THE SABIN-ASPEN
VACCINE SCIENCE & POLICY GROUP

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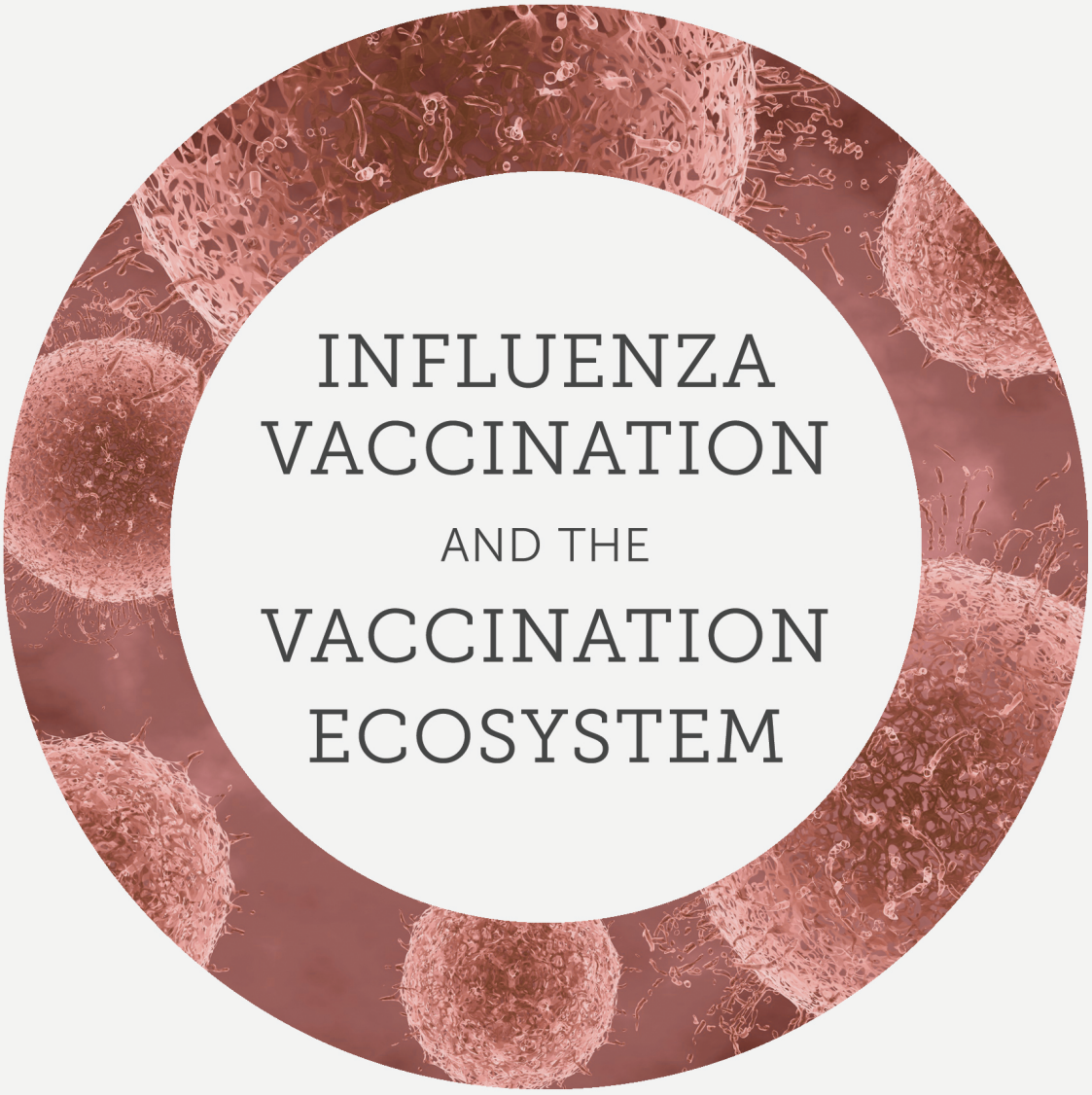

INFLUENZA VACCINATION AND THE VACCINATION ECOSYSTEM

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

An excerpt from
Accelerating the Development of a Universal Influenza Vaccine

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FOREWORD

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

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

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

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

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

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

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

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

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

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

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

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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.

