Influenza

Past, Present and Future

The flu virus has claimed millions of lives. Examining past outbreaks, researching strain mutations and monitoring global epidemic statistics may help us better predict and possibly prevent future pandemics.

By Trudie Mitschang

It was a pandemic unlike any other. The 1918-19 influenza outbreak at the end of World War I killed more people than the Great War itself, claiming the lives of as many as 50 million men, women and children. The Spanish flu has been called the most devastating epidemic in recorded world history, with more people dying of influenza in a single year than in four years of the black death bubonic plague.[1] A global disaster of this magnitude is hard to imagine today, especially when so many people view the flu as little more than a very bad cold. History, unfortunately, contradicts that cavalier point of view. And when it comes to flu, experts believe history may have a tendency to repeat itself.

Understanding Influenza

Influenza, commonly known as the flu, is actually a general name given to any one of a number of viruses that can cause serious illness. There are three types of the flu: influenza A, B and C — each one with its own viral strain that replicates and changes independently from the other types. Seasonal strains of human influenza change constantly, which is why people can catch the flu multiple times. It is also why the flu shot is the only vaccination that is continually updated; influenza is a rare type of virus that is constantly mutating.

Each year, a certain strain becomes prevalent and strikes, typically between the months of October and March, a time period now referred to as flu season. When a flu outbreak occurs in one country or region, it is referred to as an epidemic, whereas outbreaks around the world are called pandemics. Because of the global nature of our world today and the speed and frequency of international air travel, the likelihood of another great pandemic is not farfetched; a flu strain that originates in China, for example, could land in New York in less than a day's time, infecting everyone en route.

Large-scale events that create a draw for tourists are a concern for those who study flu outbreaks. A recent report suggests that the 2012 Summer Olympic Games pose an extreme threat for a serious flu outbreak within the United Kingdom as an extra 5.3 million tourists descend 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 will exacerbate the already significant risk to this particular region of the world.[2]

A Viral Link to the Past

The flu virus mutates and changes each year, but many researchers believe the specific strain that wreaked worldwide havoc in the mid-1900s may have birthed a viral dynasty with ramifications that can still be seen today. According to scientists from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, it may even be linked to the now infamous H1N1 outbreak of 2009. In an article published online by the *New England Journal of Medicine*, authors Anthony S. Fauci, MD, Jeffery K. Taubenberger, MD, PhD, and David M. Morens, MD, argue that we have lived in an influenza pandemic era since 1918, and they go on to describe how the H1N1 virus that circled the globe in 2009 was merely another manifestation of the same viral family that killed millions nearly a century ago.[3] "The 1918-1919 influenza pandemic was a defining event in the history of public health," said Dr. Fauci, director of NIAID and a co-author of the study. "The legacy of that pandemic lives on in many ways, including the fact that the descendants of the 1918 virus have continued to circulate for nine decades."[4]

The study went on to explain that all flu viruses have eight genes, including two that are coded to produce the proteins hemagglutinin (H) and neuraminidase (N) that allow the virus to enter a host cell and spread from cell to cell. There are 16 H subtypes and nine N subtypes, making 144 possible HN combinations. But only three — H1N1, H2N2 and H3N2 — observed to date are fully adapted for infecting humans. Other combinations such as the H5N1 bird flu virus have only occasionally infected small numbers of humans. "The eight influenza genes can be thought of as players on a team: Certain combinations of players may arise through chance and endow the virus with new abilities, such as the ability to infect a new type of host," said study co-author David Morens. "That is likely what caused the 1918 pandemic."

The Fight Against Flu

From a public health perspective, the flu has become easier to manage in recent decades. Improved healthcare conditions, greater understanding of the virus itself, more sophisticated means of communicating the risks of flu and, of course, the creation of the flu vaccine all have contributed to this achievement.

When it comes to flu, experts believe history may have a tendency to repeat itself.

The influenza virus was first identified in the early 1930s, and scientists developed a working vaccine by the 1940s, which was used on soldiers during World War II. At the time of the great pandemic during the first World War, the flu virus and its means of transmission were not familiar to the medical community, and there was no such thing as a vaccine. By 1957, the time of the next major flu outbreak, doctors had developed an arsenal of vaccines and were able to alert the public to the risks of not being vaccinated. Casualties were still high — 70,000 people in the U.S. alone.[5]

The next large flu outbreak in 1968 was known as the Hong Kong flu. Thanks to ample supplies of vaccines and public compliance to get vaccinated, only 34,000 people died in the U.S. as a result.[6] These declining mortality rates may have contributed to the growing public sentiment that the flu is not that deadly, but the appearance of several new flu strains in recent years — including the H5N1 "avian flu" strain in the late 1990s — illustrates the challenges faced annually by researchers trying to track, contain and develop vaccines for the ever-changing virus known as influenza.

