

## A spectacular decline in influenza mortality: the role of vaccination

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Every autumn sees the start of the annual flu vaccination campaign, with particular focus on older adults, high-risk individuals or those in regular contact with persons at risk. But do we know how many people die of influenza each year? And does vaccination save lives? France Meslé looks into these questions, examining influenza mortality trends in France and in industrialized countries over recent decades.

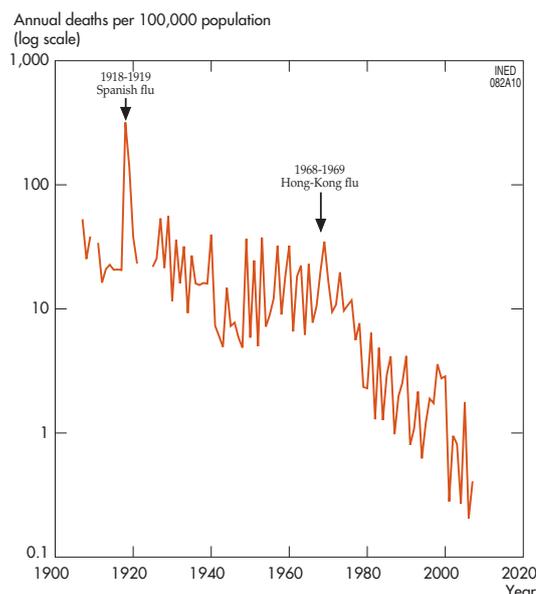
Over the last five or six years, influenza has once again become the centre of attention. The recurrent fears of an (A)H5N1 avian influenza epidemic since 2004, followed by the spread of (A)H1N1 swine flu in 2009-2010, have mobilized public health institutions worldwide, prompting an unprecedented array of preventive measures. The human transmission of avian flu remained very limited, however, and H1N1 swine flu proved to be relatively benign. In France, no deaths from avian flu have been recorded, and the 2009-2010 H1N1 swine flu epidemic had taken only 312 lives by 13 April 2010 [1]. This bears no comparison with the devastating death toll of Spanish flu in 1918-1919 (200,000 to 400,000 deaths in France according to some estimates) or even the excess mortality due to Asian flu in 1957-1958 (more than 20,000 deaths) and to Hong Kong flu in 1968-1969 (more than 30,000 deaths). Until the discovery and use of a polyvalent vaccine, influenza and its complications were one of the main causes of death in the winter months. The decline in flu deaths is a major success story of preventive medicine. Let's take a closer look at its history.

### ◆ A disease known since Antiquity

Influenza is a viral disease whose most common symptoms are a high fever, muscle pain, nasal congestion

and a dry cough. In its uncomplicated form, it lasts for around a week and is followed by a convalescent period of weakness and fatigue lasting one to two weeks. The complications of flu – mainly respiratory complications – make the disease very dangerous for high-risk

Figure 1 - Crude influenza death rate in France since 1907



Sources: *Statistique sanitaire de la France*, INED, CÉPIDC-INSERM (F. Meslé, *Population & Societies*, 470, INED, September 2010)

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populations, older adults in particular. Influenza is a contagious epidemic disease, transmitted by aerosols projected from the mouth (coughs) and nose (sneezes), which spreads more rapidly in cold and humid conditions.

Given its non-specific symptoms, there is no way to prove that the influenza virus was responsible for the epidemics described in ancient texts, but historians of medicine agree that it existed in antiquity. It wasn't until the fourteenth century that the disease was clearly identified and given the name of influenza by the Florentines [2]. The nineteenth century was hit by a series of epidemics. In 1889-1890, "Russian flu" spread from Siberia to Europe before reaching America and Asia. This is the first pandemic <sup>(1)</sup> whose progression was recorded in detail. For the twentieth century, cause-specific mortality statistics provide a means to determine the precise impact of influenza on mortality, notably during the three great pandemics of 1918-1919, 1957-1958 and 1968-1969.

