

# 2

## Lessons from past pandemics

**Pandemics are remarkable global events. They spread to all parts of the world very quickly and cause illness in more than 25% of the total population.**

**E**xplosive and unusually deadly outbreaks of influenza have occurred throughout recorded history, probably originating in the earliest cities where humans lived crowded together in close proximity to domestic animals. True pandemics, characterized by sharp increases in morbidity and mortality and rapid spread throughout the world, have been reliably documented since the 16th century. Since then, each century has seen an average of three pandemics occurring at intervals ranging from 10 to 50 years.

The speed with which pandemics can encircle the globe is well illustrated by historical accounts taken from times when international travel was far slower than today. For example, the pandemic of 1580, which began in Asia, spread to all continents in just over a year; the whole of Europe was engulfed in less than six months.

Pandemics are always remarkable global events. Caused as they are by a highly contagious virus to which populations have little if any immunity, they benefit from almost universal susceptibility to infection. This gives them their distinctive features: they spread to all parts of the world very quickly, usually within less than a year, and cause illness in more than a quarter of the total population. It is this abrupt upsurge in illness, outstripping response capacity, that makes pandemics so disruptive, in addition to the excess mortality they invariably cause.

The pandemics of past centuries have typically hit world populations like the epidemiological equivalent of a flash flood. They have started abruptly without warning, swept through populations with ferocious velocity, and left considerable damage in their wake. They could not be stopped, but peaked rapidly and then subsided almost as abruptly as they began. Recovery was, however, impeded



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### Estimated deaths (in millions)

1918 pandemic	40
World War I	8.3

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by the tendency of pandemics to recur in second and sometimes third waves, often causing more severe disease. Subsequent waves often began simultaneously in several different parts of the world, intensifying the abrupt disruption at the global level.

The three pandemics of the 20th century are the best documented in terms of their origins (Box 3), patterns of international spread, and impact. They provide a useful basis for preparedness planning as they illustrate both worst- and best-case scenarios, show the many different turns a pandemic can take, and allow assessment of some control interventions.

## 1918–1919

Of all pandemics, the one that began in 1918 – in a world wearied by war – is generally regarded as the most deadly disease event in human history. Not only did it kill upwards of 40 million people, but it did so in less than a year. For comparison, total military deaths on all fronts during the first world war have been estimated at 8.3 million over four years.

The beginnings were inauspicious. The first simultaneous outbreaks were detected in March 1918 in Europe and in different states within the USA. The infection then travelled back and forth between Europe and the USA via ships carrying troops and then, by land and sea, to Asia and Africa. That first wave, which took place in the spring and summer, was highly contagious but not especially deadly; its significance as a warning signal was missed. When the second wave began near the end of August, no country was prepared.

The experience was unprecedented. That second wave, which began almost simultaneously in France, Sierra Leone and the USA, saw explosive outbreaks characterized by a 10-fold increase in the death rate. The disease had features that were not seen before and, fortunately, have not been seen since. Deaths from influenza, whether during seasonal epidemics or pandemics, usually occur at the extremes of the lifespan – in the very young or very old. “Spanish flu” preferred the prime of life, causing most



*Spanish flu caused a form of viral pneumonia that could kill the perfectly fit within 48 hours or less.*

**The disease was so severe and the symptoms so unfamiliar that some doctors initially feared a return of the Black Death.**

### **Why “Spanish” flu?**

The designation of the 1918 pandemic as “Spanish” flu is a misnomer, as no evidence suggests the pandemic originated in that country or was more severe there than elsewhere. The first cases were detected in Europe and the USA. As Spain was neutral during the first world war, its media covered the epidemic there without restraint. The popular association of the 1918 pandemic with Spain (in name only) is thought to have arisen from that high-profile news coverage.

deaths in young and healthy persons in the age range of 15 to 35 years. In a complete reversal of previous patterns, 99% of deaths occurred in people younger than 65 years.

As expected, many of the deaths in 1918 were from pneumonia caused by secondary bacterial infections. But Spanish flu also caused a form of primary viral pneumonia, with extensive haemorrhaging of the lungs, that could kill the perfectly fit within 48 hours or less. The disease was so severe and its clinical course so unfamiliar that influenza was not even considered when the first cases appeared. Doctors suspected cerebrospinal meningitis or, more grimly, a return of the Black Death.

