenza vaccines and, ideally, overcome the obligation to annually develop and produce seasonal or pandemic strain-specific vaccines (Belongia et al., 2016).

Influenza is a global problem, and effective vaccination relies on a global, interconnected ecosystem of policymakers, funders, producers, innovators, vaccinators, and vaccinees (Figure 1). A healthy influenza ecosystem would ensure that vaccines are available (researched, developed, and produced in sufficient quantities), accessible (through vaccination recommendations, distribution, and administration), and affordable (for both the producer and purchaser) and that potential vaccinees are aware of the availability and

benefits of vaccination (health promotion; Watson & Faron de Goër, 2016). People need to accept being vaccinated as well as physically seek vaccination (activation; Thomson, Robinson, & Vallée-Tourangeau, 2016). A functioning, healthy, and sustainable ecosystem would make research, development, and production of vaccines a priority, technically possible, affordable, and rewarding for both producers and purchasers. It would also ensure the political will and priority essential for recommendations; health promotion; surveillance and virus sharing; and the infrastructure, process, and people needed to get from vaccine to vaccination. Finally, it would require a society that seeks, accepts, and values vaccination (Thomson et al., 2016).

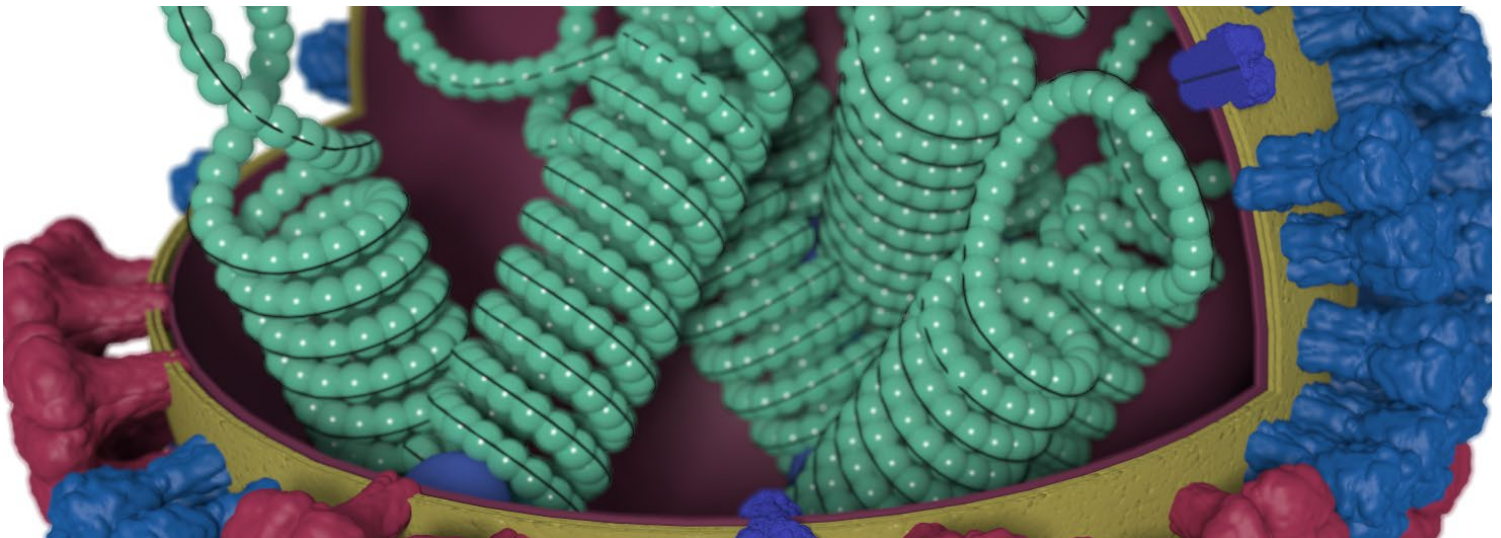
Figure 1: Global influenza vaccination ecosystem



Source: Adapted with permission from Watson & Faron de Goër (2016)



However, vaccination is presented with a perceptual dilemma. It sits at the interface between social and market norms (Elster, 1989). Society expects social norms, such as education, clean water, clean air, and vaccination, to be free or very inexpensive to minimize the possibility that access to vaccination might be denied due to cost. Yet, sustainability relies on a healthy market norm to incentivize and reward a reliable, high-quality, rapid vaccine supply as well as investment in innovation for the future. The social norm that tempts procurers and policymakers to reduce vaccines to a short-term commodity puts the long term at risk (English, 2015). Such short-term, static efficiency has played a role in the market failure of antibiotics and snake anti-venoms. (Brown, 2012; Projan, 2003). The economic reality is that longer-term, dynamic efficiency is essential for sustainability, entrepreneurship, and innovation (Saadatian-Elahi et al., 2017; Scherer, 1986; Watson & Faron de Goër, 2016). It is essential for all public health innovation, including influenza, that we build and preserve an ecosystem that balances the short- and long-term and the social and market norms to protect the triangle of affordability, quality, and innovation.



## THE PROBLEM TO SOLVE

Seasonal influenza's high annual global burden of excess morbidity and mortality affects all ages and has high associated medical, economic, and social costs. The estimated 291,243 to 645,832 influenza-associated respiratory deaths annually (4.0 to 8.8 per 100,000 individuals) are highest in older and younger populations. There are 17.9 to 223.5 deaths per 100,000 in those over 75 years of age and an estimated 9,243 to 105,690 deaths among children younger than 5 years of age. An estimated 2.8 to 16.5 per 100,000 individuals die from

influenza in Sub-Saharan Africa and 3.5 to 9.2 per 100,000 in Southeast Asia (Iuliano et al., 2018). In the U.S., the annual total economic burden of influenza is an estimated \$11.2 billion (\$6.3 billion to \$25.3 billion) made up of \$3.2 billion (\$1.5 billion to \$11.7 billion) direct and \$8.0 billion (\$4.8 billion to \$13.6 billion) indirect costs. This is driven by 3.7 million office-based outpatient visits, 650,000 emergency department visits, 247,000 hospitalizations, 36,300 deaths, and 20.1 million days of lost productivity (Putri, Muscatello, Stockwell, & Newall, 2018).

Influenza pandemics occur every 10 to 40 years, typically with at least 1 million excess deaths but ranging from 120,000 to more than 50 million deaths. The 1918-19 (H1N1) pandemic killed an estimated 50 million people (Taugenberger & Morens, 2006), the 1957-59 (H2N2) pandemic killed 1.1 million (Viboud et al., 2016), and the 1968 (H3N2) pandemic took 1 million lives. The 2009 (H1N1) pandemic caused between 123,000 and 203,000 excess deaths globally (Simonsen et al., 2013). This atypically low pandemic mortality in 2009 was associated with residual immunity from previously circulating H1N1 strains, especially in the elderly. The downside was that 85 percent of deaths occurred in those less than 65 years of age. It could be postulated that the high 1918-19 H1N1 mortality is also an outlier, related to the exceptional confluence of world war and mass population movements. However, these conditions have been largely recreated with a global population that has risen from 1918's 2 billion to today's 7 billion, crowded megacities, conflicts, and ever-increasing intercontinental travel volumes. If the 1918-19 pandemic were transposed to today's population, it would result in an estimated 51 million to 81 million excess deaths (Murray, Lopez, Chin, Feehan, & Hill, 2006).

