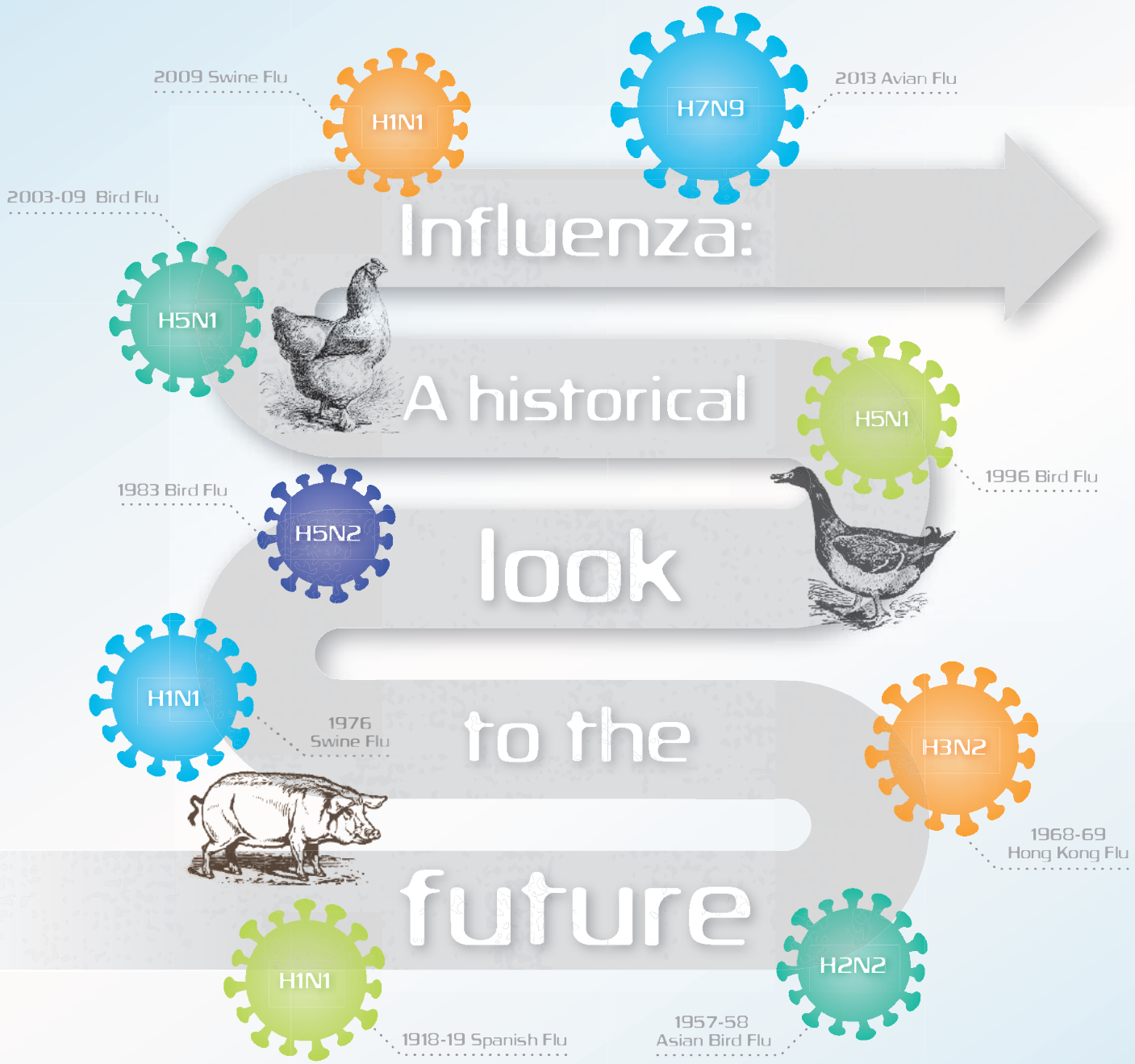
2009 Swine Flu
H1N1
H7N9
2013 Avian Flu
2003-09 Bird Flu
H5N1
Influenza:
A historical
look
to the
future
H5N1
1996 Bird Flu
1983 Bird Flu
H5N2
H1N1
1976
Swine Flu
H3N2
1968-69
Hong Kong Flu
H1N1
1918-19 Spanish Flu
H2N2
1957-58
Asian Bird Flu

During the past quarter of a century and beyond, the influenza virus has mutated into countless strains, some of which have threatened a worldwide pandemic. As this threat continues to grow, critical advances have been made — from an understanding of how strains mutate and the risks they pose, to the ways in which vaccines can be manufactured and strengthened — to provide greater immunity to this often deadly virus.

It's almost a century since the first and most devastating flu epidemic in recorded world history: the 1918-1919 Spanish flu that killed more than 50 million people.[1] Scientists have learned a great deal about the influenza virus since that time. Even so, this year, the Centers for Disease Control and Prevention (CDC) reports that the 2012-2013 flu season was notable for widespread disease and a higher mortality rate than in previous years. In addition, the predominant subtype was an H3N2, in contrast to dominance by H1N1 subtypes in recent years.[2] Why this disease continues to plague society and frustrate scientists is no secret. The disease mutates and changes at a rate that science simply hasn't been able to predict to provide adequate protection. And, it is feared that the newest avian strains of the influenza virus could become the most deadly — possibly infecting 40 percent of the world's population.[1] Yet, despite these grave concerns, the greatest gains in our understanding about this highly infectious, sometimes virulent disease have perhaps been made in the last quarter of a century. And, while scientists are still far from being able to predict when the next pandemic will threaten, improved vaccines and their manufacturing processes offer hope for better protecting the public's health should one occur.

