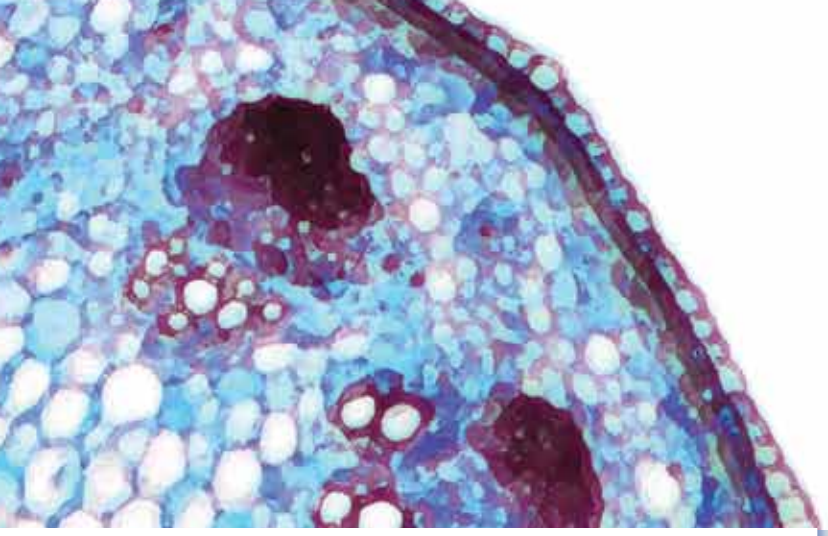

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WHITE PAPER

Chasing Influenza

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A look at the history of flu vaccine production and how previous outbreaks set the stage for a comprehensive global response to the H1N1 pandemic.

Executive Summary

The arrival and swift spread of the H1N1 influenza virus, or "swine flu," in 2009 was a surprising but not entirely unexpected global event. Influenza pandemics, in which new virus strains against which the population has little or no immunity spread globally and infect a large number of people in a short amount of time, occur on average three or more times per century — and history shows that we were due. Scientists and public health experts had anticipated that the next pandemic would be due to H5N1 Avian influenza (i.e., "bird flu"), but it was a novel H1N1 strain that actually emerged. The pandemic strain of H1N1 will likely continue to spread globally and cause significant morbidity and mortality. An open question that will be followed very closely is whether the virus will mutate to a more pathogenic form and become more deadly in successive waves, as flu pandemics have been known to do.

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Preparing for the Next Influenza Pandemic

The 2009 influenza pandemic was not the first to hit the United States. The most notorious — and most lethal — was the so called "Spanish flu" pandemic of 1918, which killed more than 50 million people worldwide and sickened as much as 40 percent of the global population. Subsequent pandemics, notably the "Asian flu" of 1957 and the "Hong Kong flu" of 1968, killed hundreds of thousands of people in the U.S. and across the globe.

Frequently lost in discussions of pandemic influenza is the fact that typical annual seasonal flu epidemics cause significant excess morbidity and mortality. During a typical year in the United States, 30,000 to 50,000 people die as a result of influenza virus infection,[1] with global death rates substantially higher.

The good news is that lessons learned over the past several years from influenza-related events have set in motion global preparedness steps that have enabled governments and pharmaceutical manufacturers to rapidly react to the H1N1 virus. Advances in global disease surveillance, vaccine technology and production capabilities have allowed the industry to develop and mass-produce a single dose H1N1 vaccine dramatically more quickly than in the past.

> As few as 10 years ago, little thought or investment was made in improving the way influenza vaccines were made and distributed.

From Apathy to Action

The biopharmaceutical industry and governments have not always been so proactive and involved when it comes to influenza. As few as 10 years ago, little thought or investment was made in improving the way influenza vaccines were made and distributed, in large part because the commercial market wasn't strong enough to warrant investment in new production facilities or technologies. Despite the potentially deadly nature of influenza, fewer than 50 percent of people at high risk get flu shots each year.

With little incentive to invest in new manufacturing facilities or technologies, influenza vaccines historically were produced by a small number of manufacturers, all of whom have utilized a five decade-old, time-consuming and resource-constrained poultry egg-based technology. Every year, the WHO makes a recommendation regarding the three most likely strains for the coming flu season; the influenza vaccine manufacturers inject a mix of those strains in chicken eggs exactly 11 days after they've been fertilized; the eggs incubate for several more days, then the resulting virus is purified, inactivated and used to produce the vaccine.