One million excess deaths would rank an "average" pandemic between 14th and 15th in the World Health Organization's (WHO) 2016 global mortality listings, ahead of hypertensive heart disease and just below HIV/AIDS. Two million deaths would raise it to fifth, above Alzheimer's; 10 million deaths or more would raise it to first place (WHO, 2018).

**Influenza pandemics occur every 10 to 40 years, typically with at least 1 million excess deaths but ranging from 120,000 to more than 50 million deaths.**

## WHAT THE SOLUTION MIGHT LOOK LIKE

A healthy influenza ecosystem (Figure 1) would enable the world to be equally prepared to handle both seasonal and pandemic influenza. Ideally this would come from a UIV able to protect against all influenza A and B strains over multiple years. Such a vaccine would ideally be produced rapidly in sufficient quantities and used by everyone. But this has yet to be achieved (Plotkin, 2018; Valkenburg et al., 2018). Meanwhile, current technology requires the vaccine to be redeveloped each year.

A healthy ecosystem would provide sufficient incentive for policymakers to make and enforce universal vaccination policy, budget holders to create fiscal space to purchase vaccines and fund vaccination, producers to produce, purchasers to purchase, vaccinators to vaccinate, and vaccinees to be vaccinated. Such an ecosystem would minimize influenza virus circulation and prevent or react rapidly to pandemics. This demands a production technology that is faster than the current egg-based approach. In addition, many improvements are needed in surveillance, vaccine efficacy, and speed and scale of production. The ecosystem should, therefore, also incentivize innovators to innovate. Finally, the seasonal ecosystem must be connected to the pandemic ecosystem. This would ensure vaccines rapidly matched to emerging and emerged pandemic strains and scalable production was able to meet global pandemic needs for a single strain (monovalent) vaccine in days or weeks, not months or years.

### What Are the Key Elements of the Ecosystem?

Figure 1 is a schematic overview of the influenza ecosystem derived from a more general global vaccine ecosystem model (Watson & Faron de Goër, 2016). The main components are:

- **Surveillance and Data-Sharing System:** The system must include real-time global access to and sharing of both animal and human influenza strains to minimize the time between a strain's emergence, its detection, and a response.
- **Policymakers, Payers, and Implementers:** At a global and national level, it must be clear who will centralize and share surveillance data and who will make and implement policy for whom, when and how, and who will pay.
- **Vaccine Producers:** They may be purely producers of vaccines as a high-volume public health commodity, or they may also be innovators seeking to innovate the vaccine, its production, and administration.
- **Vaccine Innovators:** These may also be producers, but they may equally be academic institutions, biotech companies, or non-governmental organizations. Innovation may encompass the vaccine itself, its production, and delivery and the way we prepare for and respond to seasonal and pandemic influenza.
- **Vaccine Purchasers:** These may be individual governments, or pooled procurers for groups of nations such as Gavi, the Vaccine Alliance (Gavi); The Revolving Fund; or UNICEF.
- **Vaccinators:** Inclusion of those that organize and perform the vaccination is essential (European Centre for Disease, Prevention and Control [ECDC], 2009).
- **Vaccinees:** There is no protection without vaccinees seeking and accepting vaccination (Thomson et al., 2016).

## LEARNING LESSONS FROM SARS, H1N1 (2009), AND H5N1 INFLUENZA SURVEILLANCE

Global influenza surveillance is led by the WHO's Global Influenza Surveillance Network and coordinated through five WHO Collaborating Centers (in Atlanta, Beijing, London, Melbourne, and Tokyo) and 136 National Influenza Centres (NICs) in 106 countries. They monitor human influenza disease burden, antigenic drift, and antiviral drug resistance in seasonal influenza viruses. They also obtain virus isolates for updating influenza vaccines and detect and obtain isolates of new influenza viruses infecting humans, especially shifted strains with pandemic potential.

The surveillance system learned and implemented valuable lessons from the SARS, H1N1 (2009), and H5N1 influenza experiences. There are, however, remaining challenges in virus collection and sharing needed to overcome national stigma, smooth communication channels, address claims to intellectual property rights, and manage the timing of seasonal (the later the better) and pandemic (the faster the better) strain selection.



### 2003 SARS Outbreak

The 2003 SARS outbreak illustrated that epidemics can be inconvenient and embarrassing for governments, especially at election time. Public acknowledgement of an outbreak risks socioeconomic instability and a negative impact on the image of a region or a country and its government. It is also a reminder that bureaucratic communication can be long and subject to bottlenecks from holiday periods, legal restrictions, and political sensitivities and that for emergencies, other communication mechanisms may be needed. Finally, it is a reminder that cellular and internet media and networks may be more effective surveillance tools (Smolinski et al., 2015).

The SARS outbreak began in November 2002 as an unusual respiratory disease in the province of Guangdong, China. The national expert team report reached Beijing on January 27, 2003 (Huang, 2004), and a warning bulletin was issued to hospitals, but it coincided with the Chinese New Year (Pomfret, 2003). Further unofficial reporting of the outbreak risked punishment for leaking "state secrets." By February 8, reports of a "deadly flu" circulating on mobile phones and increased local internet searches for bird flu and anthrax prompted

official acknowledgement of the disease with reassurance that the illness was under control (Hai & Hua, 2003). However, a reporting blackout was reimposed on February 23 prior to the National People's Congress in March. As a result, little information on the first outbreak of SARS was shared with the WHO until early April 2003, 5 months after it began.

The subsequent reaction of the Chinese government was swift — against both the SARS epidemic and those who had not managed it well. But earlier notification and collaboration may well have prevented some of the approximate 400 further SARS deaths in Hong Kong, Canada, Taiwan, Singapore, Vietnam, the U.S., and the Philippines and the estimated gross domestic product loss of \$4 billion in Hong Kong, \$3 billion in China, \$6 billion in Canada, and \$5 billion in Singapore (Keogh-Brown & Smith, 2008).



### **2009 Influenza Pandemic**

The 2009 influenza pandemic demonstrated the value of rapid, open communication by the Mexican authorities and the value of the media for surveillance. It also reinforced the importance of accessing genetic sequencing capability as soon as possible.

The first (H1N1) 2009 cases occurred in Mexico during February and early March 2009. On April 12, the Pan American Health Organization's (PAHO) media surveillance picked up local media suggestions that pollution from oxidation tanks in swine farms was to blame for the fact that a fifth of the pig-farming community of La Gloria, Veracruz, was sick. This was rapidly shared with Canada and the U.S. Meanwhile, Mexican laboratories identified a novel

influenza A virus suggestive of a pig origin. However, the strain was not genotyped until the Centers for Disease Control and Prevention (CDC) analyzed samples from two affected children in California, leading to its “Cal09” strain designation. The WHO’s Strategic Health Operations Centre was activated in the early hours of April 24, Central European Time.