A Timeline of Influenza Viruses

The Spanish flu occurred prior to an influenza vaccine being developed and prior to the era of antibiotics that are now essential in treating the secondary bacterial infections that often kill flu-weakened patients. In 2005, researchers at the Armed Forces Institute of Pathology in Rockville, Md., reconstructed the genetic code of the deadly Spanish flu and found it was caused by the H1N1 type of influenza virus, which is similar to the bird flu virus today, mainly H5N1 and H5N2.[3]

The next major flu outbreak was the Asian bird flu, the second pandemic of the 20th century. Caused by an H2N2 virus, the Asian flu began in China and killed one million people worldwide, including 70,000 Americans. Then, in 1968 and 1969, the Hong Kong flu was the last flu pandemic of the 20th century, caused by an H3N2 virus and killing some 34,000 Americans. The relatively low death toll is thought to have been due to two factors. First, the virus contained the neuraminidase 2 (N2) subtype protein to which humans had previously been exposed. Second, a hemagglutinin 3 (H3) virus circulated around the turn of the century, giving some immunity to elderly people who had caught the flu during that time.

The first swine flu outbreak in the 20th century occurred in 1976 among a handful of soldiers stationed at Fort Dix, N.J. That H1N1 virus resulted in one death, and at the time, health officials worried that they were seeing the return of the 1918 H1N1 Spanish flu pandemic. As the virus was circulating among U.S. pigs, then-President Gerald Ford called for a crash vaccination program, and a quarter of the U.S. population was inoculated, resulting in 25 deaths from Guillain-Barré syndrome. No one else died of swine flu, and it never caused an epidemic.

In 1983, the second high pathogenic (HPAI) bird flu outbreak occurred in the U.S. caused by an H5N2 virus. However, while it did not spread among humans, the severe poultry epidemic struck chickens, turkeys and guinea fowl in Pennsylvania and Virginia. It was finally brought under control after the destruction of 17 million birds.

Why this disease continues to plague society and frustrate scientists is no secret.

In 1996, an HPAI H5N1 bird flu was isolated from a farmed goose in Guangdong, China, and in May 1997, the first person known to catch H5N1 bird flu died in Hong Kong. There were then 18 new human cases of H5N1 bird flu in Hong Kong in 1997 and 1998, 12 with direct contact with infected poultry, causing the deaths of six people, after which officials destroyed 1.4 million chickens and ducks.

The bird flu surfaced again in 2003 in Vietnam, and from 2003 through 2009, cases were reported in Hong Kong, Korea, Thailand, China, Laos, Cambodia, Pakistan, Indonesia, the Netherlands, southern Ukraine, Romania and Turkey, resulting in hundreds of humans infected and dozens killed. In April 2009, Egypt reported the first suspected human-to-human transmission of bird flu, which the World Health Organization (WHO) denied.

Also in April 2009, a swine flu outbreak originated in Mexico City, with human-to-human transmission confirmed. That flu was then confirmed in U.S. schools, and WHO raised the pandemic threat level to Phase 4, but recommended against air travel restrictions. At the end of April, the first U.S. death from swine flu was reported. Outbreaks were then confirmed as spreading to Israel, Spain and New Zealand.[4] In May, WHO declared the H1N1 the first flu pandemic of the 21st century because it was a new, mutated strain for which there was no built-up immunity. Ultimately, the H1N1 pandemic of 2009-2010 resulted in a million and a half infections and more than 17,000 deaths.[5]

This year on March 31, the Chinese CDC reported the first cases associated with the H7N9 influenza virus. H7N9 is a serotype of the avian influenza virus, and it's one of the most lethal of its kind. H7 normally circulates among avian populations with some variants known to occasionally infect humans. But there are worries that it could mutate into a form that could be passed from one person to another. Five mutations are known to be necessary for that to happen, and H7N9 already has two of them. If mutations continue, it could spread worldwide with lethal effect. To date, the outbreak has been limited to eastern China and Taiwan, and there's been no evidence of transmission between people.[6] But, it has killed one-fifth of those infected, and health experts predict that it will spread worldwide.[7]

The Health Threat

Each year, influenza-associated illnesses affect from 5 percent to 20 percent of the population, claim a range of about 3,000 to 49,000 lives and require hospitalization of more than 200,000 in the U.S. alone. Globally, the death rate exceeds

500,000. And, a study conducted by CDC found that there is an upward trend in the rates of flu incidence.[1] The death rate between 1972 and 1992 doubled in just 20 years — an especially alarming trend considering in 1997, flu vaccine coverage had reached 65 percent of those most vulnerable. The intensity of flu epidemics is also increasing. In the 1970s and 1980s, the average length of an epidemic period was eight to 10 weeks. Today, it is closer to 16 to 18 weeks.[8]

With the flu viruses mutating constantly, health experts identify a number of characteristics to determine how serious a threat a new flu virus strain poses. There are two primary characteristics of a disease: pathogenicity and virulence. If a virus readily causes disease and is easily spread, it is considered pathogenic. The severity of the symptoms from the virus determines its virulence. For instance, in the 1918 Spanish flu pandemic, the virus spread easily from person to person and the symptoms were severe, resulting in millions of deaths, which means it was highly pathogenic and highly virulent. On the other hand, the H5N1 bird flu, while it was highly virulent with a high mortality rate, spread poorly from person to person, making it mildly pathogenic.[9]

The flu is also much more contagious than once thought. In a recent study, researchers at the Wake Forest School of Medicine in North Carolina sampled the air for flu viruses in rooms of patients who visited the hospital during the 2010-2011 flu season. Using devices that were placed 1, 3 and 6 feet away from the patients while they lay in bed, they found potentially infectious flu virus particles at each of the sample locations. It was previously thought that the flu spreads mainly through large particles, or droplets, in the air that travel short distances, from 3 to 6 feet. But this study showed that most flu viruses are found in very small particles, which can travel farther than larger ones, in the air. And because the study didn't look at distances beyond 6 feet, the researchers can't say whether the flu virus can travel farther.[10]