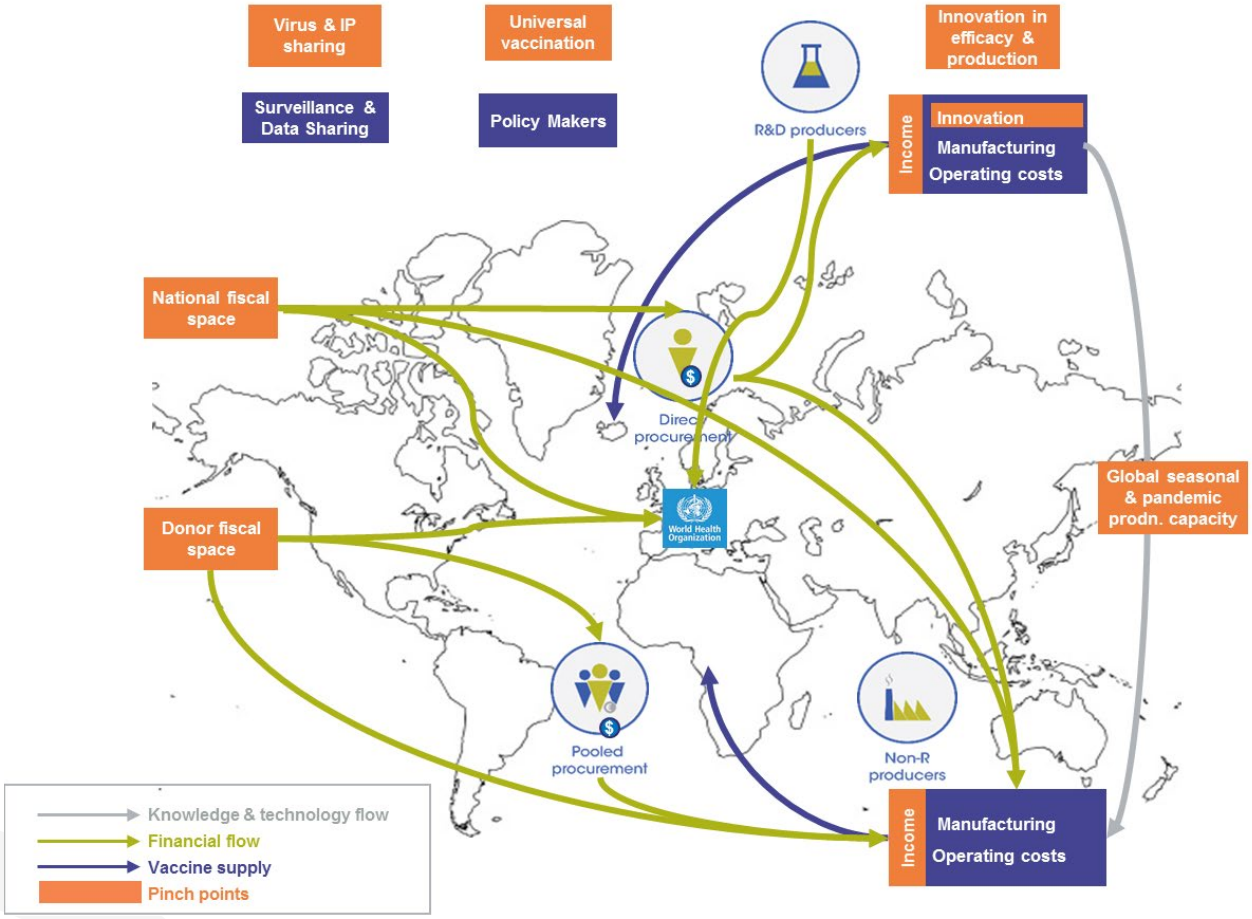
Every 10 to 40 years, a more significant shift in the influenza strain results from wholesale swapping of human influenza genetic segments (Hemagglutinin [H] and/or Neuraminidase [N]) with segments from bird or pig strains. Our immunity to these shifted strains ranges from partial to usually non-existent,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