### **H5N1 Indonesia, Pandemic Intellectual Property, and Nagoya Protocol**

The H5N1 experience illustrated how critical and vulnerable real-time surveillance and strain sharing is and how global response and solutions may be needed. Indonesia’s refusal to share its H5N1 strains was only resolved through three far-reaching initiatives:

- In 2007, the WHO awarded \$18 million to Brazil, India, Indonesia, Mexico, Thailand, and Vietnam to develop their own vaccine manufacturing capability (Gostin, Phelan, Stoto, Kraemer, & Reddy, 2014).
- In May 2011, the WHO’s Pandemic Influenza Preparedness (PIP) framework was established to define responsibilities for countries, national laboratories, vaccine manufacturers, and the WHO (n.d.-b). It included obligations for sharing viruses and set up a global benefit-sharing system, including multi-million-dollar contributions from influenza vaccine manufacturers.
- Finally, in October 2014, the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits came into force (Rabitz, 2017).

Highly pathogenic H5N1 influenza A was first identified in poultry in Indonesia in December 2003. By the end of 2007, Indonesia had the largest number of human cases (116), with a case fatality rate of over 80 percent. There were fears of a widespread pandemic, and international preparation was in full flow. However, in 2007, the Indonesian government pulled out of the Global Influenza Surveillance Network. It had discovered that an Australian pharmaceutical company had developed a vaccine based on an Indonesian strain without Indonesia’s knowledge or consent (Lancet Infectious Diseases, 2008). Indonesia was concerned that this vaccine, based on their “sovereign property,” would either not be available to their country or sold at unaffordable prices.

**The H5N1 experience illustrated how critical and vulnerable real-time surveillance and strain sharing is and how global response and solutions may be needed.**

### Ongoing Surveillance and Intellectual Property Issues

The lessons learned from the SARS, H1N1 (2009), and H5N1 pandemics have improved influenza preparedness and response. However, this has not prevented subsequent attempts to patent emerging pathogens and delays in virus sharing. Most recently, the Erasmus University of Amsterdam has been criticized for patenting the MERS-CoV genome that it had received from the Saudi Arabian authorities after the index cases in 2012 (Arnold, 2013), and China has been called out by the U.S. and the U.K. for not sharing current H7N9 influenza samples to allow the world to track and prepare for the current, most significant pandemic threat (Baumgaertner, 2018; Majid, 2018).

### Elements for Better Harmonizing Global Influenza Vaccination

In 2003, the WHO urged member states to provide influenza vaccination to high-risk groups and to achieve a vaccination coverage rate of 75 percent in the elderly (World Health Assembly, 2003). Some high-income and middle-income countries have since gone beyond this and target annual vaccination for the entire population. However, many countries have yet to implement even the most basic influenza vaccination program. As a result, 15 years after this WHO recommendation and 9 years after the 2009 pandemic, the variation in influenza vaccine use globally is marked.



The WHO Regional Office for the Americas (AMRO) and the U.S. lead the way in influenza vaccination (Palache et al., 2017). In the U.S., over 50 percent of children below 17 years of age are now vaccinated annually, as are close to 50 percent of all adults (CDC, 2017). This is driven by clear recommendations from the CDC and its Advisory Committee on Immunization Practices (ACIP) which has, in turn, stimulated domestic vaccine supply and access initiatives, such as vaccination in pharmacies. In Europe, all but two countries have national policy recommendations for seasonal influenza vaccination. However, only 10 of 44 countries have reached population-wide coverage of 50 percent or higher (Jorgensen et al., 2018). In contrast, the vaccination coverage in China in 2- to 7-year-old children is just 12 percent and lower in the rest of the population (Xu et al., 2017).

Whilst a recommendation to vaccinate is essential, it is not sufficient. Successful vaccination also requires:

- Political commitment that prioritizes influenza and the necessary fiscal space to purchase vaccines and fund vaccination.
- Policy implementation activities to build public trust and to monitor adverse events; disease surveillance to monitor seasonal influenza incidence and the public health and economic impacts as well as to provide a broader evaluation of vaccination program impact and communication of this impact. Capabilities and capacity are needed for real-time management of a vaccination program, including monitoring vaccination coverage and communication of progress against targets, as well as real-time adjustments to improve vaccination performance, including correction of supply issues, access issues, communication issues, etc.
- Vaccinators also need support through reminder letters, expert training, conferences, university lectures, education on the risk and benefits of seasonal influenza, as well as very practical training on how to achieve high vaccination coverage.
- Vaccine advocacy and education targeted at all audiences; that may include media campaigns, with or without high profile public figures, as well as campaigns targeted at critical populations, such as the elderly, high-risk target groups (such as those with Chronic Obstructive Pulmonary Disease or COPD, heart disease, etc.).
- Access to vaccination may require increases in delivery points, including many/all public or private health care facilities, such as pharmacies; elimination of restrictions, such as location of residence, to access delivery points; elimination of or reduction in payment for vaccination; and potentially, a provision for vaccination at no out-of-pocket expense to vaccinees.
- Incentives. It may help to provide monetary incentives to vaccinators and compensate vaccinators for vaccination.

### **Vaccine Innovators**

Until recently, influenza vaccine production was exclusively egg-based. However, this process requires 4 to 6 months for production, and efficacy is variable and, in most seasons, suboptimal, especially in the elderly. Over the past decade, the pooled vaccine efficacy for such vaccines was 33 percent (95 percent confidence interval [CI] 26 to 39) for H3N2; 54 percent (95 percent CI 46 to 61) for type B; 61 percent (95 percent CI 57 to 65) for H1N1pdm09; and 67 percent (95 percent CI 29 to 85) for H1N1. Efficacy was 73 percent (95 percent CI 61 to 81) for monovalent vaccine against H1N1pdm09. Among older adults



(age 60 years and older), vaccine efficacy was 24 percent (95 percent CI -6 to 45) for H3N2; 63 percent (95 percent CI 33 to 79) for type B; and 62 percent (95 percent CI 36 to 78) for H1N1pdm09 (Belongia et al., 2016).

The two main drivers of innovations in influenza vaccines today are the size and growth of the global influenza vaccine market (approximately \$3.8 billion, albeit increasingly commoditized and low margin) and governmental investment in pandemic preparedness (KPMG, 2017). The market value drives those seeking to increase their market share to develop differentiated seasonal vaccines, but government investment aims to incentivize innovation in pandemic preparedness, which, in turn, may bring an opportunity to enter the seasonal flu market.

Differentiation has included moving from trivalent to quadrivalent seasonal vaccines (Barberis et al., 2016), moving from egg- to cell-based production (e.g., Novartis and Seqirus), seeking improved efficacy in the elderly (Sanofi Pasteur's high dose vaccine [DiazGranados et al., 2014] or Seqirus's MF59 adjuvanted vaccine), alternative routes of administration (Sanofi Pasteur's intradermal vaccines), or a combination of these (Medimmune's intranasal CAIV vaccine). These recently licensed vaccines represent evolutionary, rather than revolutionary, innovations in influenza prevention.

However, there are also several potential revolutionary vaccines in prelicensure development, many driven by government funding and investment of recent technologies through the U.S. Biomedical Advanced Research and Development Authority (BARDA) and the National Institutes of Health (NIH), including the National Institute of Allergy and Infectious Diseases (NIAID).

Table 1 summarizes the R&D pipeline for vaccines intended to provide protection for more than a single season. Table 2 summarizes the R&D pipeline for pandemic influenza vaccines.