This makes large-scale events that draw tourists a concern for those who study flu outbreaks. For instance, in 2012, a report suggested that the year's Summer Olympic Games posed an extreme threat for a serious flu outbreak within the United Kingdom as an extra 5.3 million tourists descended upon the area. The report, which was conducted by global risk research firm Maplecroft, revealed that such a large influx of visitors during the summer months coupled with an increase in the use of public transportation would exacerbate the already significant risk to that particular region of the world.[1]

For young children, the elderly and people with certain chronic diseases, contracting seasonal influenza can sometimes lead to hospitalization with bacterial pneumonia or other serious complications and death. The reason is simple: Natural protective immunity in young children is still underdeveloped, while in the elderly it is in a long decline.[11]

People over 65 years of age, and particularly those well beyond 65, are hit especially hard by seasonal influenza. In fact, in this age group, a case of the flu is most likely to lead to serious or life-threatening complications, especially in those with chronic pre-existing conditions, such as cardiac and pulmonary disease. In the elderly in particular, a bout of the flu also can progress to primary influenza pneumonia or secondary bacterial pneumonia.

Each year, seniors account for an estimated 46 percent of all flu-related clinic visits, nearly 60 percent of all annual flu-related hospital days, three-quarters of life-years lost and 90 percent of this country's annual flu-related deaths. And, while the seasonal flu vaccine has been said to protect this group from contracting the flu, new research suggests that this has not been the case.[12]

When you consider how far we've come from the fearful days when flu was an indiscriminate killer and no protection existed, it seems odd that each year thousands of people still die from flu-related complications.

The Issue of Vaccine Adoption

When you consider how far we've come from the fearful days when flu was an indiscriminate killer and no protection existed, it seems odd that each year thousands of people still die from flu-related complications. While there may be many extenuating reasons for these statistics, the sad fact remains that widespread avoidance of the influenza vaccination remains an issue.[1]

On average, the number of people who get a flu shot each year hovers in the 40 percent range. The reasons vary, but mainly it's due to misconceptions that the flu shot causes the flu, that the flu shot causes unwanted side effects and that it

doesn't work. For many, it's a fear of needles. While the first three reasons are known to be myths, a fear of needles is all too real.

Another issue surrounding influenza vaccines are additives that are introduced into the vaccines through the manufacturing process. These additives include thimerosal, antibiotics and latex — all of which may cause problems in individuals with allergies to them. Thimerosal is a mercury-containing organic compound that has been widely used since the 1930s as a preservative in vaccines to help prevent potentially life-threatening contamination with harmful microbes. Because public concerns about the use of thimerosal in vaccines and other products have been raised, the U.S. Food and Drug Administration (FDA) is working with manufacturers to reduce or eliminate thimerosal from vaccines. Most influenza vaccines have very low, trace or no thimerosal levels.[13]

Certain antibiotics also may be used in making inactivated influenza virus vaccines to help prevent bacterial contamination during manufacturing, including neomycin, polymyxin B, streptomycin and gentamicin. Antibiotics used in vaccine production are present in some vaccines, but they are reduced to very small or undetectable amounts during subsequent purification steps. And, the very small amounts of antibiotics contained in vaccines have not been clearly associated with severe allergic reactions.[14]

For years, the main thrust of flu vaccination campaigns has focused on the very young and the elderly.

Some influenza vaccine packaging, including syringes, plungers and vial stoppers, may contain latex, to which some people are allergic. According to the 2011 general recommendations on immunization by the Advisory Committee on Immunization Practices: "If a person reports a severe (anaphylactic) allergy to latex, vaccines supplied in vials or syringes that contain natural rubber should not be administered unless the benefit of vaccination outweighs the risk for a potential allergic reaction. In these cases, providers should be prepared to treat patients who are having an allergic reaction. For latex allergies other than anaphylactic allergies (e.g., a history of contact allergy to latex gloves), vaccines supplied in vials or syringes that contain dry natural rubber or rubber latex may be administered."[15]

Studies show young healthy adults are chief among the population groups who skip immunization because they feel they are not at high risk, they think that the vaccine doesn't work, and/or they believe that getting the flu vaccine will make them sick.[1]

For the elderly, vaccination rates have risen, but there is still doubt by many in this age group about whether there is an actual life- and health-sparing value of flu vaccine. Nearly all the evidence for protective benefit in this population comes from non-randomized observational studies. Typical of these was a large 2003 medical record review of 286,000 community-dwelling Americans at least 65 years old. In this review, those who got a flu vaccine experienced nearly a 20 percent reduction in risk of hospitalization for cardiac disease, about a 30 percent lower risk of hospitalization for pneumonia or influenza, and an impressive 49 percent average reduction in risk of death from all causes over the span of two flu seasons.

But many experts have pointed out the strong potential for bias when studies look at health outcomes in people who choose themselves whether to get a flu vaccine or not. One research team decided to take a closer look at the issue. They followed a large cohort of 72,527 people aged 65 and older during an eight-year period to assess the risk of death or hospitalization for pneumonia or the flu before, during and after flu seasons. Their findings have all but discredited the results of earlier observational flu studies in seniors. Before the flu season arrived, the relative risk of death for vaccinated persons compared with unvaccinated persons was 0.39. In other words, people who received the flu shot were about 60 percent less likely to die from any cause compared with those who didn't — before they received the vaccine or got exposed to the new flu virus. It is believed, then, that people who choose on their own to get the vaccine tend to be much healthier than those who don't, and they appear to take better care of themselves when they do get sick.

