

The Effectiveness of Flu Drugs

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Albert Mitchell, a cook at Fort Riley's Camp Funston in America, felt unwell on the night of March 10 1918 due to a bad headache, a runny nose, and a sore throat. The next morning, he was simply too sick to cook breakfast for the men. The doctor informed him that plenty of bed rest was all that he needed. The symptoms seemed to be those of a particularly bad cold. By lunchtime, 107 soldiers were sick, and by the end of the week the disease had immobilized 522 men. The camp set up emergency hospitalization tents but was simply unequipped to deal with either the volume or the rate of infection. On March 30, the chief medical officer sent a frantic letter to the army Surgeon General begging for aid [1]. The disease in question was a new strain of influenza. The situation did not improve. An old wives tale spread around the country that told of three women who sat down to play bridge. By morning, all were dead. Funerals lasted no more than fifteen minutes as the work of morticians and gravediggers became lucrative [2]. Although an extreme portrayal of the virus, the tale highlights the unprecedented virulence of the 1918 H1N1 strain of influenza. Given the speed with which it swept through the human population, what technological and immunological responses saved the human population from annihilation? And with the developments of the 20th century, will the human population be better equipped to deal with new forms of the influenza virus?

A first wave of the pandemic struck in the late spring of 1918, followed by a much stronger surge in the autumn [3]. Descriptions of symptoms were consistent with those of normal flu, including dizziness, weakness, and joint pain followed soon thereafter by sneezing and then by vomiting, diarrhoea, constipation, and "mental psychoses" [4]. Perhaps most startling to clinicians was the virus's predilection for young and healthy individuals. Given the emphasis of medicine as a diagnostic science, treatment was focused primarily on pain management—*aspirin*, *epinephrine*, and *salicin*—along with plenty of bed rest [5]. Although discussion was circulating amongst academics, the use of nascent immunological techniques was limited. O'Malley and Hartmen, two practicing scientists, did suggest the use of the serum (the liquid component of clotted blood that contains antibodies) from convalescing patients in order to protect the general population [6]. Another team of scientists, Ross and Hund, proposed that the only effective solution would be to "...neutralize or render the intoxicant inert." [7] The concept of neutralising a "toxin" represented the highest level of scientific thinking available at the time. Although they did not succeed with their proposed serum, within two years, the population began to exhibit a potent immune response to the virus, resulting in a much milder annual seasonal flu virus based upon the H1N1 strain.

Seasonal influenza and the available resources to stave off infection have undergone an elaborate dance of genetic adaptation as each attempts to stay one turn ahead of the other. Medical advances, improved public health, and

How effective is Tamiflu? Reproduced from [18]



“ Tamiflu has now lost effectiveness against 99.6% of all strains of influenza. ”

the introduction of drugs have lessened the effects of flu with each subsequent pandemic. Pharmaceutical companies have flooded the market both as a means to manage pain and to provide antivirals. Antihistamines, combination drugs, and a variety of folk remedies all profess to provide a panacea for seasonal flu. Recent studies have shown that the most commercially successful antiviral drug, Tamiflu, has now lost effectiveness against 99.6% of all strains of influenza [8]. Unlike pandemic influenzas, these seasonal bugs affect high-risk groups such as pregnant women, elderly persons, and those individuals with compromised immune systems. Changes in seasonal flu viruses are caused by minimal mutations, termed "genetic drift." [9] The potency of these viruses has decreased over the years not only as a result of increased public health awareness but also due to the evolutionary advantage of less virulent strains. In other words, viruses with the greatest transmissibility, (i.e. those that are pathogenic but do not kill their hosts as readily), are more likely to survive within the human population.

By contrast, pandemic successors of the 1918 influenza virus are noted for their high levels of mutability. Unlike with seasonal flu viruses, pandemic successors are those viruses that have undergone major changes in their genome, otherwise known as genetic "shift" [9]. These "shifts" occur in the genes that code for the surface proteins neuraminidase (NA) and hemagglutinin (HA) (although the term global pandemic is usually reserved for shifts in the HA protein) [10]. The mechanisms by which the flu virus jumps between species are unknown, but the variation in the DNA sequences encoding for the two surface proteins NA and HA suggest a means by which flu has continued to thwart the immunity of the human population for over 90 years. With over 144 possible combinations, genomic reassortment and genetic



How flu was "prevented" in the 1930s. Reproduced from [19]

drift have clearly facilitated the adaptation of the viral genome [10]. In addition, the ability of the influenza virus to move in and out of animal populations (aviary and mammalian) has led to the three-hybrid form of flu known colloquially as "swine flu." [10]

