Source: University of Melbourne Archives, "Inoculation of eggs for production of influenza vaccine, Commonwealth Serum Laboratory," Sir Macfarlane Burnet collection Acc. No. 89/34, item 14-16

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Flu Vaccines: WH

The influenza virus, the vaccine, and the poultry

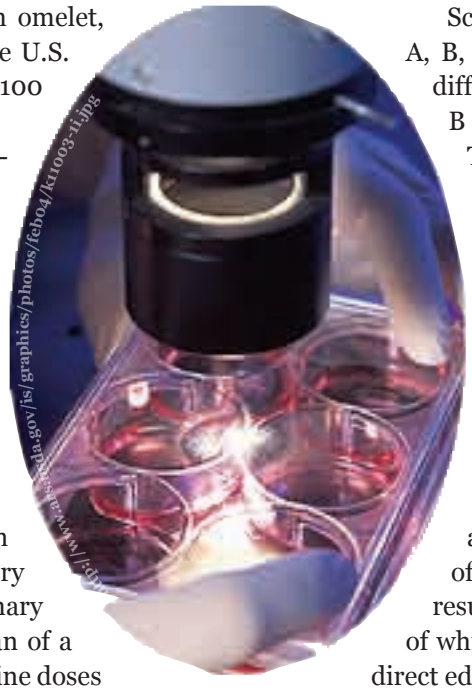
By Anjali Vaidya

Scrambled. Poached. Sunny-side up. Benedict. What do these words have in common? Why, they are all ways of preparing eggs, of course.

IO Cares?

Eggs are a wonderfully versatile food. However, most people don't realize that the very same grub we devour each morning along with our coffee and toast is not only a culinary chameleon, but a medical growth medium. To make yourself an omelet, you might break one egg. To make the U.S. flu vaccine, researchers break about 100 million every year.

Now that the United States' flu vaccine supply has been abruptly cut in half, more people are paying attention to the process of vaccine development and the vulnerabilities of using our multipurpose chicken eggs. In early October 2004, British health officials pulled their license from Chiron Corporation, one of only two major manufacturers of the influenza vaccine for the American public, because its eggs had become contaminated with Serratia bacteria (a common laboratory contaminant also responsible for urinary and respiratory infections). In the span of a few hours, an expected 46 million vaccine doses were off the market, Chiron's stock plummeted 17%, and our collective headache had begun before flu season had even arrived.



Now the media has already bombarded us with the statistics – 36,000 Americans die from the flu each year, 25% of the population contracts it annually, 100,000 people are hospitalized every flu season, and the shortage is predicted to cost the U.S. economy as much as $ 20 billion – but very little has been said about what exactly is involved in making the flu vaccine, or about the characteristics of that sneaky little influenza virus which frustrate researchers and patients alike.

An Underestimated Virus

So what is behind our perpetual runny nose, fever, and general feelings of "ickiness" come the winter? While most regard it as merely a minor annoyance, the influenza virus has a long and violent history. Persisting in various forms for several centuries, the virus gained international attention when it caused a 1918 pandemic killing somewhere between 20 and 40 million people worldwide, 2.5% of the entire global population. Believed to have consisted of an unusual recombination of pig and human flu genes, this "Spanish flu" infected one fifth of the world population.

Scientists now classify the virus into types A, B, and C, according to respective antigenic differences on the viral coat, with only A and B causing any clinical disease of concern. The influenza genome consists of eight segments of single-stranded RNA which encode at least ten proteins. As with all viruses, it hijacks the host's cellular machinery to produce viral proteins which are involved in replicating the viral genome and synthesizing new viral capsids (outer coverings) and cores. Type A viruses are primarily found in pigs, horses, and avian species, and are generally considered more severe than Type B, which affect only humans. In 1997, an outbreak of avian influenza occurring in Hong Kong resulted in 18 confirmed cases in humans, six of which were fatal, and prompted scientists to direct education and medical resources to rural areas where humans and livestock come into close contact. Unfortunately, there is still no vaccine for the bird flu.