**Table 1: Global universal flu candidate pipeline as of March 2016**

Approach	Sponsor	R&D Phase
M2e fusion peptide in nanoparticle carriers	KJ BioSciences LLC	Pre-Clinical
HA stalk nanoparticle	NIAID	Pre-Clinical
Trimeric HA Stem	Janssen	Pre-Clinical
Chimeric HA stalk	GSK	Pre-Clinical
Nanoparticle	NIAID	Pre-Clinical
COBRA	Sanofi Pasteur/UPMC	Pre-Clinical
Locked Soluble Headless HA	Avatar Medical LLC/NIAID	Pre-Clinical
AM2 LAIV	FluGen	Pre-Clinical
MVA with NP/M1	Vaccitech	Phase 1
Rep Def hAs5 with HA/TLR3 agonist	Vaxart	Phase 1
NPA/NPB/M1/M2	SEEK	Phase 1
Nanoemulsion T-cell vaccine	NanoBio	Phase 1
DNA HA/M2e/NP	Inovio	Phase 1
$\Delta$ NS LAIV	Vivaldi Biosciences	Phase 1
Ad5	Nasovax	Phase 1
Conserved HA/NP/M1	BiondVax	Phase 2
VLP – Plant-based	Medicago	Phase 2
Rep Def Adenovirus	Altimune	Phase 2

Source: Donis (2016)

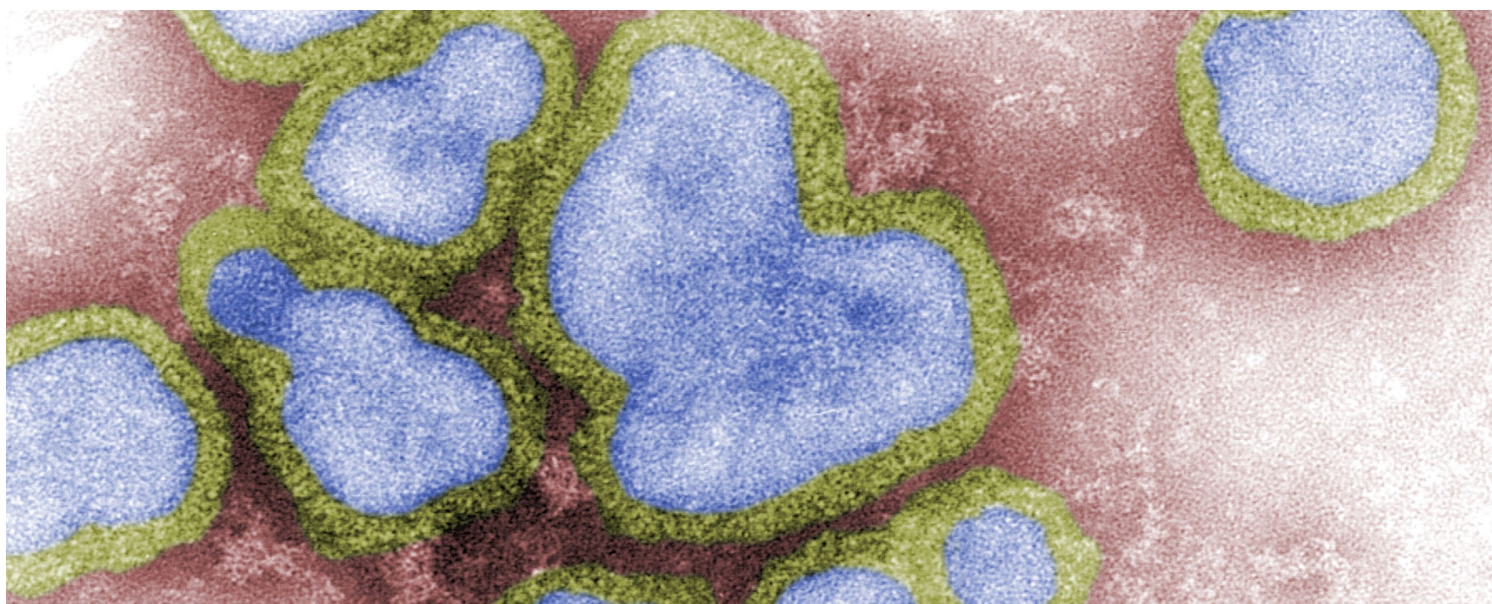
**Table 2: Global clinical-stage pipeline for pandemic influenza vaccines**

Influenza Indication	Vaccine Name	Sponsor	R&D Phase
Prevention	influenza A virus vaccine H1N1 (li-key hybrid cancer vaccine)	Antigen Express	Phase 1
Prevention	influenza A virus vaccine H5N1 (li-key hybrid cancer vaccine)	Antigen Express	Phase 1
Prevention	influenza A virus H5N8 vaccine	Seqirus	Phase 1
Prevention	influenza A virus H7N9 vaccine	EpiVax	Phase 1
Prevention	influenza H3N2 vaccine (intranasal)	FluGen	Phase 1
Prevention	mRNA-1440 (influenza virus H10N8 messenger RNA vaccine)	Moderna	Phase 1
Prevention	mRNA-1851 (influenza virus H7N9 messenger RNA vaccine)	Moderna	Phase 1
Prevention (elderly)	MER4101 (MAS-1-adjuvanted seasonal inactivated influenza vaccine)	Mercia Pharma	Phase 1
Influenza (prevention) (6-<48 months of age)	Flucelvax® influenza vaccine	Seqirus	Phase 1/2 completed
Prevention	deltaFLU-LAIV (influenza virus delta NS1 vaccine)	Vivaldi Biosciences	Phase 2
Prevention	FluNhance™ recombinant influenza vaccine	Protein Sciences	Phase 2
Prevention	M-001 (universal influenza vaccine)	BiondVax; NIAID	Phase 2
Prevention	VXA-A1.1-H1 (H1N1); (oral influenza vaccine)	Vaxart	Phase 2
Prevention (6-59 months of age)	Afluria Quadrivalent® influenza vaccine	Seqirus	Phase 3 completed
Prevention (adults, elderly)	influenza A virus H5N1 vaccine	Seqirus	Phase 3
Prevention (elderly)	Fluzone® QIV HD quadrivalent inactivated influenza vaccine – high dose	Sanofi Pasteur	Phase 3
Prevention (6-35 months of age)	VaxiGrip® QIV IM quadrivalent inactivated influenza vaccine	Sanofi Pasteur	Phase 3
Prevention	Influenza virus vaccine quadrivalent (aQIV-aQIV)	Seqirus	Phase 3

Note: Grey shaded boxes are egg-based platforms; white are non-egg-based platforms.

Source: U.S. Department of Health and Human Services (2017)

Tables 1 and 2 show that innovation in influenza vaccines is not from established players alone. New entrants are attracted by the size of the influenza market as well as the significant incentives offered by BARDA and the NIH/NIAID for pandemic influenza preparedness and improved seasonal efficacy. The NIAID 2018 budget includes \$2.17 billion for biodefense and \$312 million for influenza. This places biodefense and influenza on par with NIH/NIAID spending on HIV/AIDS, emerging infectious diseases, mental health, minority health, all other infectious diseases, neurodegenerative diseases, health disparities, and cardiovascular diseases (NIH, 2019). In addition, there is approximately \$1.5 billion available from the Assistant Secretary for Preparedness and Response (ASPR) at the U.S. Department of Health and Human Services (HHS) for BARDA for diagnostic tools, vaccines and therapeutics, and international preparedness for pandemic influenza and emerging infectious diseases (ASPR, 2018).