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IMPORTANT SAFETY INFORMATION

INDICATION

Fluzone Intradermal vaccine is an inactivated influenza virus vaccine indicated for active immunization of persons 18 through 64 years of age against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

SAFETY INFORMATION

The most common local and systemic adverse reactions to Fluzone Intradermal vaccine include erythema, induration, swelling, pain, and pruritus at the vaccination site; headache, myalgia, and malaise. Other adverse reactions may occur. Fluzone Intradermal vaccine should not be administered to anyone with a severe allergic reaction (eg, anaphylaxis) to any vaccine component, including egg protein, or to a previous dose of any influenza vaccine. The decision to give Fluzone Intradermal vaccine should be based on the potential benefits and risks, especially if Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine. Vaccination with Fluzone Intradermal vaccine may not protect all individuals.

Before administering Fluzone Intradermal vaccine, please see brief summary of full Prescribing Information on next page.

CPT®[a] Code: 90654

[a] CPT = Current Procedural Terminology is a registered trademark of the American Medical Association.

Fluzone Intradermal vaccine is manufactured and distributed by Sanofi Pasteur Inc.

To order Fluzone Intradermal vaccine or learn more about the Fluzone Vaccine Partners Program, please log onto **VaccineShoppe.com** or call **1-800-VACCINE** (1-800-822-2463).

References: 1. Laurent PE, Bonnet S, Alchas P, et al. Evaluation of the clinical performance of a new intradermal vaccine administration technique and associated delivery system. *Vaccine*. 2007;25:8833-8842. **2.** Immunization Action Coalition. Administering vaccines: dose, route, site, and needle size. http://www.immunize.org/catg.d/p3085.pdf. Accessed November 8, 2011.

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Fluzone® Intradermal (Influenza Virus Vaccine)
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BRIEF SUMMARY: Please consult package insert for full prescribing information.

INDICATION AND USAGE

Fluzone Intradermal vaccine is an inactivated influenza virus vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. Fluzone Intradermal is approved for use in persons 18 through 64 years of age.

DOSAGE AND ADMINISTRATION

Dosage and Schedule

The dose, schedule, and route of administration for Fluzone Intradermal is presented in Table 1.

Table 1: Fluzone Intradermal

	Dose/Route	Schedule
18 through 64 years of age, any vaccination status	0.1 mL/Intradermal	1 dose

Administration

Inspect Fluzone Intradermal microinjection system visually for particulate matter and/or discoloration prior to administration. If either of these conditions exist, the vaccine should not be administered.

Gently shake the microinjection system before administering the vaccine.

1. Remove Needle Cap: Remove the needle cap from the micro-injection system.

2. Hold Microinjection System Between Thumb and Middle Finger: Hold the system by placing the thumb and middle finger only on the finger pads, the index finger remains free. Do not place fingers on the windows.

3. Insert Needle Rapidly and Perpendicular to the Skin: Insert the needle perpendicular to the skin, in the region of the deltoid, in a short, quick movement.

4. Inject Using the Index Finger: Once the needle has been inserted, maintain light pressure on the surface of the skin and inject using the index finger to push on the plunger. Do not aspirate.

5. Remove Needle from Skin and Activate Needle Shield by Pushing Firmly on Plunger: Remove the needle from the skin. Direct the needle away from you and others. With the same hand, push very firmly with the thumb on the plunger to activate the needle shield. You will hear a click when the shield extends to cover the needle.

DOSAGE FORMS AND STRENGTHS

Suspension for injection is supplied in a single-dose prefilled microinjection system, 0.1 mL, for adults 18 through 64 years of age.

CONTRAINDICATIONS

A severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or to a previous dose of any influenza vaccine is a contraindication to administration of Fluzone Intradermal.

WARNINGS AND PRECAUTIONS

Guillain-Barré Syndrome

The 1976 swine influenza vaccine was associated with an elevated risk of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than 1 additional case per 1 million persons vaccinated.[1] If GBS has occurred within 6 weeks of previous influenza vaccination, the decision to give Fluzone Intradermal should be based on careful consideration of the potential benefits and risks.

Preventing and Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

Altered Immunocompetence

If Fluzone Intradermal is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the expected immune response may not be obtained.