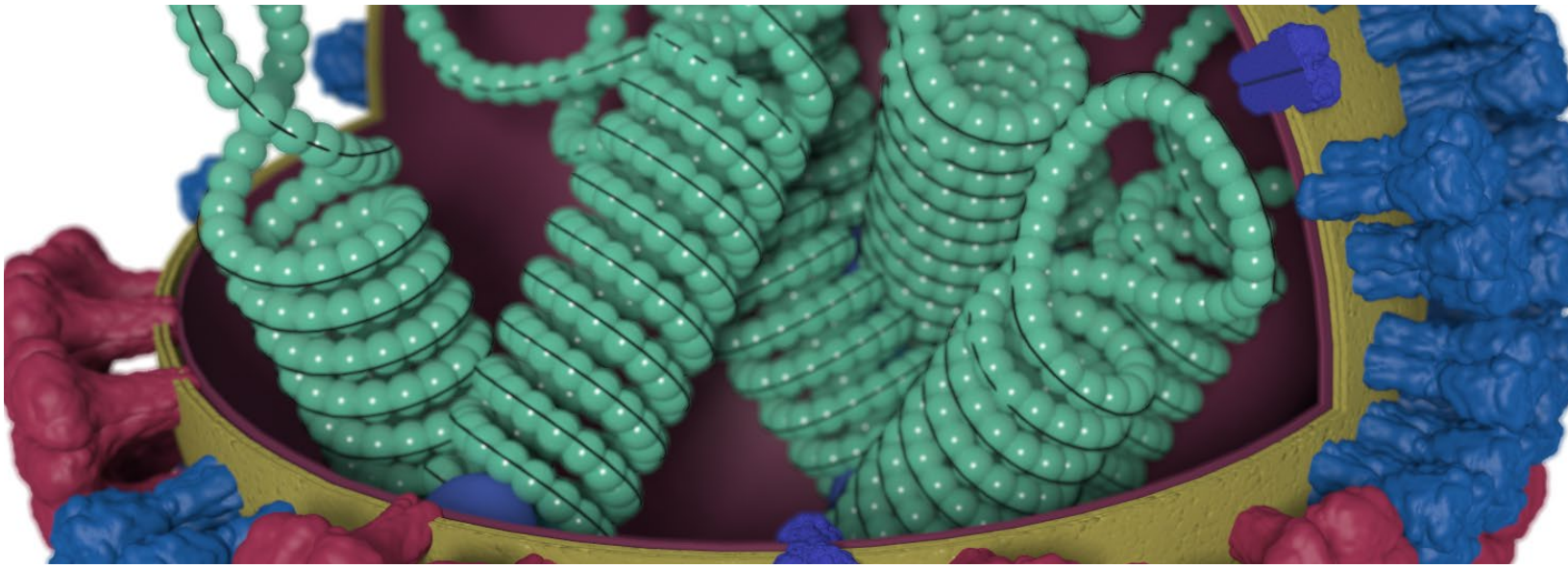
benefits of vaccination (health promotion; Watson & Faron de Goër, 2016). People need to accept being vaccinated as well as physically seek vaccination (activation; Thomson, Robinson, & Vallée-Tourangeau, 2016). A functioning, healthy, and sustainable ecosystem would make research, development, and production 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).

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

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.