Yet, even though more older adults receive the flu vaccine these days, there are still more flu-related deaths. The reason: Standard trivalent inactivated influenza vaccine (IIV3) isn't nearly as protective for older adults as it is for non-elderly adults. After age 65, the competency of a person's immune system steadily declines with passing years. Sooner or later, this natural course of "immunosenescence" translates to a poor, nonprotective antibody response to the standard dose of influenza vaccine. It also accounts for why people 85 years of age and older are roughly 16 times more likely to die of any flu-related cause and more than 30 times more likely to die of influenza or associated pneumonia than those between age 65 and 69.

The overall chances that elderly persons will have a potentially protective antibody response to flu vaccine has been estimated to be somewhere between 24 percent and 59 percent of that of younger adults. According to CDC estimates, healthy adults under age 65 can expect a 70 percent to 90 percent overall clinical vaccine efficacy rate when the vaccine and circulating virus are antigenically similar. But the clinical efficacy of flu vaccine is clearly far lower in the elderly. As flu experts have pointed out for decades, what is needed is a more immunogenic flu vaccine for the elderly, one that more consistently and effectively mobilizes their available antibody and cellular immunity.[12]

Aside from age groups, healthcare workers represent an important cohort for curbing the spread of flu. Every day on the job, these workers have a high rate of contact with those who are most vulnerable such as the very young, the very old and the immunocompromised — populations that are most susceptible to suffering severe consequences from the flu, including death. In fact, the 2012-2013 strain of the influenza virus killed the elderly at the highest rate (116 deaths per 100,000 cases) since age-related tracking began in 2005.

Because healthcare ranks among the nation's largest industries, providing more than 14 million jobs, healthcare workers represent a significant source of potential spread of the flu. And when they're infected by the flu virus, patient avoidance isn't always an option. Indeed, a little-known fact is that a person who has acquired the influenza virus is contagious for nearly a week, starting a day before any symptoms appear. Thus, it is possible to spread flu over the course of an entire working day before workers even know they are sick.

Why would people committed to protect sick patients refuse a flu shot? The reasons vary, from religious objections to skepticism about whether the vaccine works and whether vaccinating healthcare workers will prevent flu in patients, to allergies or complications arising from the vaccine. But serious reactions to the flu shot are extremely rare: Fewer than five in a million. And, according to Dr. Carolyn Bridges, associate director for adult immunization at CDC, the strongest evidence that vaccinating healthcare workers prevents flu in patients is

from studies in nursing homes that link flu vaccination among healthcare workers with fewer patient deaths from all causes.[10]

Adopting Herd Protection to Halt the Spread of Flu

For years, the main thrust of flu vaccination campaigns has focused on the very young and the elderly. This emphasis may be misplaced since, as previously discussed, the immune systems of the old and infirm don't always respond efficiently to the flu vaccine, nor are these populations usually responsible for spreading the virus. That's why some suggest that a better tactic may be to focus vaccination efforts on healthcare workers, school-age children and working adults — those who consistently come in contact with others and are more likely to infect others. Embracing this concept, called "herd protection," has its roots in the idea that you protect the weakest members of a flock by strengthening the defenses of its strongest members and, in doing so, bolster the herd's communal defenses.

CDC's goal is for 90 percent of healthcare workers to receive influenza vaccinations by 2020.

Paul Glezen, MD, Baylor College of Medicine, Houston, Texas, is one of a growing number of physicians who subscribe to the idea of herd protection with regard to vaccinations for the flu virus. Glezen argues that focusing vaccination efforts on the very young and old, which had been the favored recommendation, is less effective because these people, while most susceptible to the effects of the flu, are not in contact with mass numbers of the population, and, ironically, may not respond as well to the vaccine. According to Glezen, herd protection is a well-established concept and a reasonable approach to a systematic immunization program.

Another benefit of the approach is that school-age kids and working adults, because of their need to congregate in schools and the workplace, are accessible populations for rapid deployment of flu vaccine and, in turn, offer the greatest chance for success for the vaccination to actually reduce the incidence of flu in a community.

There are many examples of herd protection success. In a Japanese study from 1977 to 1987, it was mandatory for school-age kids to get the flu vaccine. Most households in Japan at that time were three-generation households and the flu vaccine was not given to the elderly or high-risk. Japan saw a reduction in flu-related mortality of 35,000 to 47,000 per year. Incidentally, after 1987, due to parental concerns about the vaccine being mandatory, the program was ceased and the death rates from flu reverted back to pre-program levels within a few years.

In the U.S., an ongoing program in Temple, Texas, near Austin, is also proving the herd protection strategy a most effective one. Started in 2001, school-age children have been receiving the yearly live attenuated flu vaccine, and preliminary data from the 2005-2006 school year showed almost no incidents of influenza. In the 2008-2009 school year, Temple, Texas, escaped the flu again, while nearby cities had large outbreaks that resulted in school closures, hospitalizations and even deaths.[8]

CDC's goal is for 90 percent of healthcare workers to receive influenza vaccinations by 2020. According to Dr. Arthur Caplan, a bioethicist at New York University's Langone Medical Center, 90 percent is the level of immunity that will provide sufficient protection to the sick. "You don't get the 'herd immunity' until you hit 90 percent," said Caplan, a proponent of mandatory vaccinations.

