doi: 10.5123/S2176-62232018000300001

# The next pandemic: Are we ready?

## A próxima pandemia: estamos preparados?

Haroldo José de Matos[1,2]

[1] *Editor Científico da Rev Pan-Amaz Saúde, Instituto Evandro Chagas/SVS/MS, Ananindeua, Pará, Brasil*
[2] *Instituto Evandro Chagas/SVS/MS, Serviço de Epidemiologia, Setor de Atendimento Médico Unificado, Ananindeua, Pará, Brasil*

### A LOOK AT THE 1918 PANDEMIC, 100 YEARS AFTER

This year, 2018, marks the 100th anniversary of the greatest influenza pandemic ever recorded, the famous Spanish Flu of 1918[1]. Although known as "Spanish", it did not originate in Spain. The first wave of that epidemic was detected in Kansas, United States. In that pandemic, called the "mother of all pandemics"[2], there are different estimates of deaths from infection, ranging from 20 to 50 million deaths worldwide. The cause of that pandemic was the Influenza A (H1N1) virus. This virus was recently isolated and sequenced, making it comes back[3]. There is still much debate about the possible causes associated with the magnitude of its lethality. Possible explanations range from a special virulence of this H1N1, which was not observed in the circulating strain of the 2009 flu pandemic, to factors of the hosts' immune system, which are undoubtedly susceptible.

### THE ORIGIN OF DIVERSITY

There are two types of changes in the genetic material of the Influenza virus that are the source of its diversity and that challenge the animal's immune system. They are called antigenic drift and antigenic shift[4]. Antigenic drifts are minor changes in the Influenza genes that produce viruses very similar to the viruses that gave rise to them, which puts them in a very close position in the phylogenetic tree. These closely shared antigenic properties enable the immune system to recognize them and answer to this antigen challenge more or less effectively.

However, these small genetic changes can accumulate over time and result in different antigenic viruses that the immune system no longer recognizes effectively. This diversity explains how it is possible to acquire repeated episodes of infection by the Influenza virus and why the vaccine ingredients need to be updated annually.

The antigenic shift brings a much more complex challenge. It represents an expressive change in the structure of genetic material and occurs suddenly in Influenza A viruses, giving rise to a new subtype of that virus. These major changes result in new proteins that are not recognized by the immune systems in animals previously infected by other Influenza viruses. These are new hemagglutinin and neuraminidase proteins in the capsid, giving rise to new combinations of these proteins (e.g., H3N2; H7N9, H1N1, etc.). This antigenic shift occurred in 1918, resulting in the largest known Influenza pandemic, the Spanish Flu, and happened again in 2009, in a new pandemic that also quickly spread across five continents, but fortunately without the tragic outcomes of 100 years ago.

While the antigenic drift process commonly occurs in types A and B, the antigenic shift occurs only in type A viruses.

### THE PANDEMIC CYCLES

Pandemic infections are, in fact, a trademark of the Influenza type A virus, and these marks have been recorded throughout human history. Charlemagne's conquest of Europe had been delayed because of an influenza epidemic that spread across Europe and wiped out part of his army. However, the one that had a credible record was the 1850 pandemic, which spread through trade routes reaching Europe, the Americas, and Africa. Data show that some Spanish colonies in America were almost depopulated[1]. Pandemics that have occurred since the 18th century, in 1729, 1732, 1781, 1830, 1833, and 1889, until we reached the great pandemic of 1918–1919, were also recorded. So, there seems to be a specific temporal pattern, causing each generation (around 80 years) to repeat cycles, including a challenging antigenic shift.