### ◆ Large annual fluctuations in mortality

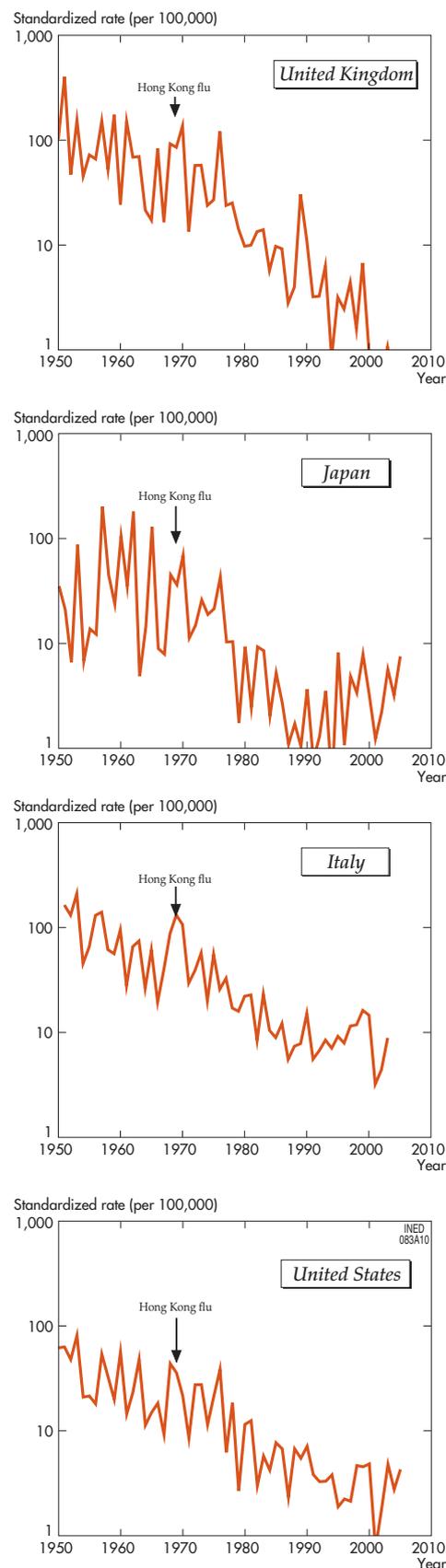
Mortality from influenza, an epidemic disease, varies considerably from year to year. In France, precise statistics are available from 1907 onwards (Figure 1). The Spanish flu mortality peak is impressive. In 1918-1919, 200,000 deaths were explicitly attributed to influenza, but after adding deaths resulting from respiratory and other complications, the total is generally estimated at around 400,000. Fortunately, mortality levels never again reached such extremes, but up until the late 1960s each flu epidemic killed 10,000 to 20,000 people, and probably double that number if all deaths from complications are included. The Hong Kong flu outbreak of 1968-1969 (27,000 direct deaths) was the last pandemic to have visible effects on overall mortality levels. Since 1970, although epidemics still occur on a regular basis, influenza mortality has declined spectacularly. In the last 40 years, the risk of dying has been divided by ten, and in 2005, the year of the last major epidemic in France, the number of direct deaths was barely above 1,000. This radical decrease in influenza mortality is the direct consequence of an effective prevention policy, based on the vaccination of high-risk individuals combined with better therapeutic management of complications.

### ◆ A vaccination success story

The influenza virus was first isolated in pigs in the 1920s, and then in humans in 1933 [3]. Since then, three different types (A, B and C) have been isolated, but only the influenza A virus is responsible for deadly human pandemics. The genetic information of the virus is

(1) A pandemic is an epidemic which affects a very large share of the population over an extensive geographical area.

Figure 2 - Influenza deaths since 1950 in four industrialized countries



Note: Deaths per 100,000 population that would be observed if the population age structure was the same in all four countries and corresponded to the WHO standard population (standardized rate).

Source: WHO (mortality database)

(F. Meslé, *Population & Societies*, 470, INED, September 2010)

contained in the viral RNA, whose segmented structure allows for the exchange of genetic material between different viral strains. This results in frequent viral mutations. The major pandemics are thus caused by the unpredictable emergence of new virus subtypes, generally a recombination of a human and an animal strain, against which humans have little natural immunity. Less dangerous but much more frequent, mutations of the human influenza virus occur from year to year, making it impossible to acquire long-term immunity. Consequently, to produce an effective vaccine, a different set of viral strains must be used each year.