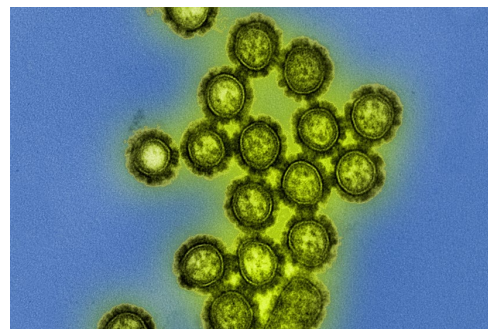
The elevated level of U.S. government investment in influenza contrasts sharply with spending in other countries. For example, the United Kingdom's total R&D investment in all diseases is \$3.5 billion, Germany's is \$1.9 billion, and Japan's is \$1.4 billion. It is difficult to identify any other countries that are making significant investments in seasonal or pandemic influenza vaccine innovation.

## OPTIONS FOR IMPROVING THE HEALTH OF THE GLOBAL AND NATIONAL INFLUENZA VACCINATION ECOSYSTEM

### **Diagnostics, Surveillance, and Data-Sharing System**

Strengthening the tools (diagnostics), systems, data-sharing, and analysis for the rapid detection and surveillance of influenza is essential to better respond to both seasonal and pandemic influenza. Such innovations would have benefits beyond influenza to both established and emerging infectious diseases. It is incredible that we do not have the diagnostics that would enable rapid, point-of-care identification of all respiratory disease presenting to primary care. Imagine the benefit this would bring to better antibiotic husbandry and understanding of disease.

The SARS and 2009 H1N1 experiences illustrate the potential of cellular- and internet-based search and messaging data as early warnings for both seasonal and epidemic activity. Implementing “chatter”-based surveillance could make us less dependent on the fundamentally risky international sharing of viruses and data (Smolinski et al., 2015).



### **Sharing of Best Practices**

Clear and implemented policies for seasonal and pandemic influenza are at the core of an effective ecosystem. The WHO’s Global Action Plan for Influenza Vaccines (GAP; WHO, n.d.-a) and PIP (WHO, n.d.-b) programs are designed to support a broad range of nations in being better prepared for pandemic influenza. However, there is so much expertise and good practice around the world for both seasonal and pandemic influenza preparedness that there may be many more opportunities for sharing good practices among nations.

### **Incentives for Vaccine Production**

Influenza vaccines are currently produced in the U.S., Canada, Russia, China, Japan, South Korea, U.K., France, Italy, Germany, Austria, the Netherlands, and Belgium, and there are WHO prequalified vaccines produced in India, Indonesia, Brazil, Vietnam, Thailand, Argentina, and Romania. There are also BARDA/WHO grantees in Mexico, South Africa, Egypt, Kazakhstan, and Vietnam. And there are emerging or potential influenza vaccine manufacturers in Iran and Serbia (Bright, 2013). However, producers can and will only sustainably produce vaccines if there are the appropriate incentives and predictable demand, driven by policy, implementation, and sufficient, protected fiscal space.

## Vaccine Innovation

We need faster production and greater scalability of more effective influenza vaccines. Ideally, these would be multi-season, multi-strain, or even universal influenza vaccines that would be highly effective, safe, and long-lasting. We could also benefit from more effective antiviral drugs and antibodies. The time from strain identification to vaccination and protection needs to be reduced from the current 4 to 6 months to less than 1 month. We need to move away from egg-based production to platforms such as mRNA that can be faster and precisely strain and antigen matched based simply on knowing the nucleotide sequence of the epidemic or pandemic strain (Bahl et al., 2017). The basic reproductive number of influenza is less than two in most settings. As a result, even moderate improvements in efficacy along with improved coverage would provide a huge impact pending the arrival of universal vaccines (Biggerstaff, Cauchemez, Reed, Gambhir, & Finelli, 2014; Eichner, Schwehm, Eichner, & Gerlier, 2017). The investment by BARDA and NIAID in novel influenza vaccines is critical, but given the global threat of influenza, greater contributions from other governments and organizations could be invaluable (Innovation Partnership for a Roadmap on Vaccines in Europe [IPROVE], 2016).

**We need faster production and greater scalability of more effective influenza vaccines. Ideally, these would be multi-season, multi-strain, or even universal influenza vaccines that would be highly effective, safe, and long-lasting.**

## The Affordability, Quality, and Innovation Triangle

The purchasers of vaccines need to purchase as many vaccines as they need at a price that they can afford. When no innovation is sought and production and delivery and speed and quality are at the required levels, then it is reasonable to purchase vaccines as a commodity (Watson & Faron de Goër 2016). When improvements are needed across the full innovation, quality, and supply chain — as they are for influenza — then it is critical that procurement practices factor these into their strategy and incorporate tactics to ensure that there are true incentives for innovators. A car manufacturer may treat O-rings as a commodity, but the development of the electronic engine management system for the next model will require careful partnership and incentivizing pricing with the manufacturer's supplier/innovation partner. However, the market failures of antimicrobials and anti-venoms demonstrate the dangers of a short-term, static efficiency approach and commoditization of interventions, such as vaccines, that deliver so much societal value and that need investment in innovation (Brown, 2012; Potet & Cohn, 2015).

## CONCLUSION

Influenza is one of the most predictable and potentially catastrophic threats to human health, wealth, and happiness. Successful global protection from influenza depends on a healthy ecosystem. Whilst “ecosystem” may be an overused analogy for complex systems, influenza and at-risk natural ecosystems have much in common. For neither, is it clear who owns the problem or the solution, especially globally, and without ownership the necessary focus and investment are unlikely to materialize. For both, there are conflicts between the short- and long-term goals, needs, and incentives of providers and producers. Like natural ecosystems, innovation will be essential, but the low probability of a single solution emerging straightaway means that incremental wins should not be ignored. Markets and ecosystems both fail or succeed on their ability to adapt sustainably to a changing habitat. Both may surprise us with their resilience or with their calamitous decline, and we worry that intervening in such “wicked problems” could have significant unintended consequences (Peters, 2017). However, whilst inaction in the face of such uncertainty and complexity is very tempting for both, such collective procrastination will lead to grave consequences.



The influenza ecosystem is sensitive to the conflict between social and market norms and the tendency to commoditize “public goods” so no one is excluded. Increasing commoditization of the U.S. influenza vaccine market may be good for the purchaser in the short term, but it could fail in the long term if it deprives the ecosystem of the investment necessary for a reliable, quality supply and fails to reward and incentivize innovation for the future.

However, ecosystems and markets adapt. Today's seasonal influenza ecosystem continues to function through fewer, larger species (producers). Simultaneously, these species are adapting by seeking new, unoccupied and potentially larger niches through differentiation. These include higher dose and adjuvanted vaccines for the elderly, novel vaccination routes, and quadrivalent, rather than trivalent, vaccines.

