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

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# INFLUENZA VACCINES AND SCIENTIFIC PRIORITIES

## IN THE UNITED STATES

Michael Specter

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.

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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.

# 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.

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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.

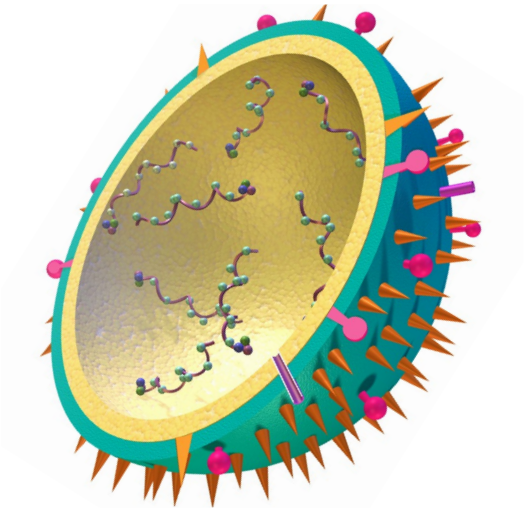
It takes years to develop a concept for a new medical product, carry out pre-clinical research, test a candidate, and turn it into a drug or vaccine. Historically, the NIH created the intellectual property and industry took it from there. But industrial production is driven by markets, and markets do 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.

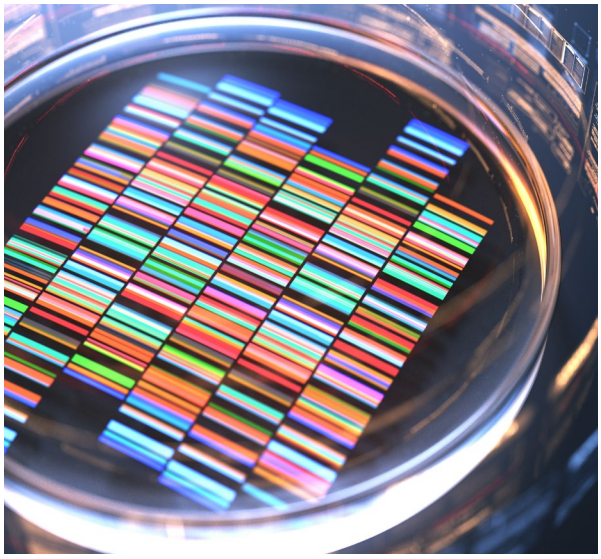
Certainly, making the switch to a universal vaccine will be difficult scientifically, economically, and ethically. There has been a lot of influenza research in the past 15 years, some of it highly promising; essentially all that money stems from three events: 9/11, the H5N1 scare of 2004, and the 2009 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.