Yet while the percentage of healthcare workers receiving flu vaccine is growing, the CDC's goal remains elusive. According to a CDC survey of 2,006 healthcare personnel, the overall rate of flu vaccination for healthcare personnel across all settings is only 62.9 percent. So far this year, pharmacists have led the way with 88.7 percent receiving a flu vaccination, followed by 83.8 percent of physicians, 81.5 percent of nurses, 73.3 percent of nurse practitioners and physician assistants, and 76.7 percent of other clinical professionals (allied health professionals, dentists, technicians and technologists). When looking at the healthcare setting, 83.4 percent of workers at hospitals were vaccinated in 2012, compared with 77.8 percent in 2011; 65.4 percent of staff at physician offices or ambulatory care settings were vaccinated in 2012, compared with 64.4 percent in 2011; and 56.6 percent of workers at other facilities such as dental offices, pharmacies, home-medical sites and medical schools were vaccinated in 2012, compared with 57 percent in 2011. What's particularly disturbing in this survey, though, is that only 48.7 percent of healthcare workers at long-term-care facilities, where patients are particularly susceptible to succumbing from flu, were vaccinated in 2012.[10]

The Challenge of Vaccine Efficacy

Because of the evolving nature of flu, developing an effective vaccine each year is no small task. Each year, a global network of scientists are tasked with surveying flu virus mutations and

making vaccine recommendations. WHO holds two vaccine strategy meetings annually, one for the Northern Hemisphere (in February) and one for the Southern Hemisphere (in September). As soon as the organization announces which influenza subtypes should be targeted by the vaccine, medical labs go to work developing strain-specific vaccines.

In some years, influenza vaccines protect only 50 percent to 70 percent of people who receive them. According to CDC's mid-season vaccine effectiveness (VE) estimates published on Feb. 21, 2013, the 2012-2013 VE for protecting against having to go to the doctor because of flu illness was 56 precent for all age groups. When broken down by age groups, the VE against flu A and B viruses ranged from 27 percent in people 65 and older, to 64 percent in children aged 6 months to 17 years.

Predicting which strains of the virus to include in the influenza vaccines is difficult at best, not only because the virus mutates from year to year but the number of influenza subtypes A and type B that can be selected for inclusion is limited. Trivalent influenza vaccines (IIV3s) help protect against the two A virus strains most common in humans and the B strain expected to be predominant in a given year. But, since the year 2000, two influenza B lineages (Victoria and Yamagata) have co-circulated to varying degrees each season. Various degrees of mismatch have occurred between the B lineage included in IIV3s and the B lineage that actually circulated, causing an increased risk of influenza-related morbidity across all age groups. "Trivalent influenza vaccines have helped protect millions of people against flu, but in six of the last 11 flu seasons, the predominant circulating influenza B strain was not the strain that public health authorities selected," says Dr. Leonard Friedland, vice president and head of GlaxoSmithKline North America Vaccines Clinical Development and Medical Affairs.

Adding a second B strain to the seasonal vaccine had been discussed for years. The problem with doing this, however, was the lack of adequate manufacturing capacity to produce quadrivalent influenza vaccines (IIV4s) that still allowed manufacturers to make enough doses to meet projected demand. "From the 2001-2002 through the 2005-2006 flu seasons, fewer than 100 million doses of seasonal flu vaccine were produced and distributed in the U.S.," says Keith Berman, founder of Health Research Associates. "But since 2005-2006, flu vaccine manufacturing capacity has dramatically expanded — a direct byproduct of avian and swine flu outbreaks that prompted the U.S. government to help industry improve preparedness for a potential global flu pandemic." Over the last two flu seasons, manufactured doses of influenza vaccines have outpaced market demand, and "for the first time, the vaccines industry finds itself with the capacity to inoculate many millions more eggs to produce large stocks of IIV4s without jeopardizing its ability to make enough doses to satisfy market demand," adds Berman.

The benefit of adding a second B lineage to influenza vaccines is "essentially a matter of chance," says Berman. However, as an example of how it could make a difference, in the 2007-2008 flu season, B viruses accounted for 29 percent of all flu infections. Unfortunately, WHO and FDA virologists picked the wrong B lineage: the Victoria lineage vs. the Yamagata lineage. Had they added the Yamagata lineage that was identified in 98 percent of flu cases with a B virus infection, CDC estimates that nearly one million flu illnesses and 484 deaths could have been averted. The next year also serves as an example. In the 2008-2009 flu seasons, officials picked the wrong lineage again. Had both B lineages been included in the influenza vaccines, CDC estimates that 169 lives could have been saved.

In February 2012, the FDA approved the first live attenuated quadrivalent influenza vaccine (LAIV4), FluMist Quadrivalent, manufactured by MedImmune. The vaccine is approved for individuals aged 2 years through 49 years, and it contains four strains of the influenza virus: two A strains and two B strains. Like the LAIV FluMist (which has been removed from the market for the new flu season), the LAIV4 contains weakened forms of the virus strains and is administered as a nasal spray. The safety and effectiveness of FluMist Quadrivalent is supported by studies conducted previously for LAIV FluMist, as well as three new clinical studies conducted in the U.S. involving 4,000 children and adults, that demonstrated that the immune responses were similar between FluMist and FluMist Quadrivalent. Reported adverse reactions also were similar, including runny or stuffy nose in both children and adults and headache and sore throat in adults.[11]

Adding a second B strain to the seasonal vaccine had been discussed for years.

Then, in December, a second IIV4 was approved by the FDA. Fluarix Quadrivalent, manufactured by GlaxoSmithKline, is the first intramuscular vaccine to protect against four influenza strains, and it is approved for individuals aged 3 years and older. In clinical trials, the most common adverse reactions in adults were pain at the injection site, muscle aches, headache

and fatigue. In children between 3 years and less than 6 years, the most common adverse reactions were drowsiness, irritability and loss of appetite. And, in children 6 years to less than 18 years, the most common systemic adverse reactions were fatigue, muscle aches, headache, arthralgia and gastrointestinal symptoms.[15]

All of the major players in the vaccine industry have long recognized the need for a more expeditious vaccine production technology.