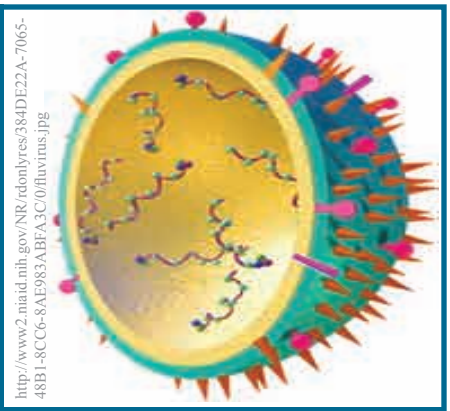
How exactly might you "catch" the flu from someone? The virus is spread through respiratory secretions, typically as small particle aerosols propelled by someone sneezing, coughing, or talking. It can, however, endure on your hands for hours, which is why many contract the disease by shaking hands, putting their finger in their mouth, or rubbing their eyes. Amazingly resilient, influenza can survive within a wide range of environmental conditions but prefers low relative humidity and low temperature. After an incubation time of 1 to 5 days (2 days on average), during which time the virus begins to attack respiratory cells in the ear, nose, and throat, symptoms such as fever, runny nose, headache, and sore throat begin appearing. A runny nose, like the fever, is an artifact of our immune response to the virus. When cells in the nose and lungs are irritated, our mucous membranes go into overdrive to pick up and expel irritants. Same with the cough. So the next time you're buried under a glacier of used Kleenex, coughing away and generally loathing life, take comfort in the fact that your body is waging a considerable effort on your behalf. You are basically your own prisoner-of-war.

The Efficacy of the Vaccine

In Liverpool, England, a Chiron plant develops flu vaccines today using a technology developed 50 years ago. A chicken eggshell is cracked and the influenza virus is injected into the embryonic fluid. The egg is resealed, the embryo

Facing Page: Since the 1940s, scientists have prepared the flu vaccine by using chicken eggs as a growth medium for the virus.
Above: Researchers observe cells for presence of influenza A virus.

http://www.fda.gov/is/graphics/photos/feb04/k11000-



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^ Cellular structure of influenza: the RNA segments are contained within an envelope that is coated with protein antigens.

< A medical officer retrieves embryonated chicken eggs that are used to propogate swine influenza A viruses.

becomes infected, and the resulting virus is then harvested, purified and used to create the vaccine, which may take one of three forms: whole inactivated virus vaccine, split virus vaccines that consist of viral particles disrupted by detergent treatment, or subunit vaccines composed of the two antigens responsible for viral attachment and penetration of human cells. These two antigens, haemagglutinin (HA) and neuraminidase (NA), also organize the release of progeny virus from the infected cells and determine the subtypes of Influenza A viruses. Complicating the vaccination process is the adaptive nature of the influenza virus. Aided by a high mutation rate, influenza is continually evolving new surface antigens by natural selection ("Antigenic Drift"), frequently rendering the virus immune to last year's flu vaccine.

Here at Stanford, Dr. Harry Greenberg and his colleagues in the School of Medicine are members of an influenza research team examining such mutations, specifically studying the efficacy of different types of vaccines and the determinants of post-vaccination immunity to influenza. Greenberg and collaborators (including Drs. A. Arvin, C. Dekker, D. Lewis, E. Mellins, E. Butcher, M. Davis, G. Nolan, and P. Parham) have just finished a full season of comparing two licensed vaccines: one an attenuated live virus infection and the other a killed virus styled similarly to most modern immunizations. The two vaccines work by different mechanisms but ultimately achieve the same ends. The team aims to collect conclusive data to analyze the efficacy of the two different types of vaccines.

In September and February of each year, based on surveillance data from the worldwide network of national influenza centers which track the various forms of the virus, the World Health Organization (WHO) recommends the composition of the vaccine for the next season. Manufacturers such as Chiron and Aventis Pasteur then modify their production to fit the WHO's recommendations. On the whole, flu vaccinations have been very successful in lowering the disease's prevalence and severity among the public. Among healthy adults, the vaccine significantly reduces respiratory illness, while among the more high risk groups like the elderly, the vaccine prevents more serious complications such as pneumonia and death. Provided a good antigenic match between vaccine and the viral strain causing the outbreak, the vaccine has been shown to prevent laboratory confirmed illness in adults by 70% - 90% and lower overall mortality among the elderly by 39% - 75%.

While flu antiviral drugs have shown similar efficacy, resistant viral mutants to most of these drugs have been detected. Dr. Greenberg notes that the practicality of such antivirals has also been limited; to fully prevent the flu, the drugs have to be administered for six to eight weeks and could not be provided for large numbers of the population without incurring exorbitant costs. Furthermore, he observes that once infection has occurred, most antiviral drugs have a critical window of time during which they are highly efficacious, usually shortly after infection. By the time symptoms appear and people begin taking the drugs, it is often too late. Dr. Greenberg describes vaccination as a single intervention strategy with a greater efficacy and lower cost than the antiviral drug option. Other researchers argue that antiviral drugs would also not be available in mass scale during a flu outbreak. Ironically, this season, neither will the vaccine.