The Mother of All Pandemics

In the Spring of 1918, the worst epidemic the U.S. has ever experienced began with an unremarkable case of the flu at a military base in Kansas. A mess cook fell ill complaining of a sore throat and fever, and within days more than 500 soldiers had fallen ill. In a matter of weeks, the virus swept through Europe, Asia, Africa and South America.

The first wave was relatively mild. But the virus mutated quickly, transforming itself into the most virulent and deadly influenza pandemic the world has ever witnessed. It killed 675,000 Americans, and 50 million people worldwide before subsiding in the summer of 1919 — a mere 15 months after it began. It was so deadly, in fact, that it was initially misdiagnosed as cholera, typhoid or dengue fever, and it wasn't until the 1930s, when related H1N1 influenza viruses were isolated from pigs and then humans, that the 1918 strain was officially verified to be Influenza A.

To this day, many questions remain about where the Spanish flu originated and how it managed to mutate into such a deadly and contagious strain, infecting as much as one-third of the world's population and showing the highest mortality rates among young healthy victims rather than the elderly.

Read more about what we know in Addendum 1: The Mother of All Pandemics on page 8 of this White Paper.

Separating Fact from Fiction

To allay fears of vaccine side effects, and to more effectively track the true impact of vaccines on the population, several government sponsored projects were launched to monitor the side effects of influenza vaccines in the 2009 flu season. These include:

> *A Harvard Medical School program in which scientists will link insurance databases that cover up to 50 million people with vaccination registries to track whether people see their doctor in the weeks following a flu shot*

> *A Johns Hopkins University program through which researchers will e-mail 100,000 vaccine recipients to track complaints following the flu shot*

> *A CDC-sponsored take home to encourage vaccine recipients to report side effects through the Vaccine Adverse Event reporting system.*

This culture of fear that has built up around vaccines puts people at unnecessary risk and results in thousands of preventable deaths every year.

Hopefully these and other tracking programs can clarify the truths about vaccines, and spur our most vulnerable population to protect themselves.

For related information, see Addendum 2: The Swine Flu Debacle of 1976 on page 8 of this White Paper.

Egg-Based Production Limitations

Although it is cost-effective, this production strategy is time-, labor- and material-intensive. Moreover, there is only a limited supply of 11-day-old fertilized poultry eggs at any given time, reducing the industry's ability to respond rapidly to a sudden need for new vaccines.

These limitations were underscored in 2004, when bacterial contamination in a manufacturing facility led to a massive vaccine shortage. Chiron Corporation, the fifth largest vaccine maker in the world and one of only two companies licensed to provide injectable flu vaccines in the United States, had to dump nearly 50 million vaccines from its Liverpool, England manufacturing plant because they were contaminated with Serratia bacteria. Suddenly, the U.S. was unable to provide flu shots for almost half of the 100 million people seeking them, and the industry and government had to take a hard look at its domestic production limitations.

Beginning in 2003, a small but growing number of people in Asia became infected with a virulent but not terribly contagious strain of influenza. Characterization of the virus demonstrated that it was an H5N1 strain of Avian origin. This particular "Avian flu" strain was unusual, however, in that it appeared to spread directly from birds to humans, without need for adaptation through an intermediate host as is typical of other influenza strains.

Adding to the anxiety, Avian influenza is lethal to poultry, and the viruses are pathogenic for hens' eggs.

Walking on Eggshells

Although H5N1 infections occur primarily among people who work and live among poultry, infections have proved to be highly lethal; mortality rates have frequently ranged from 50-60%. Furthermore, the spread of the virus across the globe since 2003 has been alarming, with a total of 442 cases confirmed from 15 countries as of September 24, 2009. Fortunately, fewer than 100 people have died in a given year from this strain, presumably because of its ineffective transmission capability, but there are concerns that it could mutate and become more easily spread.

Adding to the anxiety, Avian influenza is lethal to poultry, and the viruses are pathogenic for hens' eggs. As a consequence, egg-based influenza vaccine production technologies are highly vulnerable to Avian influenza, and should Avian influenza become a pandemic, the industry could not rely on its traditional method of developing vaccines to protect the population.

A Call to Action

This confluence of events was a call to action. The pharmaceutical industry, global governments and health organizations recognized that influenza posed serious health risks that transcended geographic boundaries and that new vaccine manufacturing technologies and disease monitoring strategies were necessary.