Last month, the FDA approved Sanofi Pasteur's Fluzone Quadrivalent for use in children 6 months and older, adolescents and adults. It is the first IIV4 option for children as young as 6 months. The vaccine comes in preservative-free, prefilled syringes and single-dose vials for intramuscular administration. In clinical trials, the most common local and systemic adverse reactions were pain, erythema and swelling at the vaccination site; myalgia; malaise; headache; and fever. In some young children, the vaccine also caused irritability, crying and drowsiness.

As previously discussed, the number of strains in the vaccines isn't the only efficacy issue. While conventional flu vaccines generally provide protection to 70 percent to 90 percent of healthy young adults, the protection rate is far lower in young children and people in their mid-60s and older.[10] The need for a more immunogenic flu vaccine for the young and elderly who most need it has driven intensive research efforts for decades. And, for the first time since the flu vaccine's introduction in the 1940s, Americans aged 65 and older have the option of receiving a high-potency flu vaccine, which was introduced to market in the 2010-2011 season.

Instead of the 15 micrograms (mcg) of each of the three hemagglutinin viral surface antigens included in standard IIV3 preparations, Sanofi Pasteur's Fluzone High-Dose delivers 60 mcg — four times as much — in the same 0.5 mL dose for intramuscular injection. A different colored syringe plunger distinguishes it from regular Fluzone provided in a prefilled syringe. Everything else about the two products is the same.

Immunogenicity findings from three clinical trials in persons 65 years of age and older demonstrate that Fluzone High-Dose elicits substantially higher hemagglutinin inhibition (HI) titers than the standard dose. In the largest of these studies, the mean post-vaccination antibody titer elicited by Fluzone High-Dose against the A/H1NI, A/H3N2 and B flu strains was 70 percent, 80 percent and 30 percent higher, respectively, than the titer elicited by the standard-dose vaccine.

In studies over the last 40 years, higher HI titers have been shown to directly correlate with lower rates of influenza infection. Yet, with four times as much hemagglutinin antigen (HA) being introduced into the muscle tissue as the same volume of traditional flu vaccine, more injection site and systemic reactions are possible. This is what was observed in a pivotal trial involving 2,573 subjects aged 65 years and older who were administered Fluzone High-Dose and 1,260 subjects who were given Fluzone. Most of these local and systemic reactions were mild and resolved within three days. However, significantly more Fluzone High-Dose recipients (1.1 percent) reported moderate to severe fever than those who received standard Fluzone (0.3 percent). The more important comparative measure — the rate of serious adverse events — was not found to be different between subjects who received the high-dose (156/2573; 6.1 percent) and standard (93/1260; 7.4 percent) Fluzone products.

While no one looks forward to a higher likelihood of injection site reactions, transient headaches, fever and the like, there is an upside: Along with increased anti-HA antibody titers, a higher frequency of these events signals a more active and potentially more protective immune response. As noted earlier, better HI antibody responses are known to correlate with protection against influenza infection and reduced clinical disease risk. Yet while it is very encouraging that Fluzone High-Dose induces higher serum antibody titers without significant safety concerns, the jury is still out on whether this actually translates into fewer confirmed cases and serious complications from the flu.

As a condition of licensure under FDA's "accelerated approval" process, Sanofi Pasteur is conducting a head-to-head study to compare Fluzone High-Dose and Fluzone (the "active control") in 27,000 to 30,000 adult subjects 65 years of age and older. That study is being conducted over three flu seasons to try to account for typical fluctuation in vaccine efficacy, which is related to differences between the flu virus that arrives and the strains picked in advance to make the vaccine. Until that study is finished and the results are known, Fluzone High-Dose labeling informs providers and recipients that "there have been no controlled studies demonstrating a decrease in influenza disease after vaccination with Fluzone High-Dose."[12]

There is also another vaccine that promises to fill the void

for both the elderly and the young: Fluad, which is approved in Canada. In five pivotal trials involving 1,168 subjects aged 65 and older, those immunized with Fluad experienced consistently higher HI antibody titers than subjects who received conventional IIV3. Greater percentages also achieved seroconversion or a significant increase in HI titers for homologous virus strains.

The safety profile for Fluad is based on 39 studies in which a total of 12,889 subjects were exposed to at least one dose, 492 of whom received a second consecutive dose one year later, and 150 a third dose the following year. Pooled safety data showed that the most frequently reported local adverse events within four days of vaccination were injection site pain (26 percent in the Fluad group vs. 14 percent in the comparator group) and a "warm" or "hot" temperature at the injection site (18 percent vs. 11 percent). Generally of mild or moderate intensity, these reactions usually resolved within two or three days. Systemic reactions, most notably headache, fatigue, malaise and myalgia, were reported by similar percentages of subjects after the first, second and third vaccinations in both the Fluad and comparator vaccine groups.

Whether the superior immunogenicity of Fluad to IIV3 translates into reduced influenza-related complications and mortality remains to be answered by future clinical studies. But, Fluad's safety and immunogenicity record in the elderly population has raised hopes that this adjuvanted seasonal flu vaccine can be shown safe and protective in the next-largest at-risk group: children under 6 years of age. Findings from a newly published study involving 4,707 previously unvaccinated German and Finnish children ages 6 months to 72 months appear to have justified these hopes.

Over two influenza seasons, children were stratified first by age — 6 months to less than 36 months and 36 months to less than 72 months — and then randomly assigned in a ratio of 2:2:1 to receive two doses, 28 days apart, of 1) MF59 adjuvant-containing IIV3 (AIIV3; Fluad), 2) conventional IIV3 with HAs from the same three viral subtypes, or 3) a non-influenza "control" vaccine (meningococcal C conjugate vaccine given in 0.25 mL doses in children 6 months to <12 months of age, and tickborne encephalitis vaccine given in 0.5 mL doses to children 12 months to <72 months of age).