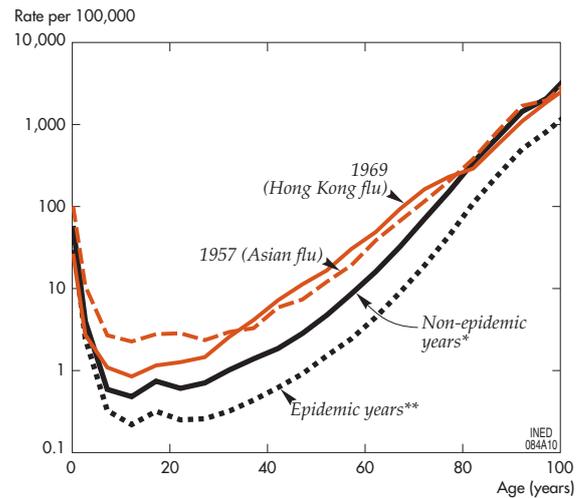
The first vaccine was developed at the end of the Second World War in the United States. Intended mainly for the US military, it was not widely used, probably because of its limited efficacy. It was not until the 1970s, after the Hong Kong flu epidemic, that a more effective vaccine, containing a mixture of viral strains, was produced. It was also more widely administered, and its immediate impact on influenza mortality in France, as elsewhere, was remarkable (Figure 1).

Flu vaccination has since become standard practice in France and mortality has declined steadily thanks to a rigorous prevention policy that targets high-risk individuals, and older adults in particular. In 1985, free vaccination became available for all persons aged over 75. The age limit was lowered to 70 in 1989 and then to 65 in 2000 [4]. In 2003, the vaccination coverage rate for the over-65s, estimated at 65% in France, was among the highest in Europe [5]. The coverage rate is much lower among high-risk individuals below 65, and among health professionals who, if unvaccinated, are liable to transmit the virus to the persons in their care. Better vaccination coverage of these populations would further reduce the number of influenza deaths.

### ◆ Influenza mortality has fallen in all industrialized countries

Influenza mortality declined in all industrialized countries in the second half of the twentieth century. Trends in four countries (United Kingdom, United States, Japan and Italy) are shown in Figure 2. The pattern observed in the United Kingdom is very similar to that of France. In the United States, where mass vaccination probably began earlier than in Europe, influenza deaths have declined steadily since 1950. By contrast, in Japan the decline has been more uneven, with influenza mortality dropping sharply in the 1970s, as in France, before levelling off or even rising again slightly in more recent years. In Japan, influenza was removed from the target diseases list of the Vaccination Law in 1994. This probably reduced vaccination coverage, which in turn halted progress. It was not until the early 2000s that the over-65s were included in the high-risk group and targeted by vaccination campaigns [6]. Influenza

Figure 3 - Age-specific influenza death rates in epidemic and non-epidemic years



\* 1951, 1953, 1956, 1959, 1960, 1962, 1963, 1965, 1968, 1970

\*\* 1950, 1952, 1954, 1955, 1958, 1961, 1964, 1966, 1967, 1971

Source: INED

(F. Meslé, *Population & Societies*, 470, INED, September 2010)

mortality has also risen slightly in Italy, after falling less sharply than in the other countries. The reasons for this slightly less positive trend are unclear. We note, however, that up until 2003, vaccination coverage of the over-65s was lower in Italy than in France and the United Kingdom (48% versus 65%).

### ◆ Children and older adults are the most vulnerable

In both epidemic and non-epidemic periods, the age-specific influenza mortality rates follow a classic curve. They are very high for young children, they fall to a minimum at ages 10-15 and then rise steadily with age. For this reason, vaccination campaigns target older adults and, in certain countries, young children. This curve may change shape, however: this is the case during major pandemics, when young adults are more severely affected. Figure 3 compares the age-specific death rates observed in 1957 and 1969, the years when the two major pandemics of the twentieth century reached France, with the mean curves for other years of high influenza mortality<sup>(2)</sup> and for years of low mortality<sup>(2)</sup> between 1950 and 1971. These two last curves are perfectly parallel: the arrival of a seasonal epidemic produces the same proportional increase in mortality at all ages. The picture is very different for the two pandemic years (Asian flu in 1957 and Hong Kong flu in 1969), with much higher excess mortality among children and young adults. In 1957, mortality in the 20-25 age group was ten times higher than in non-epidemic years, but only 3.5 times higher for the 80-85 age group. In 1969, on the other hand, the highest excess mortality was observed for the 40-60 age group.