A number of scientific and policy initiatives emerged in response to these events. Perhaps the most important of these were the allocation of resources by, and the creation of infrastructure within, the U.S. government for developing new approaches to preventing and controlling influenza.

Much of the federal investment went toward research into alternatives to egg-based methods for producing vaccines, approaches to minimizing the amount of influenza antigen required in vaccines, techniques for enhancing immunity through use of adjuvants and alternative delivery approaches, and strategies to improve the effectiveness and speed to develop and produce vaccines.[2]

Billion Dollar Boost

In March 2006, the U.S. government awarded more than $1 billion to five drug manufacturers to support development of cell culture-based technologies that could more rapidly produce influenza vaccines on a mass scale in response to a pandemic, and to diversify domestic vaccine production in the U.S.[3] The goal was to be able to distribute a vaccine to every American within six months of a pandemic striking. The five-year contracts went to GlaxoSmithKline, MedImmune Inc., Novartis Vaccines and Diagnostics, DynPort Vaccine Co. (and its partner, Baxter BioSciences), and Solvay Pharmaceuticals Inc.

Cell-based production techniques have been used to produce certain licensed viral vaccines, including those for polio and rabies, yet the adaptation of this technology for a new virus type is long and complex.[4] Pharmaceutical manufacturers have been researching and developing cell-based influenza vaccines for several years. This technology has yet to achieve global regulatory approval; however, a vaccine is expected to be produced in Europe using modern cell culture technology and a cell culture production facility is currently under construction in the United States.

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Exploring and Improving Solutions

Much time and money has also been spent in developing government and industry pandemic preparedness plans that lay out the response strategies for tracking and vaccinating against new influenza strains.[5] These efforts were ramped up after the emergence of the deadly H5N1 Avian strain, and included efforts to stockpile antiviral drugs, which could potentially blunt the spread of a pandemic; greater exploration of how previous pandemics spread in order to develop better control methods; more sophisticated statistical modeling of various aspects of influenza; and run-throughs of pandemic preparedness and response exercises in various countries.

It's Here

The global investment in this previously dormant sector of the pharmaceutical industry was well timed, as a mere three years later, in March 2009, the first cases of influenza caused by the novel H1N1 virus, commonly known as Swine Flu, occurred in Mexico.[6] Within months, the virus had spread across the globe, and by June WHO declared it a pandemic.

Although apparently not as deadly as the H5N1 Avian influenza, this virus is highly contagious, and has shown itself to be lethal among unexpected segments of the population: namely, otherwise healthy older children and young adults. The rapidity of the virus' spread and its virulence for individuals both within and outside traditional high-risk groups has created grave concerns for public safety among officials worldwide.

Immunizing Attitudes Against Delays

Fortunately, the events in the recent past set in motion research and monitoring that enabled governments to quickly get a handle on the spread and impact of this influenza strain. Disease surveillance strategies led to early restrictions on travel and guidance for school closures. Meanwhile, public and private sector researchers, working together with the U.S. Center for Disease Control (CDC), were able to quickly isolate the virus and provide it for use in vaccines. By September, regulatory authorities had licensed novel H1N1 vaccines in Australia, China and the United States, just three months after the pandemic was declared.[7] Japan and several EU countries followed shortly.

Initial expectations were that two doses of vaccine would be necessary to induce protective immunity in a population with no prior exposure to this virus. However, clinical trials have demonstrated that in older children and adults, amounts of antibody that correlate with protection from disease are induced by a single injection of vaccine. Despite this development, however, there was not enough vaccine to go around.

As of September, 2009, WHO estimated global worldwide production capacity for pandemic vaccines at approximately 3 billion doses per year. The estimated global population is closer to 6.8 billion people, leaving more than half of the world's population unprotected.[8]

For related information, refer to Addendum 3: Time Line on page 8 of this White Paper.

WHO reports that many affluent countries previously contracted with manufacturers to obtain vaccine supplies to cover their entire populations, while most low- and middle-income countries lack the financial resources to compete for an early share of limited supplies. Vaccine supplies in these countries will largely depend on donations from manufacturers and other countries.