Limitations of Vaccine Effectiveness

Vaccination with Fluzone Intradermal may not protect all recipients.

ADVERSE REACTIONS

Clinical Trial Experience

Adults 18 through 64 years of age were randomized to receive Fluzone Intradermal or Fluzone (year 2008-2009 formulation) in a multi-center trial conducted in the US. The trial was open-label for administration route. The safety analysis set included 2855 Fluzone Intradermal recipients and 1421 Fluzone recipients. Table 2 summarizes solicited injection-site reactions and systemic adverse events reported within 7 days post-vaccination via diary cards. With the exception of pain, solicited injection-site reactions were more frequent after vaccination with Fluzone Intradermal compared to Fluzone. Nine percent of Fluzone recipients and 49% of Fluzone Intradermal recipients had an injection-site reaction present beyond Day 3 post-vaccination. Approximately 20% of subjects in both groups had a solicited systemic adverse event present beyond Day 3 post-vaccination.

Table 2: Frequency of Solicited Injection-Site Reactions and Systemic Adverse Events Within 7 Days After Vaccine Injection, Adults 18 Through 64 Years of Age

	Fluzone Intradermal (N[a]=2798-2802) Percentage			Fluzone (N[a]=1392-1394) Percentage		
	Any	Grade 2[b]	Grade 3[c]	Any	Grade 2[b]	Grade 3[c]
Injection-site reactions						
Erythema	76.4	28.8	13.0	13.2	2.1	0.9
Induration	58.4	13.0	3.4	10.0	2.3	0.5
Swelling	56.8	13.4	5.4	8.4	2.1	0.9
Pain	51.0	4.4	0.6	53.7	5.8	0.8
Pruritus	46.9	4.1	1.1	9.3	0.4	0.0
Ecchymosis	9.3	1.4	0.4	6.2	1.1	0.4
Systemic adverse events						
Headache	31.2	6.4	1.5	30.3	6.5	1.6
Myalgia	26.5	4.6	1.5	30.8	5.5	1.4
Malaise	23.3	5.5	2.2	22.2	5.5	1.8
Shivering	7.3	1.5	0.7	6.2	1.1	0.6
Fever[d]	3.9	0.6	0.1	2.6	0.4	0.2

[a] N is the number of vaccinated subjects with available data for the events listed.

[b] Grade 2 - Injection-site erythema, Injection-site induration, Injection-site swelling, and Injection-site ecchymosis: ≥2.5 cm to <5 cm; Injection-site pain and Injection-site pruritus: sufficiently discomforting to interfere with normal behavior or activities; Fever: >100.4°F to ≤102.2°F; Headache, Myalgia, Malaise, and shivering: interferes with daily activities.

[c] Grade 3 - Injection-site erythema, Injection-site induration, Injection-site swelling, and Injection-site ecchymosis: ≥5 cm; Injection-site pain: incapacitating, unable to perform usual activities; Injection-site pruritus: incapacitating, unable to perform usual activities, may have/or required medical care or absenteeism; Fever: >102.2°F; Headache, Myalgia, Malaise, and Shivering: prevents daily activities.

[d] Fever - Any Fever indicates ≥99.5°F. The percentage of temperature measurements that were taken by oral or axillary routes, or not recorded were 99.9%, <0.1%, and 0.1%, respectively for Fluzone Intradermal; and 99.6%, 0.0%, and 0.4%, respectively for Fluzone.

Within 28 days post-vaccination, a serious adverse event was reported by 10 (0.4%) Fluzone Intradermal recipients and 5 (0.4%) Fluzone recipients. Within 6 months post-vaccination, a serious adverse event was reported by 47 (1.6%) Fluzone Intradermal recipients and 20 (1.4%) Fluzone recipients. No deaths were reported during the 6 months post-vaccination. Throughout the study, one reported serious adverse event was considered to be caused by vaccination: a pruritic rash on the extremities and torso that began 48 hours after receipt of Fluzone Intradermal and resulted in hospitalization and treatment with an antihistamine and steroids.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category B. Fluzone Intradermal should be used during pregnancy only if clearly needed.

Pediatric Use: Safety and effectiveness of Fluzone Intradermal in persons <18 years of age have not been established.

Geriatric Use: Safety and effectiveness of Fluzone Intradermal in persons 65 years of age and older have not been established.