Over both influenza seasons, the absolute efficacy of Fluad

against all influenza strains was 86 percent (95 percent confidence interval [CI], 74 to 93) and 89 percent against vaccine-matched strains (95 percent CI, 78 to 95). Just 13 confirmed cases of influenza occurred among 1,937 children immunized with Fluad — an attack rate of less than 0.7 percent. By contrast, 47 of 993 control group children (4.7 percent) contracted influenza. Relative to IIV3, Fluad was 75 percent effective (95 percent CI, 57 to 87) against all flu strains.

Even more striking was the superior efficacy of Fluad in infants from 6 months to less than 24 months of age — the least immunocompetent and thus the least responsive to conventional flu vaccine. While IIV3 didn't show significant efficacy in relation to control vaccination (11 percent, 95 percent CI, -89 to 58), Fluad was effective relative to both control vaccine (77 percent) and IIV3 (93 percent), albeit with wide confidence intervals due to the low (2.3 percent) overall influenza attack rate.

As we approach the century mark of the deadliest flu pandemic in history, much still needs to be learned about how to best protect the public from flu and a possible future pandemic.

A subanalysis showed that Fluad was efficacious in both younger and older age groups. Fluad efficacy against all flu strains was 79 percent in children 6 months to less than 36 months and 92 percent in those 36 months to less than 72 months of age. IIV3 efficacy versus controls was just 40 percent (with 95 percent CI overlapping zero) and 45 percent in the younger and older age cohorts, respectively.

As with previous studies of Novartis' MF59-adjuvanted seasonal and pandemic flu vaccines, Fluad induced a significantly greater antibody response than IIV3, both against homologous (vaccine) and other flu strains. Remarkably, the response to the first of two Fluad injections in these young children met the standard seroprotection threshold (HI antibody titer ≥40) for both A-subtype viruses.

Vaccine-related adverse events were generally mild to moderate in both age cohorts. Systemic reactions, including mild fever, were slightly more frequent in older children after Fluad, but they were mostly mild and of short duration. Rates of serious adverse events were similar in the IIV3 and Fluad group, and confirm previous experience with MF59 adjuvant in trials of other vaccines involving some 33,000 children.

With these supportive data, together with experience from more than 50 million Fluad doses supplied to the elderly population since 1997 and twice that number of doses of MF59-adjuvanted pandemic influenza vaccine administered to all age groups, the prospects appear good that Fluad will eventually become available in the U.S.

A new U.S. Phase III clinical trial is now underway to evaluate Fluad in persons ages 65 years and older. But still lingering in some minds are safety questions raised by studies in small animal models describing induction of arthritis-like inflammation and lupus autoantibodies following administration of small quantities of squalene, as well as other endogenous lipids. A core concern is whether injection, year after year, of even the minute quantity of squalene (about 10 mg in a 0.5 mL dose) in Fluad could trigger immune cross-reactivity with endogenous squalene found in the joints, nervous system or other parts of the body. This hypothetical concern that injection — rather than ingestion — of an important lipid tissue component could trigger autoimmune disease likely figures into the conservative, "go slow" approach of FDA with respect to vaccines generally that include oil-in-water emulsions.[11] Novartis is now in Phase III testing for Fluad.

Just recently, more concern has been raised about adjuvanted vaccines such as Fluad with GlaxoSmithKline's adjuvant-containing H5N1 influenza vaccine proposed for inclusion in the U.S. pandemic emergency stockpile. The vaccine, informally known as Q-Pan H5N1, contains GSK's proprietary AS03, which is used in several other GSK vaccines licensed in other countries. One of these, Pandemrix, was used in Europe during the 2009-2010 H1N1 flu pandemic. Since then, studies in Finland, Sweden, Ireland and Britain have found the risk of developing narcolepsy is between seven and 13 times higher in children immunized with Pandemrix than in those who were not. The purpose of the adjuvant is to induce a stronger immune response with less antigen or active ingredient, which AS03 achieves; the vaccine contains 3.75 micrograms (mcg) of antigen, compared with 15 mcg in standard flu vaccines without adjuvants.

The FDA is using its accelerated approval process to review the vaccine, which means that the licensing decision will be based on immunogenicity as evidenced by antibody response rather than actual protection against flu as demonstrated in clinical trials or observational studies. In one trial involving 680 adult volunteers comparing Q-Pan with the same vaccine

without an adjuvant, results supported the 3.75 mcg dose of antigen but showed that two doses were required to generate an adequate immune response. A second trial involving 4,561 adults comparing Q-Pan with a saline placebo vaccine found that at least 70 percent of the younger adults met FDA's criterion (an antibody titer of 1:40 as measured by HI), and at least 60 percent of the older volunteers met the standard.

Currently, no seasonal flu vaccines in the U.S. contain adjuvants, nor does the existing H5N1 vaccine in the U.S. emergency stockpile.[17,18]

The Challenge of Vaccine Manufacturing

Compounding the issues of flu vaccines' efficacy is the increasing concern about a possible pandemic and how quickly vaccines can be manufactured to protect the public. As soon as the circulating strains to be included in the vaccines are identified, production schedules are tight and leave little room for error — FDA must approve the vaccine by the spring, the vaccine must be in production by August and be ready to be administered in September through December, giving people enough time to develop immunity before flu season is in full swing.