As the H1N1 vaccine arrives in communities, it will first be targeted to health care workers and groups at high risk for severe disease and complications, such as pregnant women, people with diabetes, chronic respiratory and cardiovascular disease, and people with weakened immune systems. In contrast to outbreaks of seasonal influenza, in which more than 90% of fatal cases occur in older adults, the H1N1 pandemic took a disproportionate toll on children and young adults. In part, this is due to some level of cross-protective antibodies present in older adults due to exposure to strains of H1N1 that circulated between 1918 and 1957.

There are other shortcomings in the system as well. Cell-based vaccine production technology is on the cusp of becoming an approved technique for rapidly producing flu vaccines; however, no cell culture-derived flu vaccine has yet achieved global regulatory approval. As such, manufacturers are still left to rely on the more time consuming and resource limited egg-based vaccine production method. And, because there are only so many 11-day-old fertilized poultry eggs available in the world, these manufacturers are being forced to make difficult decisions about which and how much vaccine to produce using the current egg supply — the H1N1 vaccine, or the seasonal influenza vaccine. In either case there are likely to be future shortages due to limits in production capacity.

Change is Coming

Without the Avian influenza outbreak and the disastrous 2004 flu vaccine shortage, the industry would likely not be in the advanced position it is in to deal with the H1N1 pandemic. Lessons learned from those events have reduced the deadly consequences of this virus.

Yet there are still challenges to be met, and progress to be made. Some of the most vulnerable segments of the population (e.g., infants, young children and elderly) don't generate protective antibodies as effectively as do younger adults in response to receiving current egg- or cell-based influenza vaccines. The need to revaccinate individuals every year in order to achieve widespread immunity across the population is a huge logistical challenge. As much of an advance as cell-based production technologies will be in terms of production efficiency, there will still be inadequate quantities of vaccine available to meet global requirements. These and other issues continue to challenge the vaccine industry as it seeks to achieve a "universal" solution for this constantly evolving and deadly public health threat.

As the industry moves further forward in its quest for safe and effective cell-based vaccines; as newer technologies are introduced that will further enhance production and delivery of vaccines; as strategies are tested for enhancing the ability of current and future vaccines to immunize all segments of the population more effectively; and as regulatory agencies streamline approval processes; the promise of conquest of this formidable foe will edge ever closer to reality.

Addendum 1: The Mother of All Pandemics

(continued from sidebar on page 3)

What We Know

Research over the past seven decades proved that the virus was novel to humans at that time – not a mutated strain, such as those causing the 1957 and 1968 pandemics; and that its genome segments are substantially different from contemporary Avian influenza genes.

In 2005, scientists at the Centers for Disease Control and Prevention successfully reconstructed the Spanish Flu virus strain using tissue samples recovered from a flu victim who was buriedin the Alaskan permafrost. This research was critical because it identifies the genes responsible for making the virus so harmful and could be used to develop future vaccines.

In 2007, monkeys infected with the recreated strain exhibited symptoms typical of the 1918 pandemic and died from an overreaction of the immune system, called "cytokine storm." This is thought to explain why the pandemic was so deadly among young healthy victims, as they would have had stronger immune systems that would have been able to more aggressively overreact.

Although we don't know exactly where it originated, we do know that all Influenza A pandemics that have occurred since 1918 — including the 2009 H1N1 — have been caused by descendants of the 1918 virus.[9]

In looking at the H1N1 pandemic of 2009, researchers cannot help but notice the similarities in the two viruses — most notably, the mortality rate among young healthy adults and the seeming lack of immunity among populations younger than 65. And although 2009's H1N1 appears far less deadly than its 1918 ancestor, it is a reminder that Influenza is a powerful and adaptable disease that must not be ignored.

Addendum 2: The Swine Flu Debacle of 1976

The emergence of H1N1 in 2009 was not the first time a virus of swine origin has appeared in the U.S. In February 1976 a recruit at a military base in Fort Dix, New Jersey, came down with flu-like symptoms, and within 24 hours he was dead. Four other recruits became ill and within two weeks the CDC determined that it was H1N1. They also concluded that the strain was very similar to the deadly virus of 1918 that killed 50 million people worldwide.

Fearing another deadly pandemic, U.S. public officials launched a mass vaccination campaign, encouraging everyone, including then President Gerald Ford, to be vaccinated.

In the end, however, there was no pandemic. The outbreak was contained to Fort Dix, with only one death and fewer than 200 hospitalizations.

Further complicating the situation, for unknown reasons the vaccine produced higher than expected numbers of cases of Guillain-Barre syndrome, a paralyzing neuromuscular disorder. While rare incidences of Guillain-Barre occur as a side effect of vaccines, in this case more than 500 people contracted the disorder which led to 25 deaths.