CLINICAL STUDIES

Immunogenicity of Fluzone Intradermal in Adults

Adults 18 through 64 years of age were randomized to receive Fluzone Intradermal or Fluzone (year 2008-2009 formulation) in a multi-center trial conducted in the US. The trial was open-label for administration route. For immunogenicity analyses, there were 2581 participants who received Fluzone Intradermal and 1287 participants who received Fluzone in the per protocol analysis set. Hemagglutination inhibition (HI) antibody geometric mean titers (GMTs) following Fluzone Intradermal were non-inferior to those following Fluzone for all three strains. (See Table 3) Seroconversion rates following Fluzone Intradermal were non-inferior to those following Fluzone for strains A (H1N1) and A (H3N2), but not for strain B. (See Table 4) At 28 days following vaccination with either Fluzone or Fluzone Intradermal, the percentages of subjects with a serum HI antibody titer of at least 1:40 ranged from 87% to 92%, depending on the influenza strain.

Table 3: Non-inferiority of Fluzone Intradermal Relative to Fluzone by HI Antibody GMTs at 28 Days Post Vaccination, Adults 18 through 64 Years of Age

	GMT		GMT Ratio (95% CI)	Non-inferior[a]
Influenza Strain	Fluzone Intradermal N=2573-2579	Fluzone N=1283-1285	Fluzone GMT divided by Fluzone Intradermal GMT	
A (H1N1)	193.2	178.3	0.92 (0.85; 1.01)	Yes
A (H3N2)	246.7	230.7	0.94 (0.85; 1.03)	Yes
B	102.5	126.9	1.24 (1.15; 1.33)	Yes

[a] Pre-defined criterion for non-inferiority: The upper bound of the two sided 95% CI of the ratio of GMTs (Fluzone divided by Fluzone Intradermal) is <1.5.

Table 4: Non-inferiority of Fluzone Intradermal Relative to Fluzone by HI Antibody Seroconversion at 28 Days Post Vaccination, Adults 18 through 64 Years of Age

	Seroconversion[a] %		Difference (95% CI)	Non-inferior[b]
Influenza Strain	Fluzone Intradermal N=2573-2578	Fluzone N=1283-1285	Fluzone minus Fluzone Intradermal	
A (H1N1)	61.2	60.5	-0.69 (-3.97; 2.56)	Yes
A (H3N2)	75.3	74.8	-0.55 (-3.49; 2.31)	Yes
B	46.2	54.2	7.99 (4.64; 11.31)	No

Note: As defined in the study protocol:

[a] Seroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination (day 28) titer ≥1:40 or a minimum 4-fold increase for participants with pre-vaccination titer ≥1:10.

[b] Pre-defined criterion for non-inferiority: The upper bound of the two sided 95% CI of the difference in seroconversion rates (Fluzone minus Fluzone Intradermal) is <10%.

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HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Fluzone Intradermal microinjection system does not contain latex.

Single-dose prefilled microinjection system, 0.1 mL, package of 10 (does not contain latex) – NDC 49281-703-55.

Storage and Handling

Store Fluzone Intradermal refrigerated at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Discard if vaccine has been frozen. Do not use after the expiration date shown on the label.

PATIENT COUNSELING INFORMATION

Inform the patient or guardian that Fluzone Intradermal contains killed viruses and cannot cause influenza. Fluzone Intradermal stimulates the immune system to produce antibodies that help protect against influenza, but does not prevent other respiratory infections. Annual influenza vaccination is recommended. Instruct vaccine recipients and guardians to report adverse reactions to their healthcare provider and contact Sanofi Pasteur Inc. at 1-800-822-2463 (1-800-VACCINE) and/or VAERS at 1-800-822-7967. Inform the patient about the Sanofi Pasteur Inc. pregnancy registry, for Fluzone Intradermal as appropriate.

Product information as of May 2011.

Manufactured by:
Sanofi Pasteur Inc.
Swiftwater PA 18370 USA

Printed in USA

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6044-6045-6046-6109

An Evolving Challenge

Because of the evolving nature of the 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.

The World Health Organization (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. As one might imagine, production schedules are tight and leave little room for error — the 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.

Today's influenza vaccine contains three strains of the virus, as determined by the World Health Organization (WHO), and researchers labor to stay one step ahead of the constantly mutating bug. For the 2012-13 flu season, the vaccine was reformulated with two new flu strains.[7] Each year, public service campaigns encourage people to get vaccinated; current Centers for Disease Control and Prevention (CDC) guidelines advise everyone 6 months of age and older to get a flu vaccine annually.

A Historical Look at Pandemic Flu

Spanish Flu, 1918–1919

- Illness from the 1918 flu pandemic, also known as the Spanish flu, came on quickly. Some people felt fine in the morning but died by nightfall.
- Approximately 20 percent to 40 percent of the worldwide population became ill.
- An estimated 50 million people died.
- Nearly 675,000 people died in the United States.