The pandemic vaccine market is, however, a true market failure. The lack of a predictable market means it cannot function sustainably without governmental or other financing. BARDA and NIAID provide much of this. The expectation is that such funding will ensure pandemic preparedness and response and that emerging innovation may reinvigorate the seasonal and even the entire vaccine ecosystem. Universal influenza vaccination would be a perfect example.

However, market and ecosystem sustainability depend on more than funding alone. The habitat itself must be kept healthy. For influenza this might include:

- Improving surveillance and diagnostics, from global strain sharing to rapid diagnosis in doctors' offices, pharmacies, or even at home.
- Increasing understanding of the immune response, its age-related development in individuals, and what differentiates responders from non-responders, including clinical research studies.
- Developing better in-vitro and in-vivo biomarkers and animal models to better predict vaccine efficacy.
- Using systems approaches to integrate heterogeneous data sets such as those above.
- Using human challenge models (CHI) for influenza to seek more rapid efficacy proof-of-concept in fewer subjects, thereby de-risking the Phase 3.
- Encouraging a more global approach to funding of innovation in influenza.
- Establishing forums and mechanisms for sharing learning, know-how, and data.
- Establishing clear policy on how better vaccines would be used and reimbursed to populate market projections made by every company when they start to develop a vaccine.
- Investing in excellent health communications and promotion to optimize coverage and acceptance.



The impact of ecosystem interventions will need to be continuously tested and adapted. Feedback of relevant data and novel market strategies, pricing, and incentives may be needed; these would reward and incentivize the significant socioeconomic value that today's vaccination generates and that future innovation can offer (Bloom, Fan, & Sevilla, 2018).



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Watson has also worked with WHO, Gavi, the Bill & Melinda Gates Foundation, and other partners on polio eradication, pandemic influenza, HIV and cholera vaccines, and the recently launched dengue vaccine and chaired the EU FP7-funded IPROVE project that recently delivered a European Vaccines R&D Roadmap for Europe. He currently leads the infectious diseases team at Moderna, which is developing a range of mRNA-based vaccines and therapeutics. The mRNA platform has enabled clinical stage vaccines against H7N9, H10N8, Chikungunya, Zika, CMV, and HPMV/PIV3 and pre-clinical projects that include yellow fever, dengue, and MERS-CoV. His efforts to understand often competing drivers and barriers to commercially viable and global health vaccine R&D, production, and sustainability has focused him on the vaccination ecosystem and possible alternative models.

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# 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:<sup>1</sup> brain cancer, arthritis, gene therapy, and genetic testing, and is roughly double the median program funding for all areas.<sup>1</sup> 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.

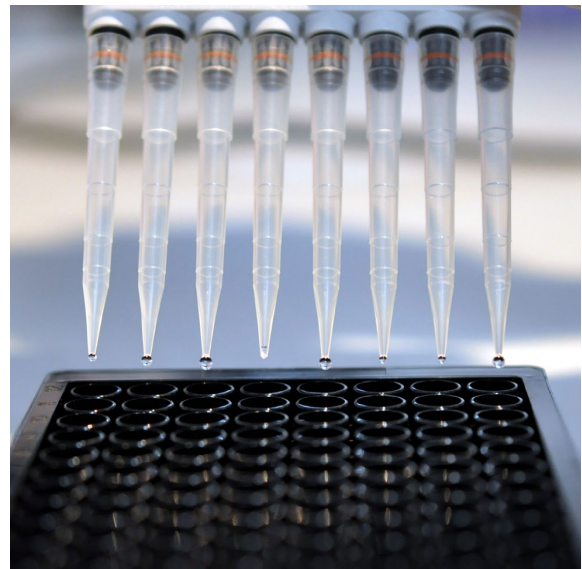
<sup>1</sup>The median value was calculated from data in 285 "Research/Disease Areas" from Fiscal Year 2014 to Fiscal Year 2018 (NIH, 2019).



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<sup>2</sup> 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.



<sup>2</sup> 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
<b>Traditional, whole pathogen vaccines</b>		
The virus is made less virulent or inactivated/killed through chemical or biological manipulation.		
<b>Live, attenuated</b>	<ul style="list-style-type: none"> <li>- Good immunogenicity</li> <li>- Long-lived immune response</li> <li>- T and B cell activated</li> <li>- Additional heterologous effects (poorly understood)</li> <li>- Can sometimes achieve cross-protection to related strains</li> <li>- Can have good effect with oral dosing (easy to administer)</li> </ul>	<ul style="list-style-type: none"> <li>- Slow timeline</li> <li>- Possible reversion to highly antigenic type</li> <li>- Depends on the mutation rate of the pathogen</li> <li>- Hard to tell what mutations were important in attenuating virulence</li> <li>- Poor stability and difficult maintenance</li> </ul>
<b>Inactivated, killed</b>	<ul style="list-style-type: none"> <li>- Good immunogenicity</li> <li>- Safer than live attenuated (low probability of disease)</li> <li>- Good stability and easy maintenance</li> </ul>	<ul style="list-style-type: none"> <li>- Can lose effectiveness over time (boosters needed)</li> <li>- Immunogenicity typically less than live attenuated</li> <li>- Cross protection rarer but still possible</li> <li>- No or poor immunity in oral dosing</li> </ul>
<b>Modern, recombinant vaccines</b>		
Specific parts of the virus (antigens) with the potential to initiate an immune response are used instead of the whole virus.		
<b>Protein/ subunit</b>	<ul style="list-style-type: none"> <li>- Safe because they cannot cause disease they prevent and there is no possibility of reversion to virulence</li> <li>- Cannot spread to unimmunized individuals</li> <li>- Stable and long-lasting (less susceptible to light, temperature, humidity)</li> <li>- Can distinguish vaccinated people from infected people</li> </ul>	<ul style="list-style-type: none"> <li>- Requires multiple doses</li> <li>- Immunogenicity typically less than whole organism</li> <li>- Can create local inflammation</li> </ul>
<b>DNA</b>	<ul style="list-style-type: none"> <li>- No risk of infection</li> <li>- Antigen presentation by both MHC class I and class II molecules</li> <li>- Polarize T-cell response toward type 1 or type 2</li> <li>- Immune response focused on antigen of interest</li> <li>- Ease of development and production</li> <li>- Stability for storage and shipping</li> <li>- Cost-effectiveness</li> <li>- Obviates need for peptide synthesis, expression and purification of recombinant proteins</li> <li>- In vivo expression ensures protein more closely resembles normal eukaryotic structure, with accompanying post-translational modifications</li> </ul>	<ul style="list-style-type: none"> <li>- Limited to protein immunogens (not useful for non-protein-based antigens, such as bacterial polysaccharides)</li> <li>- Possibility of inducing autoimmunity</li> <li>- Possibility of tolerance to the antigen (protein) produced</li> <li>- Potential for atypical processing of bacterial and parasite protein (limited effect)</li> <li>- Risk of integration into genome or other damage</li> <li>- Limited memory cell induction</li> </ul>
<b>RNA</b>	<ul style="list-style-type: none"> <li>- No risk of infection</li> <li>- Ease of development and production</li> <li>- Obviates need for peptide synthesis, expression, and purification of recombinant proteins</li> <li>- In vivo expression ensures protein more closely resembles normal eukaryotic structure, with accompanying post-translational modifications</li> <li>- Room temperature storage for at least 18 months</li> </ul>	<ul style="list-style-type: none"> <li>- Fairly low immunogenicity (requires more work on delivery and adjuvants)</li> </ul>