Traditional egg-based vaccine technology was once considered groundbreaking. And for more than 50 years, it has provided protection against influenza for 50 percent to 80 percent of the population. But a flu virus grown in chicken eggs has its complications. Vaccinating the entire population would potentially require 600 million eggs. If we were to experience an outbreak of avian flu, our egg-producing flocks could be depleted. Even more serious: A full-blown pandemic like the Spanish flu of 1918 would not be able to be contained and defeated by egg-based production; the process takes too long, and eggs don't grow on demand. And, many people are allergic to eggs and can't be vaccinated.[19]

All of the major players in the vaccine industry have long recognized the need for a more expeditious vaccine production technology. That's why, in 2006, HHS provided more than $1 billion in contracts to six manufacturers to develop cell-culture-based flu vaccine technology in the U.S. Then, in 2009 when it was difficult to grow vaccine to respond to the H1N1 swine flu pandemic, HHS granted Novartis nearly $500 million to build the first U.S. facility capable of producing cell-culture-based vaccine for seasonal and pandemic flu in the U.S. (Novartis footed the additional $1 billion price tag.) Cell-culture-based technology is not the only new approach that the U.S. is helping to fund. In 2009, HHS awarded a five-year $147 million investment to Protein Sciences, which was investigating a recombinant vaccine that is grown inside insect cells. With cell-culture-based and recombinant production techniques, influenza vaccines can be produced easier and faster — within weeks — for seasonal or pandemic influenza. And, because the vaccine is grown in sterile, controlled environments, the risk of potential impurities is significantly reduced.

In January, the FDA approved the first two new influenza vaccines using non-egg-based technologies, making flu vaccines available to the hundreds of thousands of individuals allergic to eggs, as well as providing an easier methodology of producing influenza vaccines at a faster rate both for seasonal influenza and in the event of a flu pandemic.

Currently, HHS is focusing on a genetically engineered universal vaccine that could be given every five to 10 years, much like a tetanus shot.

Novartis' Flucelvax is manufactured using MDCK cell-culture technology, and it is approved for individuals 18 years and older. The ccIIV3 vaccine is produced through four steps. First, the seed stocks for three influenza viruses are produced. Then, the virus is propagated in cells that are expanded and inoculated with the influenza viruses and allowed to replicate over several days. The virus is then isolated, inactivated and purified by removing the influenza-antigen components. Finally, the virus is formulated by combining the antigen components into one vaccine. In seven controlled studies of Flucelvax, the rates of serious adverse events were collected for 21 days in two studies and for six to nine months in five studies. Subjects were divided into three groups: one that received Flucelvax, the other that received a U.S.-licensed comparator vaccine and a third that received a placebo. In each of these groups, the rate of all serious adverse events among adults 18 through 64 years of age was 1 percent. The rate of serious adverse events among adults 65 years of age and older was 4 percent in both groups that received Flucelvax and those that received a U.S.-licensed comparator vaccine. Flucelvax contains no additives or preservatives.

The second new vaccine, Protein Science's Flublok, is manufactured using an insect virus (baculovirus) expression system and recombinant DNA technology. The recombinant production process involves programming insect cells grown in steel tanks

to produce large amounts of hemagglutinin. The RIV3 is designed to protect against the H1N1, H3N2, both A strains and one B strain of the influenza virus, and it is approved for people between the ages of 18 and 49 years. In a study of 2,300 people, the vaccine was found to be 44.6 percent effective against all strains of the flu. Flublok's safety evaluation was conducted in a study of about 2,500 people who were vaccinated with Flublok. The most common side effects included muscle aches, headache, fatigue and pain in the area the shot was administered. This vaccine also contains no additives or preservatives.

While both the cell-culture-based and recombinant technologies are new to flu vaccine production, they are already used to make vaccines that have been approved by the FDA to prevent other infectious diseases.

Two other genetically engineered flu vaccines also are under development. One by Novavax uses bits of genetic material grown in caterpillar cells called "virus-like particles" that mimic a flu virus. The other is being developed by VaxInnate Corp. In 2011, HHS awarded VaxInnate a five-year, $196 million grant to make a vaccine that combines a bacterial protein called flagellin, a potent stimulator of the immune system, with a very small portion of hemagglutinin. VaxInnate's flu vaccine is in mid-stage clinical trials. Both of these vaccines are expected to be available in the latter part of the decade.

Currently, HHS is focusing on a genetically engineered universal vaccine that could be given every five to 10 years, much like a tetanus shot. The universal vaccine also would protect against most types of flu, including seasonal varieties and the highly mutated kinds that cause pandemics.[1] However, it's not known how soon a universal influenza vaccine could be made available. While several teams have tried and failed to produce such a vaccine, scientists at the National Institute of Allergy and Infectious Disease (NIAID), a part of the National Institutes of Health (NIH), and others are making good progress, according to Dr. Anthony Fauci, director of the NIAID. Fauci and Dr. Gary Nabel, former head of NIH's Vaccine Research Center who recently joined Sanofi Pasteur as chief science officer, showed that a portion of the flu virus that is usually hidden from the immune system may be the key. Most vaccines target proteins on the bulb portion of the hemagglutinin part of the flu virus, which mutates from year to year. But, the stem portion, which contains proteins that are structurally hidden from the immune system, doesn't change much from virus to virus. A genetically engineered vaccine could overcome that by presenting only the stem proteins to the immune system. Phase I studies have begun in people to test for safety and whether the vaccine can create an appropriate immune response. Novartis Vaccines and BARDA will be handling the manufacturing of the vaccine.[16]

The Journey Continues

As we approach the century mark of the deadliest flu pandemic in history, much still needs to be learned about how to best protect the public from flu and a possible future pandemic. With the threat of the avian flu, most notably the H7N9 virus that is the most lethal of its kind, governments worldwide are committing resources to understanding how the virus mutates and how to develop innovative and more effective vaccines to halt flu's spread. And, great strides have been made, most notably in the latter part of the 20th century and the start of this century. Scientists now know what is required for flu to mutate into a pandemic, and health experts are keeping a close eye on those strains that pose the greatest risk. With the new vaccines recently introduced to market and the hope for a universal vaccine by the end of the decade, the journey continues to unravel the mystery of flu. ❖

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