The 2009 swine flu virus first garnered attention in Mexico City in the spring of 2009, although it is not entirely clear where the flu originated [11]. The genetic similarity

“ **An evolutionary preference for a balanced tug of war match** ”

to a strain of influenza commonly found in pigs led to the colloquial nomenclature. Individuals over the age of 60 have been surprisingly resistant to the bug with young, healthy adults likely to be affected. In addition, while those in high-risk groups (such as pregnant women and those with pre-existing conditions) have indeed been hit the hardest with the effects of the virus, many young, healthy individuals with no pre-existing conditions have been severely compromised [12]. This contrasts starkly with seasonal flu, which tends to affect the very elderly or the very young. Given the affinity of swine flu for the young and the healthy, the risk for mutation or increased pathogenesis has led to heightened wariness amongst health authorities and world leaders.

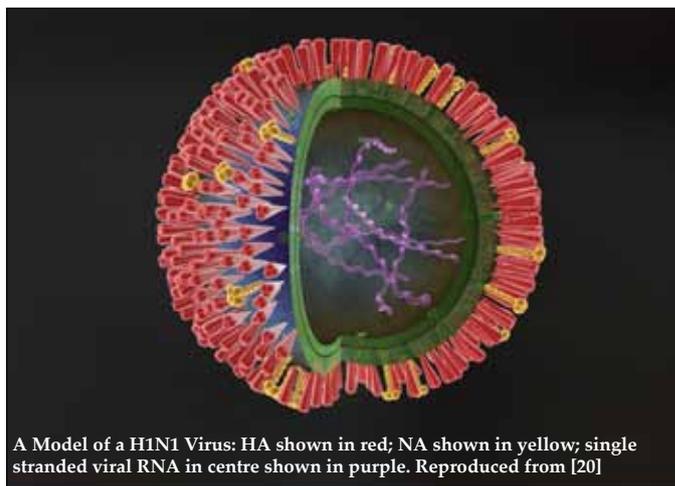
Treatment of influenza falls into three categories: antivirals, vaccines, and antibiotics for pneumonia. The last of these treatments is not in as precarious a situation as the first two. As regards current flu antivirals, "swine flu" has shown no resistance whatsoever to most of these drugs. Unfortunately, these antivirals have also conferred limited to no protection upon the human population. One exception is the drug commonly known as Tamiflu, but in Wales at least, five cases of person-to-person transmission of a Tamiflu-resistant strain of the pandemic virus have emerged [13]. In the United States and in the UK, another emergency antiviral named peramivir has emerged. Peramivir acts in a more potent manner than Tamiflu, but it should be noted

“ **There has been much emphasis on vaccine development to stem the spread** ”

that this is not a vaccine - a common misinterpretation. It has instead been seen to be effective in some severe cases of swine flu [14,15].

The risk of mutation given such factors as ease of movement and increased size in the human population is significant. As a result, there has been much emphasis on vaccine development—both in the media and at a national level—to stem the spread. Although a novel vaccine has indeed been produced, its effectiveness has yet to be tested on the wider population, and initial results in the 2009-2010 flu season have shown severe side effects [16]. Nevertheless, the current flu is mild enough in most cases that bed rest, fluids, and modern health and sanitation practices have been able to certainly contain the mortality rate to well below the 2-5% exhibited in the 1918 flu pandemic [1,17].

"Swine flu" has fully demonstrated its ability to affect the human population in the short term as it moved from Mexico to the United States and then spread globally, targeting all age and risk groups. As has been shown by the 1918 flu pandemic, for "swine flu" to optimise its potency, it must adapt a mechanism of moving in and out of the human population to be both transmissible but mild. It is this evolutionary preference for a balanced tug of war