Records of the 1918 flu pandemic show that the epidemic spread worldwide in less than five months. Some aspects of this pandemic are really impressive. There are estimates of at least 21 million deaths, and some estimates go as high as 50 million ones. A fact that draws attention is the predominant occurrence of deaths among young adults and children. There were also reports of people who boarded the Coney Island subway, in New York, with only nonspecific symptoms, such as tiredness, and were found dead at the Columbus Circle station 45 minutes later[1]. There are also reports that Eskimo villages have entirely disappeared in remote parts of Alaska[1]. Data from British pathologists indicated pulmonary hemorrhage as the main cause of death, which had not yet been observed in the epidemics of 1873 and 1889. Nevertheless, the epidemic was not restricted to the northern hemisphere. There is impressive data that one out of 20 inhabitants of Ghana, West Africa, died of Influenza virus infection between September 1 and November 1, 1918[5]. In Oceania, the population of Western Samoa was so impacted by the epidemic that almost all of the country's 38,000 inhabitants were infected, and 7,500 died (20% of the population),

an above-average estimate of mortality of that epidemic[6]. Some reflection is still needed to establish the factors associated with the high lethality of the epidemic. It must be remembered that, in 1918, an extensive and lasting war, known as World War I, was ending, and there were nutritional and socioeconomic limiting factors linked to the impoverishment and living conditions of the populations. It is crucial to notice that most fatal cases were associated with secondary infections by bacteria, and antibiotics were not yet available, except for arsenical derivatives used in the treatment of syphilis[6].

## THE RESEARCH

The Spanish Flu, however, generated intense research. In 1932, Richard Shope did a crucial experiment on the origin of the Influenza A virus, which caused the 1918–1919 pandemic. He removed nasal secretions from domestic pigs infected with the Influenza virus and rubbed them in the mouths of other animals to infect them. That is why the flu, associated with the Influenza H1N1 virus, is known as swine flu. In 1933, the virus was finally isolated, and in 1935, Shope demonstrated that individuals who had gotten through the 1918–1919 epidemic had antibodies against the swine flu virus, but not individuals born after 1920. In 1973, Kilbourne[4] demonstrated that the neuraminidase protein density on the surface of the viral structure was a factor associated with the virulence of the Influenza viruses. The higher the density of this protein on the virus's surface, the greater the ease of its ability to infect new cells in the body. This argument could be proven in the 1957 pandemic (H2N2), with high lethality. In 1968, there was still a major pandemic (H3N2), although less fatal than in 1957, but to a greater extent. In 1976, there was also evidence of the H1N1 virus circulation in the USA, which led to intense research for an effective vaccine. In 2009, while close attention was on the H5N1 avian flu, the H1N1 virus reappeared, spreading rapidly across the globe. Fortunately, however, the lethality was not like the Spanish Flu, and an effective vaccine quickly became available. Nowadays, there is evidence that the Influenza viruses originated in birds and then developed in pigs, where mutations occur that will infect the human species. But the pinnacle of research related to the 1918 influenza epidemic occurred from 1995 onwards, when research for the sequencing of the 1918–1919 epidemic virus began and, in the beginning of the 21st century, in 2005, when it was presented the sequencing of the H1N1 virus to the world from frozen material of Eskimos and other samples[3]. This research shows that strains of influenza viruses circulating worldwide have been derived mainly from the RNA of the H1N1 virus of the 1918–1919 pandemic.

## PERSPECTIVE

ARE WE READY FOR THE NEXT PANDEMIC?

A vital issue to answer this question is to return to the question of the predictability of a new pandemic. Although some cyclical patterns can be identified in influenza pandemics, as discussed above, there is a consensus today that the best approximation is probability. In fact, some epidemiologists defend the idea that the prediction of a new pandemic is similar to weather forecasting, "governed" by chaotic systems[8].

In this sense, the preparation for emergencies, such as pandemics, goes through three essential stages, improving the tools we have on a daily basis.