## SCIENCE PROGRESS IN STAGES OF INFLUENZA VACCINE DEVELOPMENT

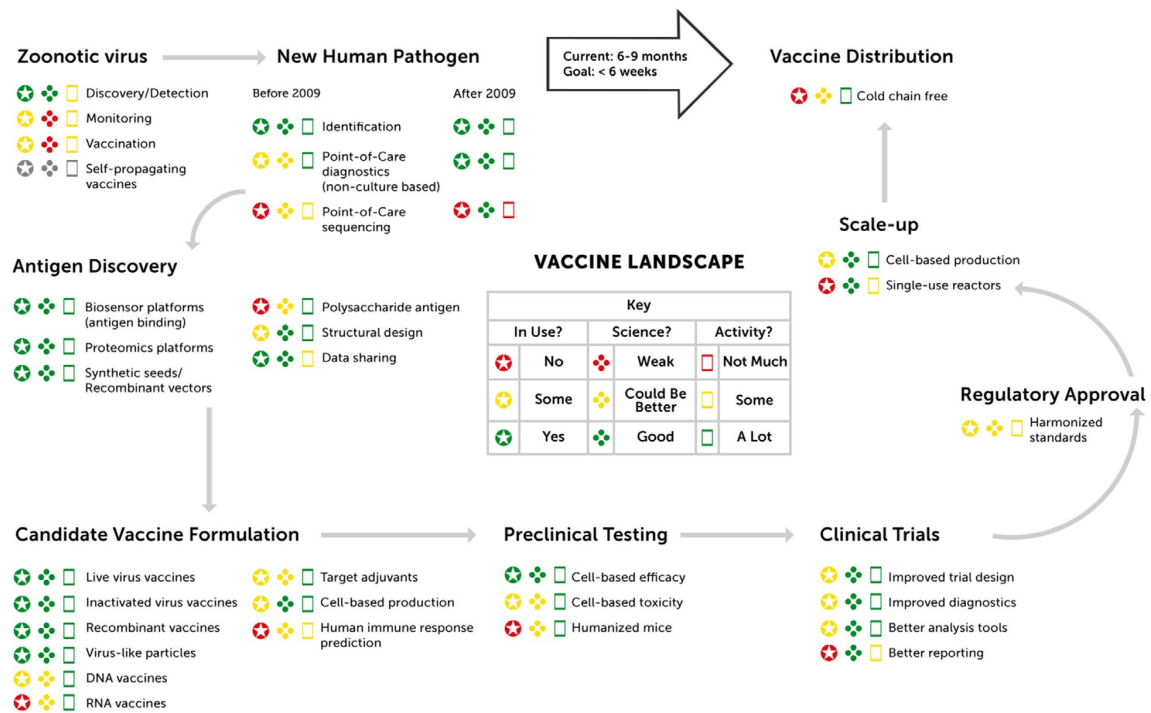
There appear to be many open science questions in general vaccine development, including:

- 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<sup>3</sup> 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.

<sup>3</sup> 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.

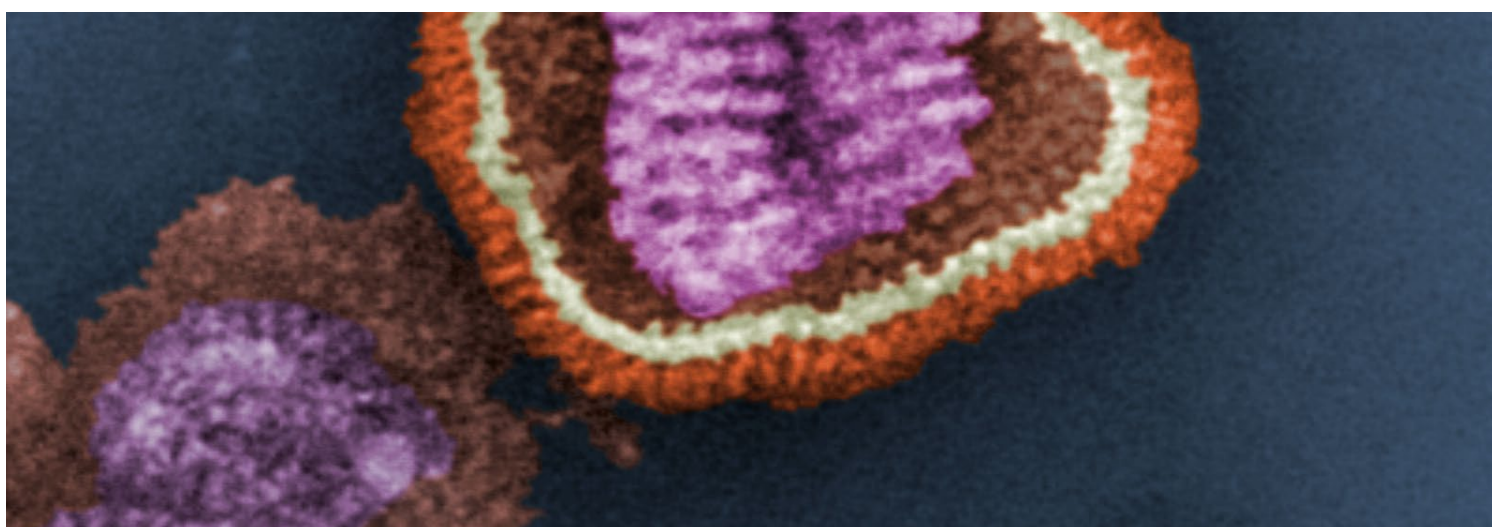
**1. Tracking Infectious Disease and Identifying New Pathogens.** There is a substantial ongoing effort to better understand the various pathways by which new influenza strains arise through host jumping. The FLURISK project, started in December 2011 through funding from the European Food Safety Authority, 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.<sup>4</sup>

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

<sup>4</sup> 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.