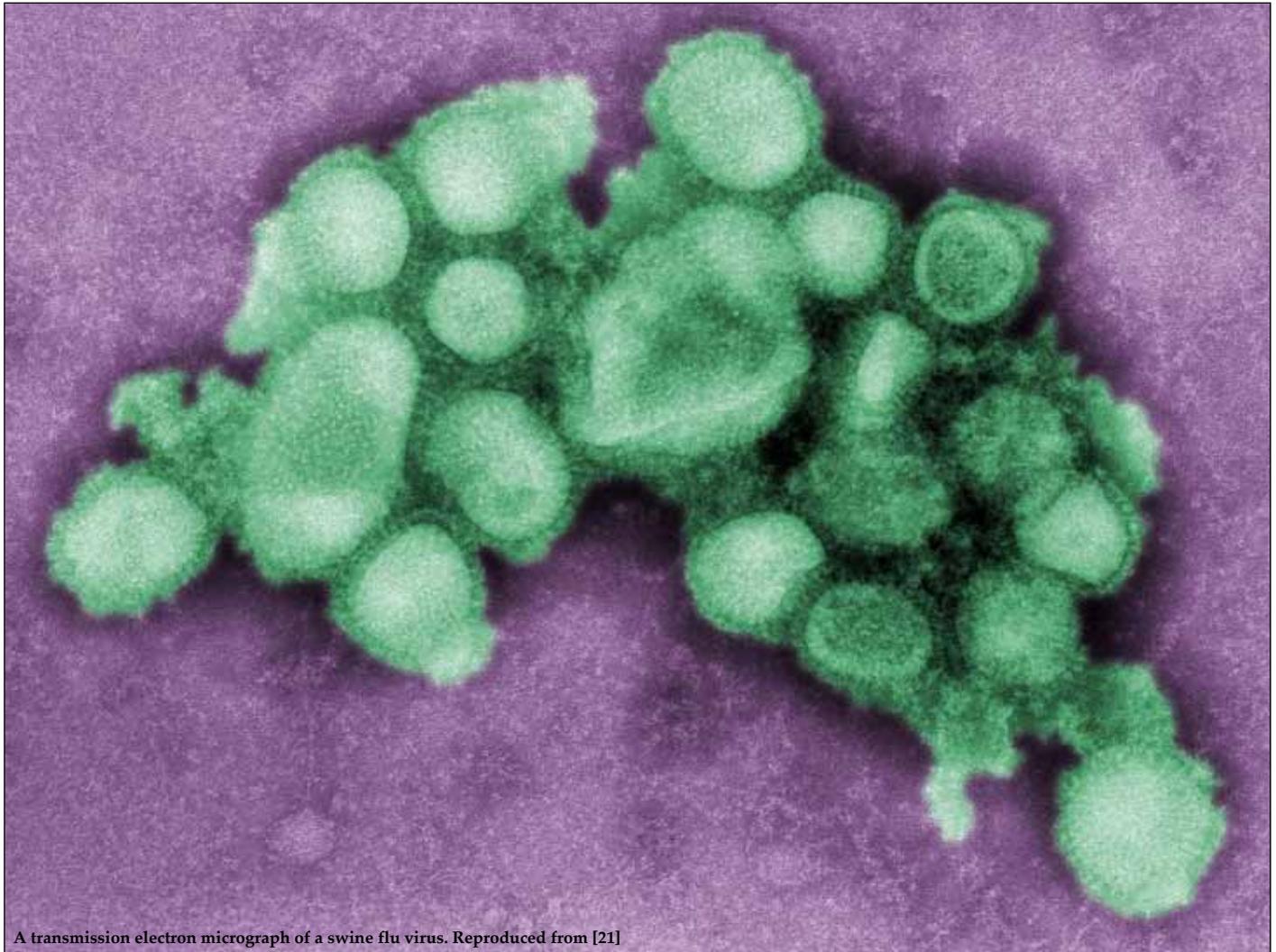


A Model of a H1N1 Virus: HA shown in red; NA shown in yellow; single stranded viral RNA in centre shown in purple. Reproduced from [20]

match that will perhaps lead to a continued and elaborate dance between the H1N1 influenza virus and the drugs developed to combat it. Humans will once again have to evolve both the technology and immunological responses to the new wave of “swine flu” in preparation for a potentially severe, clinically resistant form of the virus. This necessity is embodied in the last December 1918 edition of the Journal

of the American Medical Association, which called for the global community to turn away from the carnage of World War I and instead devote itself “to combating the greatest enemy of all - infectious disease.” ■

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A transmission electron micrograph of a swine flu virus. Reproduced from [21]

References:

- [1] Byerly, C. *Fever of War: the influenza epidemic in the U.S. Army during World War I*. New York (NY): New York University Press; 2005.
- [2] Highfield, R. A flu pandemic is long overdue. *The Daily Telegraph* [newspaper Online]. Feb 21, 2006 [cited Nov 24, 2009]; <http://www.telegraph.co.uk/>.
- [3] Taubenberger JK, Morens DM. 1918 influenza: the mother of all pandemics. *Emerg Infect Dis* [Online]. Jan 2006 [cited Nov 24, 2009]; <http://www.cdc.gov/ncidod/EID/vol12no01/05-0979.htm>
- [4] The Influenza Outbreak. *J Am Medical Assoc*. 1918;71(14):1138. Oct 5, 1918 [cited Nov 24, 2009]; <http://jama.ama-assn.org/cgi/reprint/71/14/1138>
- [5] Billings, Molly. Information page- Virology. Human Virology at Stanford University [homepage on the Internet]. Palo Alto (CA): Stanford University; 1997 [cited Nov 24, 2009]. <http://virus.stanford.edu/uda/fluscimed.html>
- [6] O'Malley, J and Frank W. Hartman. Treatment of Influenzal Pneumonia with Plasma of Convalescent Patients. *J Am Med Assoc*. 1919;72(1):34-37. Jan 1, 1918 [cited Nov 24, 2009]; <http://jama.ama-assn.org/cgi/reprint/72/1/34>
- [7] Ross, C.W. and Erwin J. Hund. Treatment of the Pneumonic Disturbance Complicating Influenza: The Transfusion of Citrated Immune Blood. *J Am Med Assoc*. 1919;72(9):640-645. March 3, 1919 [cited Nov 24, 2009]; <http://jama.ama-assn.org/cgi/reprint/72/9/640>
- [8] Royslance, Frank. Common flu strain resists popular drug Tamiflu. *The Baltimore Sun* [newspaper Online]. March 3, 2009 [cited Nov 24, 2009]. <http://www.baltimoresun.com/news/maryland/bal-md.tamiflu03mar03,0,3387360.story>
- [9] Alberts et al. *Molecular Biology of the Cell*. New York: Garland Publishing; 2007.
- [10] Morens DM, Taubenberger JK, Fauci AS. The persistent legacy of the 1918 influenza virus. *N Engl J Med*. 2009;361:225-229. Nov 12, 2009 [cited Nov 24, 2009]; <http://content.nejm.org/cgi/content/full/NEJMoa0906695>
- [11] McNeil, D. Students Fall Ill in New York, and Swine Flu is Likely Cause. *New York Times* [Online]. Apr 25, 2009 [cited Nov 24, 2009]; <http://www.nytimes.com/2009/04/26/world/americas/26flu.html>
- [12] Hospitalized Patients with 2009 H1N1 Influenza in the United States, April-June 2009. *N Engl J Med*. Oct 8, 2009 [cited Nov 24, 2009]. <http://content.nejm.org/cgi/content/full/NEJMoa0906695>
- [13] Walsh, Fergus. Tamiflu-resistant swine flu spreads 'between patients'. *BBC News*. Nov 20, 2009 [cited Nov 24, 2009]. <http://news.bbc.co.uk/1/hi/health/8370859.stm>
- [14] Shanta Bantia, C. Shane Arnold, Cynthia D. Parker, Ramanda Upshaw, Pooran Chand. Anti-influenza virus activity of peramivir in mice with single intramuscular injection. *Antiviral Research* 2006;69:39-45. Jan 2006 [cited Nov 24, 2009]; <http://tinyurl.com/yclahfu>
- [15] The Center for Disease Control. Emergency Use Authorization (EUA) of Medical Products and Devices [Online Document]. Nov 19, 2009 [cited Nov 24, 2009]. <http://www.cdc.gov/h1n1flu/eua/>
- [16] Canada's doctors told to stop using swine flu vaccine. *BBC News*. Nov 24, 2009 [cited Nov 24, 2009]. <http://news.bbc.co.uk/1/hi/world/americas/8376534.stm>
- [17] The World Health Organization. What is the new influenza A(H1N1)? [Online Document]. Jun 11, 2009 [cited Nov 24, 2009]. http://www.who.int/csr/disease/swineflu/frequently_asked_questions/about_disease/en/index.html
- [18] Andrew Wales, Flickr under CC-BY. Available from: <http://www.flickr.com/photos/stanrandom/3754123479/in/photostream/>
- [19] Wellcome Library, London, Wellcome Images under CC-BY-NC. (Iconographic Collection 546660i)
- [20] Bottom Right: Anna Tanczos, Wellcome Images under CC-BY-NC-ND. Available from: <http://tinyurl.com/h1n1model>
- [21] Centers for Disease Control and Prevention, US Dept, Health, Wikimedia. Available from: <http://commons.wikimedia.org/wiki/File:CDC-11215-swine-flu.jpg>