1) Improvement of epidemiological surveillance

This is a fundamental step to being ready for an eventual pandemic. An important step in this improvement was the new International Health Regulations (2005). This regulation establishes an epidemiological surveillance model that quickly interconnects all countries linked to the World Health Organization and also creates operating standards for local surveillance. In Brazil, this discussion gave rise to the Center for Strategic Information in Health Surveillance and the reorganization of epidemiological surveillance, including the Health Surveillance Secretariat, which is now linked to the Instituto Evandro Chagas. Improving surveillance certainly includes the development of new information and communication technologies[9]. The central aspect is the strong presence of a research base for epidemiological surveillance with the participation of research institutes and central laboratories to support surveillance. The influenza sentinel surveillance program is an example in which the Instituto Evandro Chagas also participates as a sentinel unit. Another aspect that is equally or more important than the laboratory network is the training of human resources, which includes EpiSUS, a training course for field epidemiologists by the Ministry of Health.

2) Clinical research

It is crucial to create clinical research networks to produce evidence on the effectiveness of vaccines and new drugs against potential sources of pandemics, including emerging and reemerging agents, is also essential. These clinical research networks also include the training of new clinical researchers, especially in the North and Northeast regions of Brazil.

3) Laboratories focused on the formation of new inputs and biologicals

Finally, preparation for facing new pandemics, such as influenza, includes strengthening the production capacity of new inputs and biologicals, such as vaccines and drugs, with the ability to predict an increase in production and rapid distribution in the face of emergencies.

As we look back at the 1918 influenza pandemic, we cannot help but bring a sadly nostalgic look at a world emerging from a war that changed the geography and the current world, and we recall John McCrae's sonnet...

*In Flanders fields the poppies blow*
*Between the crosses, row on row,*
*That mark our place; and in the sky*
*The larks, still bravely singing, fly*
*Scarcely heard amid the guns below.*

*We are the Dead. Short days ago*
*We lived, felt dawn, saw sunset glow,*
*Loved and were loved, and now we lie*
*In Flanders fields.*

*Take up your quarrel with the foe:*
*To you from falling hands we throw*
*The torch; be yours to hold it high.*
*If ye break faith with us who die*
*We shall not sleep, though poppies grow*
*In Flanders fields.*

John McCrae
*Canadian physician and poet who fought*
*in the trenches of Belgium, during World War I.*

## REFERENCES


1 Beveridge WIB. The chronicle of influenza epidemics. Hist Philos Life Sci 1991;13(2):223-34.

2 Taubenberger JK, Morens DM. 1918 influenza: the mother of all pandemics. Emerg Infect Dis. 2006 Jan;12(1):15-22.

3 Taubenberger JK, Reid AH, Lourens RM, Wang R, Jin G, Fanning TG. Characterization of the 1918 influenza virus polymerase genes. Nature. 2005 Oct;437(7060):889-93.

4 Kilbourne ED. An explanation of the interpandemic antigenic mutability of influenza viruses. J Infect Dis. 1973 Nov;128(5):668-70.

5 Scott D. Epidemic disease in Ghana 1901–1960. London: Oxford University Press; 1965.

6 Garrett L. The coming plague: newly emerging diseases in a world out of balance. New York: Farrar, Straus and Giroux; c1994.

7 Beare AS, Craig JW. Virulence for man of a human influenza-A virus antigenically similar to "classical" swine viruses. Lancet. 1976 Jul;2(7975):4-5.

8 Furtado BA, Sakowski PAM, Tóvolli MH, editores. Modelagem de sistemas complexos para políticas públicas. Brasília: IPEA; 2015.

9 Gates B. Innovation for pandemics. N Engl J Med. 2018 May;378(22):2057-60.


Article originally published in Portuguese (http://dx.doi.org/10.5123/S2176-62232018000300001)
**Translated by:** Patrícia Campelo Haick and Luana de Jesus Lemos

*How to cite this article / Como citar este artigo:*
Matos HJ. The next pandemic: Are we ready?. Rev Pan-Amaz Saude. 2018 july-sept;9(3):9-11. Doi: http://dx.doi.org/10.5123/S2176-62232018000300001