(2) See the list of years in Figure 3.

The Spanish flu of 1918-1919 was probably the most lethal epidemic of modern times for these young age groups. The deadly impact of the epidemic on young adults was highlighted at the time. Unfortunately, we do not have data by five-year age group for the whole of France over the period, but we know that in 1918 the influenza death rate was very high among infants below one and even higher among adults aged 20-40. This high death toll among young people is linked to the mechanism whereby major pandemics emerge. When a new pandemic virus appears (H1N1 in 1918, H2N2 in 1957, H3N2 in 1968), older adults may have acquired a certain immunity to the new strain because they have lived through a previous epidemic caused by a virus with a partially similar structure. Younger people, on the other hand, have no such immunity, not even partial [2]. The Asian flu virus of 1957 was probably quite similar to the virus that was dominant in the late nineteenth century, which explains why the over-75s were relatively less affected by the epidemic than younger people.

### ◆ The H1N1 swine flu epidemic of 2009-2010

Given the devastating effects of earlier flu epidemics, it is easy to understand why in 2009 the rapid spread of an (A)H1N1 virus comparable to that of the 1918-1919 Spanish flu virus aroused grave concern among public health authorities across the world. The H1N1 subtype had re-emerged in the mid 1970s. In 1976, a swine flu virus of this type affected a military base in the USA, causing one fatality. The American authorities, fearing a potential pandemic, began a massive vaccination campaign. The virus proved relatively non-contagious, however, and vaccination was soon stopped. This virus has persisted and flu epidemics over the last thirty years have been due to two influenza A sub-types (H1N1 and H3N2), and to influenza B. The vaccine thus aims to protect against these three strains.

In the spring of 2009, a new form of the H1N1 virus emerged. It was believed to be highly contagious and virulent, and unprecedented preventive measures were taken across the world to halt its spread. Luckily, the pessimistic forecasts proved unfounded and the epidemic was much less severe than first feared, notably among populations usually not considered at risk. In France, 312 people died in the epidemic, of whom 263 had at least one risk factor (chronic respiratory disease, diabetes, heart failure) [1]. The age profile of the 2009-2010 epidemic was nonetheless very similar to that observed during major flu pandemics. While only 20% of the 550,000 persons who die each year in France are aged below 65, almost three-quarters of the H1N1 swine flu

(3) The campaign was halted rapidly in response to an increased incidence of Guillain-Barré syndrome, a neurological disorder thought to be linked to vaccination, although the relationship has never been proved [2].

victims were in this age group. This was indeed a virus against which younger people had less immunity than their elders, but it finally proved to be less virulent than initially predicted.

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Thanks largely to the systematic vaccination of older adults, the death toll of seasonal influenza fell sharply in the last decades of the twentieth century. However, this success could be threatened at any time by the emergence of new viral strains against which the population, its youngest members especially, have no immunity. Once again, our success in combating the disease will depend upon the speed with which a suitable vaccine can be developed and administered. In this respect the alert of 2009-2010 can be seen as a useful trial run. 

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#### ABSTRACT

Up until the 1970s, flu epidemics commonly caused 10,000 to 20,000 direct deaths each year in France, not counting those who died from complications of the disease. The development of an effective vaccine, regularly reformulated in response to new viral mutations, has brought a ten-fold reduction in deaths in France and in other industrialized countries over the last 40 years. This success has been strengthened by making flue vaccination available free of charge to older adults, who are particularly prone to lethal complications.

The twentieth century was marked by three major pandemics resulting from the emergence of new viral strains: Spanish flu in 1918-1919, Asian flu in 1957-1958 and Hong Kong flu in 1968-1969, which affected children and young adults most severely. Likewise, two-thirds of all persons killed by the H1N1 swine flu virus of 2009-2010 were aged below 65. Fortunately, the epidemic proved to be much less deadly than initially feared, with just 312 deaths in France.