Because of the high number of cases of Guillain-Barre, and the extremely limited spread of the disease, this program was considered a disaster. More people died from the cure than the disease, and the experience shook the population's confidence in the safety of flu vaccines.

Contagious Misperceptions

From autism to Guillain-Barre to claims that vaccine shots can actually cause the flu, people have accumulated a host of excuses and unsubstantiated paranoia to justify opting out of the flu shot each year.

In reality, however, influenza itself — seasonal or H1N1 — is far more deadly than any real or imagined consequences of getting a flu shot. Each year in the United States, roughly 36,000 people die from seasonal influenza-related complications — most of whom are among the very young or the elderly — and more than 200,000 people are hospitalized from influenza related causes.[10] Despite these deadly statistics, only about 50 percent of the people who are at high risk of getting influenza seek flu vaccines each year.

Read more about government efforts to allay flu vaccine fears on page 4 of this White Paper.
See: Separating Fact from Fiction sidebar.

Addendum 3: Time Line

1918: The Spanish influenza pandemic. 500,000 people in the U.S. and 50 million people worldwide die from the H1N1 virus. It is the most deadly flu pandemic in modern history, with 20-40 percent of the global population falling ill, some of whom died within 24 hours of getting sick.

1940s: Flu vaccine becomes a reality. The U.S. military develops the first approved inactivated vaccines for influenza, which are used in the Second World War.

1950s: Poultry eggs used in vaccine production. The first egg-based technology for producing influenza vaccine is developed. It continues to be the sole technology used to produce for influenza vaccines for the next 50 years.

1957-58: H2N2, the Asian Flu pandemic. After cases are first reported in Asia, 70,000 people in the U.S. die during two waves of the H2N2 pandemic, most of whom are elderly. Due to advances in disease surveillance, researchers are able to identify the strain and a vaccine is made available in limited quantities by August 2007.

1968-69: H3N2, the Hong Kong Flu pandemic. 34,000 people in the U.S. die during the H3N2 outbreak, which is first observed in Hong Kong. The virus still circulates today.

1976: The Swine Flu vaccination debacle. One person dies and several fall ill at a military base in New Jersey from a flu strain that appears alarmingly similar to the one that caused 1918 pandemic. In response, public officials launch a national vaccination campaign, encouraging hundreds of thousands of Americans to get flu shots. However, this flu never spreads beyond the military base, and the vaccine causes a high incidence of the paralyzing Guillane Barre disease, leaving 25 dead and hundreds sick. The vaccination campaign is considered a disaster, and the event sparks fears about the dangers of flu vaccines that persist for decades.

1997: H5N1, Avian Flu outbreak. Although not a pandemic outbreak, this is remarkable in that it the first time an influenza virus is transmitted directly from birds to people, without first infecting pigs as an intermediate host, which is the common transmission route. Six people in Hong Kong died, and most of the severe illnesses occur in young adults.

2003: Intranasal vaccine hits the market. FluMist, the first intranasal flu vaccine manufactured by MedImmune Vaccines, is approved by the FDA and offered to patients.[11]

March 2006: Government funds influenza research. The U.S. government awards more than $1 billion to five drug manufacturers to support development of technology that can more rapidly produce influenza vaccines on a mass scale in response to a pandemic and to diversify domestic vaccine production in the U.S.[12]

2009: The H1N1 "Swine Flu" pandemic begins.

April 2009: Nine countries report 148 cases of a new H1N1 virus containing swine, Avian and human genes, which first emerged in the United States, Mexico and Canada. The World Health Organization issues a "phase 5" alert on the outbreak, signaling that a pandemic is imminent.

June 11, 2009: WHO raises the level of pandemic alert to phase 6, declaring the H1N1 virus a global pandemic.13

September 2009: Regulatory authorities license pandemic vaccines in Australia, China and the United States just three months after the pandemic is declared.14 Japan and several EU countries are expected to follow shortly. WHO estimates worldwide production capacity for pandemic vaccines at approximately 3 billion doses per year — less than half of the global population.15 In the U.K., Novartis publicizes successful clinical trials with 100 healthy volunteers of Celtura, an H1N1 vaccine produced made using cell cultures. Larger trials are underway.

October 2009: The first batch of H1N1 vaccines is released to the general population.

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