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
ΔNS 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	Altimmune	Phase 2

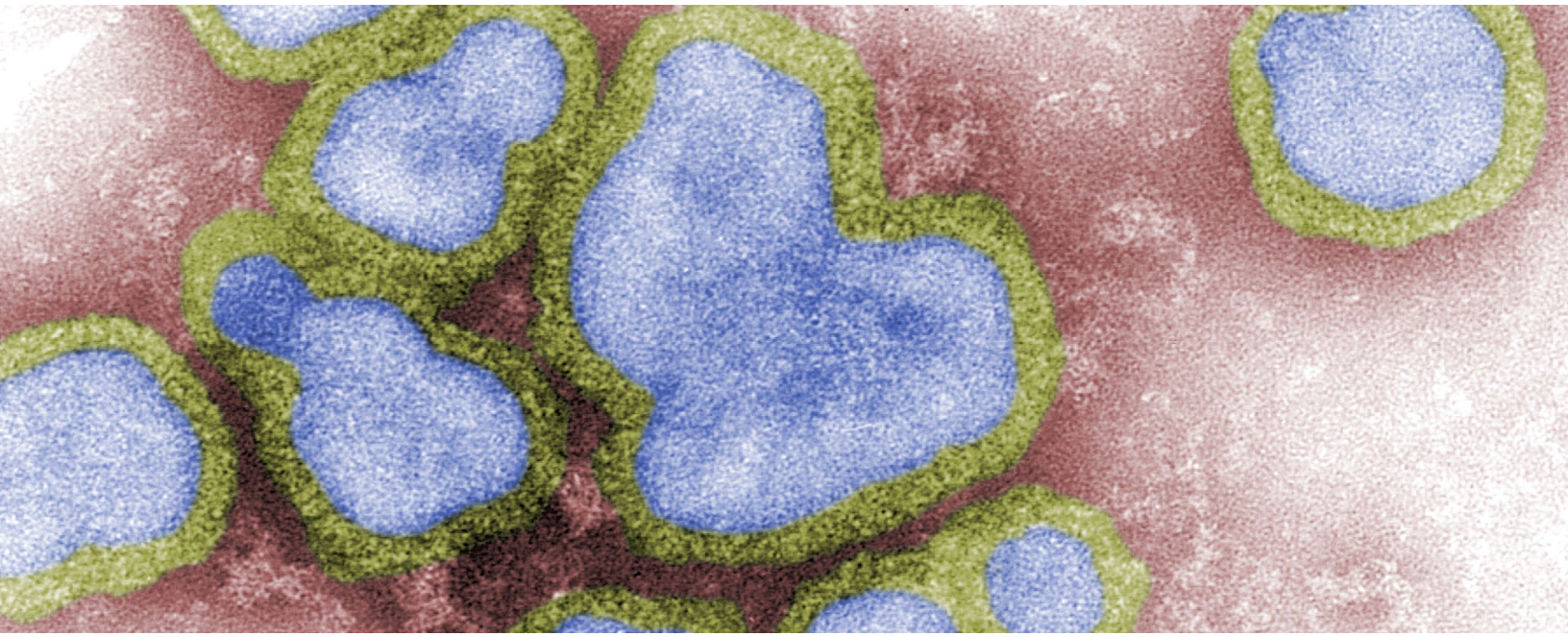
Source: Donis (2016)

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).



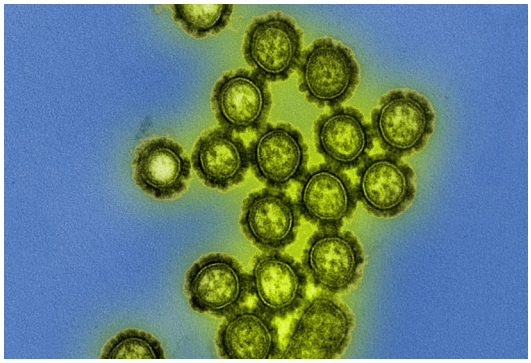
The elevated level of U.S. government investment in influenza contrasts sharply with spending in other countries. For example, the United Kingdom's total R&D investment in all diseases is $3.5 billion, Germany's is $1.9 billion, and Japan's is $1.4 billion. It is difficult to identify any other countries 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).

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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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