The Future

In light of the vulnerability of existing vaccine techniques to contamination, scientists have begun clamoring for reform. On a policy level, the media has argued that by licensing only two companies to produce the U.S. vaccine, we're effectively (and quite literally) putting all our eggs in one basket. Compare our two licenses with Britain's five, France's six, and Germany's eight. Dr. Greenberg notes however, that there is little we can do to diversify our vaccine sources if companies are not applying for licenses from the U.S. (perhaps because it is financially unrewarding and/or too great a hassle for them to do so). Nonetheless, a contamination outbreak in one manufacturer's labs would not be nearly as devastating if we had a variety of alternative sources to fall back on.

On a scientific level, reformers call for revising the vaccine development procedure itself. Even with robotic assistance, it is generally agreed that the chicken egg procedure is a tedious one, and tedious processes are susceptible to error in

the laboratory. Researchers suggest using cultured human cells to prepare the vaccine, which would bypass the need to modify the virus to get it to reproduce in chicken eggs. Working with human cells might even create a vaccine more similar to the virus which will actually be encountered by humans during the flu season. Dr. Greenberg points out, however, that creating vaccines from the immortal cell lines typically used in cell culture could have potentially damaging side effects on vaccine recipients. He highlights scientific and regulatory concerns that a piece of the nucleic acid or an adventitious agent from such immortal cells (which have abnormal genetic content to allow for their longevity and rapid cell division) could co-purify with the flu virus and be transferred as part of the vaccine. As such, since cancer is the unregulated proliferation of abnormal cells, the vaccine could potentially produce malignant tumors in its recipients. Because most vaccines are developed using mortal diploid cells, this issue lacks conclusive evidence. While it remains solely a theoretical concern, a shift from chicken eggs to human cells would necessitate a more rigorous study of this potential side effect and a possible change in current FDA regulations.

Could a vaccine cause cancer?

Where the human cell-based vaccine will become invaluable is in the event of a global pandemic of a new strain, or one that appears outside the typical flu season. Cell cultures can be scaled up much faster, allowing health officials to expedite their response to an irregular flu outbreak. In fact, companies usually have to place their orders for chicken eggs six months before they actually make the vaccine. Thus, in the event of an epidemic, it is unlikely manufacturers will be able to acquire millions of sterile chicken eggs quickly. With most other vaccines, such as that of the polio virus which is made using monkey kidney cells, a cell-based vaccination technique is already in place. Why have we stayed with the chicken egg technology for so long? Primarily because up until now, the technique has worked quite well, and the costs of a dramatic shift in vaccine preparation are daunting to manufacturers. Nonetheless, the recent crisis will likely be a catalyst for reforming the flu vaccine's preparation.

Back to the Basics

For his part, Dr. Greenberg seems confident that since the most high risk groups will receive the vaccine, serious health problems such as hospitalization and death will not increase substantially this flu season. Nonetheless, even with low mortality, the economic costs of a harsh flu season are formidable; sick days among adult workers and students could reach new highs this winter, slowing down productivity. On an even more solemn note, Dr. Greenberg observes that there are countless varieties of the flu (he estimates 15 varieties of the HA antigen alone) which we have yet to encounter. Nobody really knows how many of these forms constitute a virus harmful to humans. The scientific community seems to generally agree that while we have made major advances in our fight against the flu, our battles are far from over.

With the vaccine now limited to the elderly, children, and the immune-compromised, the rest of us will have to remember those Kindergarten lessons we know so well about how to avoid catching the flu. Wash your hands frequently and muffle coughs and sneezes not with your hands but with a sleeve or tissue. Buying sterile wipes is an effective way to insure against situations where a sink and soap are not readily available. Avoid touching your face, keep yourself heavily hydrated, and keep your immune system strong with Echinacea and vitamins (either by eating dark colored fruits and vegetables or by taking vitamin pills). Some suggest taking an occasional sauna, as its high temperature makes it more difficult for viruses to survive. Aerobic exercise has also been shown to increase production of virus killing cells in the body. If you unfortunately catch the flu, stay warm and get lots of sleep, gargle, take hot showers, and avoid interacting with other people in confined spaces. This season, most of us will have to resort to the basics in terms of avoiding the flu. In other words, we are back to breaking out the chicken soup, just not those ubiquitous eggs. **S**

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^ Vaccines are typically shipped in bottles. Hospital officials then divide the vaccine to administer through syringes.