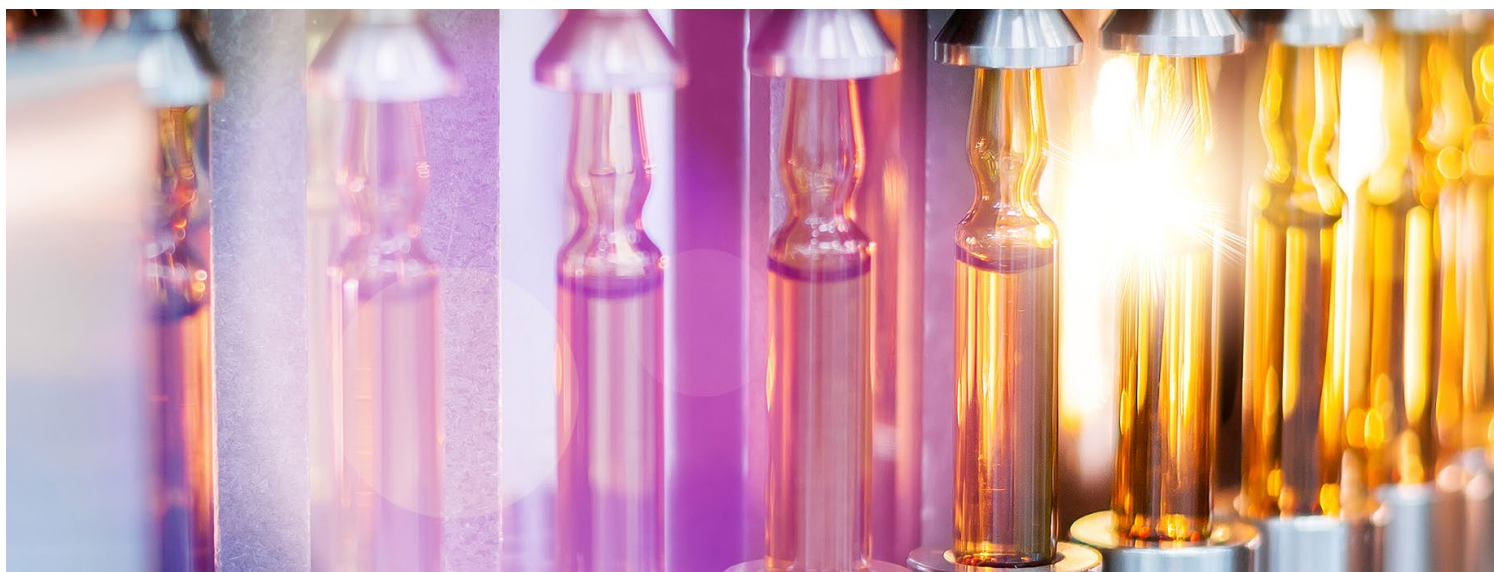
- 2. Antigen Discovery.** Antigen discovery is perhaps the most critical area for decisions in vaccine design and the most active area for vaccine science R&D. Scientists have made amazing progress in recombinant systems, structural biology, proteomic platforms, and biosensors that can measure, design, 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<sup>5</sup> 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.

<sup>5</sup> "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



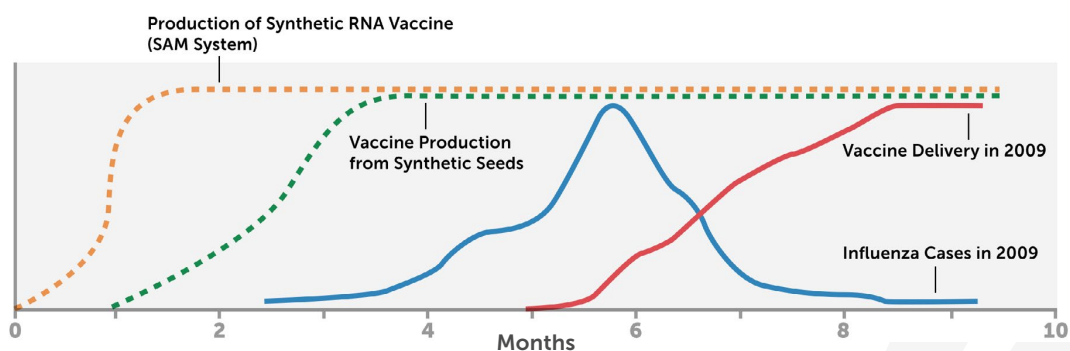
turnaround of cell-based systems, access to appropriate culture facilities that meet safety standards is required. While developed nations have some capacity for converting cell culture systems normally used to produce biomaterials or pharmaceuticals to emergency vaccine production, this conversion can 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 (Lagerwijn, 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
<b>Activities</b>					
<ul style="list-style-type: none"> <li>̣ Understanding basic immunology</li> <li>̣ Understanding population effects in humans and reservoir species</li> <li>̣ Virus evolution</li> </ul>	<ul style="list-style-type: none"> <li>̣ Screening</li> <li>̣ In vitro studies</li> <li>̣ Animal studies</li> </ul>	<ul style="list-style-type: none"> <li>̣ Kinetics</li> <li>̣ Toxicology</li> <li>̣ Formulation/production protocols</li> <li>̣ Clinical trials</li> </ul>	<ul style="list-style-type: none"> <li>̣ Scale-up</li> <li>̣ Quality control</li> <li>̣ Regulatory approval</li> </ul>	<ul style="list-style-type: none"> <li>̣ Marketing</li> <li>̣ Sales</li> <li>̣ Clinical use</li> </ul>	<ul style="list-style-type: none"> <li>̣ Sampling</li> <li>̣ Data processing</li> <li>̣ Information sharing</li> </ul>
<b>Main Barriers</b>					
<ul style="list-style-type: none"> <li>̣ Opportunity costs – other research topics better suited to achieving academic goals</li> </ul>	<ul style="list-style-type: none"> <li>̣ Opportunity costs – other research topics better suited to achieving academic goals</li> <li>̣ Lack of funding for translational work</li> </ul>	<ul style="list-style-type: none"> <li>̣ Lack of investment</li> <li>̣ Failure of candidates</li> <li>̣ Economic risk</li> </ul>	<ul style="list-style-type: none"> <li>̣ Costs</li> <li>̣ Opportunity costs for resource use</li> <li>̣ Technical barriers</li> <li>̣ Regulatory hurdles</li> </ul>	<ul style="list-style-type: none"> <li>̣ Low consumer confidence</li> <li>̣ Low price point drives down profits</li> <li>̣ Competition</li> </ul>	<ul style="list-style-type: none"> <li>̣ Opportunity costs for resource use</li> <li>̣ Non-standardized practices</li> <li>̣ Lack of coordination</li> </ul>
<b>Consequences</b>					
<ul style="list-style-type: none"> <li>̣ Research is not focused on goal</li> </ul>	<ul style="list-style-type: none"> <li>̣ Research is not focused on goal</li> <li>̣ Information generated is insufficient to move forward</li> </ul>	<ul style="list-style-type: none"> <li>̣ Research is not focused on goal</li> <li>̣ Information generated is insufficient to move forward</li> </ul>	<ul style="list-style-type: none"> <li>̣ Good candidates may be abandoned</li> <li>̣ Other products prioritized</li> </ul>	<ul style="list-style-type: none"> <li>̣ Other products take priority</li> <li>̣ Supply does not meet demand</li> </ul>	<ul style="list-style-type: none"> <li>̣ Weak information</li> <li>̣ Reduced efficacy</li> </ul>
<b>Agents</b>					
Mainly Academia Some Industry/Govt.	Academia Some Industry	Mainly Industry Some Government	Mainly Industry Some Government	Industry, Government, NGOs	Mainly Government Some NGOs/ Academia
<b>Business-As-Usual Incentives</b>					
Academia		Industry		Government/NGOs	
<ul style="list-style-type: none"> <li>̣ Funding</li> <li>̣ Publish high-profile papers (innovative new approaches)</li> <li>̣ Make progress in 3 to 5 years (student/postdoc project)</li> </ul>		<ul style="list-style-type: none"> <li>̣ Convert leads to products (path to sizable market)</li> <li>̣ Integrate activities (efficient use of resources)</li> <li>̣ Optimize financial/pipeline models (path to profitability)</li> </ul>		<ul style="list-style-type: none"> <li>̣ Address large unmet needs</li> <li>̣ Integrate activities (efficient use of resources)</li> <li>̣ Optimize political and financial capabilities</li> </ul>	

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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