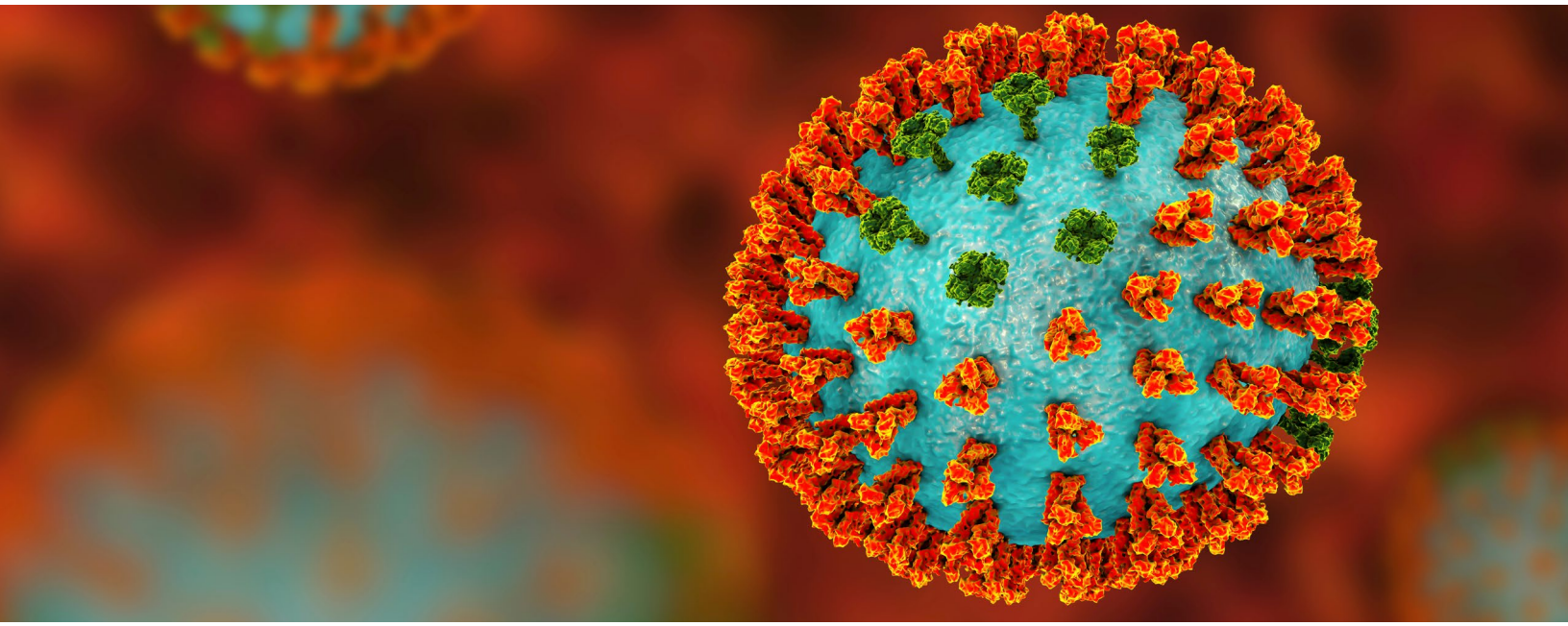
The selection process is uncertain at best. Nor is the system scientific. Influenza is not even a human virus; it's a bird virus. But it constantly mutates away from birdiness toward humans. The process we use to produce hundreds of millions of doses of flu vaccine each year is almost unimaginably out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

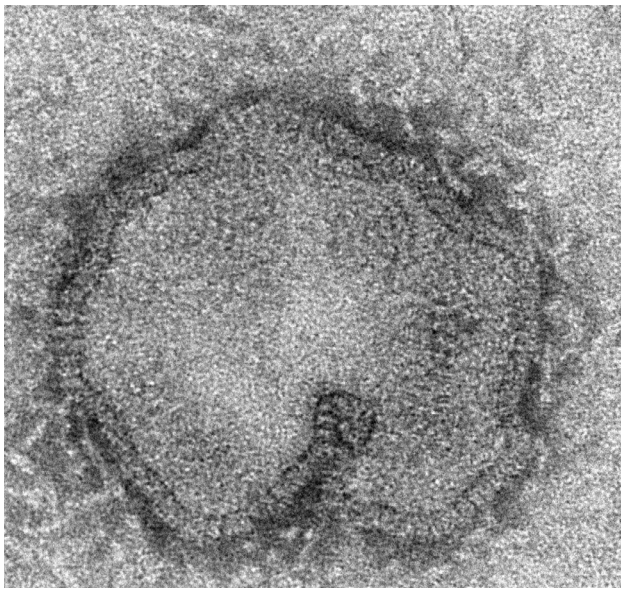
also to influenza, hepatitis C, and malaria. (Several other research teams are now taking similar approaches.) The scientists began by searching for a protein they could administer like a drug that would generate an effective immune response. They soon discovered a class of antibodies that bind to the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

THE SABIN-ASPEN
# VACCINE SCIENCE & POLICY GROUP

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## 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.

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