Asian Flu, 1957–1958

- In February 1957, a new flu virus was identified in the Far East. Immunity to this strain was rare in people younger than 65.
- Vaccine production began in late May 1957 and was available in limited supply by August 1957.
- By December, the outbreak ebbed but resurged in January of 1958.
- Although not as devastating as the 1918 pandemic, about 69,800 people in the United States died.
- The elderly had the highest rates of death.

Hong Kong Flu, 1968–1969

- In early 1968, a new flu virus was detected in Hong Kong. The first cases in the U.S. were detected as early as September 1968.
- The number of deaths between September 1968 and March 1969 was 33,800, making it the mildest flu pandemic in the 20th century.
- The flu hit hardest in December when schoolchildren were on vacation, leading to a decline in flu cases.
- Improved medical care and antibiotics effective for secondary bacterial infections were available, minimizing fatalities.

H1N1, 2009–2010

- In the spring of 2009, a new flu virus spread quickly across the U.S. and the world. The first case of H1N1 (swine flu) was diagnosed on April 15, 2009.
- By April 21, the Centers for Disease Control and Prevention (CDC) began work on a vaccine. On April 26, the U.S. government declared a public health emergency.
- A total of 74 countries were affected by the pandemic.
- During the outbreak, 80 million people were vaccinated against H1N1.
- The CDC estimates that 43 million to 89 million people contracted the virus.
- There were between 8,870 and 18,300 H1N1-related deaths.

Source: Pandemic Flu History. Flu.gov. Accessed at www.flu.gov/pandemic/history/index.html.

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 tens of thousands of people still die from flu-related complications in the U.S. While there may be many extenuating reasons for these statistics, the sad fact remains that many people still avoid getting a flu vaccine. 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. Clearly, more education, communication and effort are needed to help dispel some of these common myths surrounding flu vaccination to ensure pandemic history does not repeat itself.

For years, infectious disease experts have warned of an influenza virus that could infect 40 percent of the world's population.

The 1970s Swine Flu Scare

The ability of a virus to breed panic was perfectly illustrated when the emergence of a flu-like illness at Fort Dix, N.J., in the late 1970s became public knowledge. Federal researchers isolated a flu virus with the same H1N1 antigenic signature as the Spanish flu. Thirteen soldiers became seriously ill, and one young man died.

While hindsight is 20/20, at the time of the outbreak, the CDC recommended a massive vaccination campaign in an effort to protect the American public. The effort was initially successful, and within 10 weeks, 40 million Americans were inoculated. Unfortunately, public health officials had little time to revel in the achievement, as reports of temporary paralysis and death linked to the vaccine began to emerge. By January 1977, more than 500 cases of Guillain-Barré syndrome were counted, along with 25 deaths.[8]

To add insult to injury, the potentially deadly pandemic never really materialized, and the public backlash against government-recommended flu vaccines created skepticism about flu vaccine efficacy that continues to this day.

Pandemic Predictions: Fact or Science Fiction?

For years, infectious disease experts have warned of an influenza virus that could infect 40 percent of the world's population. Some now believe that the H5N1 virus, also known as the avian flu, could become that deadly strain. The catastrophe such a pandemic could pose has been compared to the 1918-19 Spanish flu, with the possibility of H5N1 being even more lethal.

Since it was discovered in China in 1997, the H5N1 has mutated, becoming stronger and more deadly. But whether the relentless virus ever becomes capable of being transmitted from human to human on a wide scale remains to be seen.[9] The fear of this unknown creates much unease among those whose job is to predict pandemic outbreaks.

The threat of bioterrorism is also a concern, with many in the scientific community wanting to limit the release of information garnered from studies about H5N1, lest it fall into the wrong hands. In a correspondence addressing the topic earlier this year, Michael Osterholm, director of the Center for Infectious Disease Research and Policy, which studies bioterrorism threat, stated that even if H5N1 was not spread in human populations, a terrorist group might try to infect pigs, devastating local livestock industries because people would fear infection from eating them (despite the fact that viruses are not transmitted this way).[10] "I can't think of a worse scenario than having H5N1 virus circulating widely in swine with a critical reassortment likely to occur and human transmission not far off," Osterholm said.

Developing countermeasures to hold back the flu is an even more complicated challenge to today's scientists than it was to their predecessors. Much is dependent on our current strategies and continued vigilance against the virus that has the potential to bring about global disaster.[3] ❖

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