Health authorities were at a loss. Antibiotics, which could have prevented many deaths from bacterial pneumonia, had not yet been discovered. An effective vaccine was out of the question: the first isolation of an influenza virus from humans would not take place until 1933. With no medical tools available, control efforts turned to the more prosaic measures of isolation, quarantine, good personal hygiene, use of disinfectants, and the prevention of public gatherings. These measures were imposed with varying degrees of severity and different levels of public support. Many populations began wearing gauze masks in public either voluntarily or under penalty of law. In some countries, people caught coughing or sneezing, unprotected, in public were fined or jailed. Public institutions, including schools, were often closed and public gatherings banned.

Quarantine and isolation were widely imposed, but probably did little to stop the contagion. Predictably, quarantine could delay spread somewhat but, having no impact on population susceptibility, could do nothing to reduce the numbers who would eventually fall ill. Australia was the notable exception. By maintaining a strict maritime quarantine, that country managed to stave off arrival of the epidemic until the start of 1919. By that time, the virus has lost some of its lethality, and Australia experienced a milder, though somewhat longer, period of influenza activity than elsewhere. Though less lethal, the virus retained its preference for the young and healthy, with 60% of deaths occurring in persons aged 20 to 45 years.



*In 1957, the WHO global influenza network was 10 years old. Its laboratories played an essential role in rapidly isolating the virus and alerting the world to the onset of a pandemic.*

**Within a week, network laboratories had analysed the virus and identified it as a completely new virus subtype. Using radio and telegraph despatches, WHO alerted the world.**

During the course of the pandemic, an estimated 25% to 30% of the world population fell ill. The pace of spread and the rate of death outstripped response capacity at every level – from hospital beds to burial space, from medical supplies to coffins. No part of the world was spared. Densely populated India suffered more than 10 million deaths. In the more sparsely populated countries of sub-Saharan Africa, the epidemic moved easily from port cities to the remote hinterlands, killing 1.5 to 2 million people within a few weeks. There, as elsewhere, efforts to dampen spread through quarantines and the closing of markets made very little difference. Globally, the demographic effect was enormous; in many areas, life expectancy dropped by 10 years and more.

## 1957–1958

The pandemic that began in 1957 was caused by a milder virus than the one responsible for the 1918 pandemic. In addition, the world was much better prepared to cope. Modern virology had arrived and knowledge about influenza viruses was progressing rapidly. Vaccines for seasonal epidemics had been developed and had already proven their value as the most effective method for prevention; where used, they reduced the incidence of seasonal influenza by two thirds or more. Antibiotics were available to treat complications, including bacterial pneumonia. The WHO Global Influenza Surveillance Network – a virological monitoring and early warning system – was 10 years old (Box 4). The 1957 pandemic was its first major test; it performed admirably.

At the start of May, WHO received news of extensive influenza epidemics in Hong Kong and Singapore. Subsequent information revealed that epidemics had begun at the end of February in a single province of China, spread throughout the country in March, and reached Hong Kong SAR in the middle of April. By mid-May, the virus had been isolated by laboratories in Japan and Singapore. Within a week, laboratories in the WHO network had analysed the virus and identified it as a completely new virus subtype. Using radio and telegraph despatches, WHO alerted the world to the onset of a pandemic, allowing health services to brace themselves for an upsurge of cases and deaths. Samples of the virus were immediately distributed to vaccine manufacturers throughout the world.

### **Box 3. The origin of pandemic viruses**

A pandemic virus can emerge via two principal mechanisms: reassortment and adaptive mutation.

The organization of the influenza virus into eight gene segments facilitates reassortment, which occurs when two different viruses (such as avian H5N1 and human H3N2) infect the same cell and exchange some of their gene segments. If the resulting new virus can infect humans, cause serious disease, and spread easily from person to person in a sustainable way, it will ignite a pandemic.

Genetic and biochemical analysis of viruses from the 1957 and 1968 pandemics has identified them as reassortants of human and avian viruses. During a pandemic, the causative virus achieves dominance over all other circulating influenza viruses in humans. After the pandemic, the virus continues to circulate for decades, causing severe illness, until it is replaced by the next pandemic strain. The 1957 virus (the H2N2 strain) obtained three of its genes from an avian virus and the remaining five genes from the circulating human H1N1 strain, which caused the 1918 pandemic. The 1968 virus (the H3N2 strain) also took three genes from an avian donor and the remaining five from the circulating human H2N2 strain, responsible for the previous pandemic. Both pandemics began with an explosion of human cases. Neither has been convincingly linked to influenza outbreaks in birds or other animals. For both events, experts have long assumed that pigs, which have both human and avian receptors on the cells lining their respiratory tract, served as the mixing vessel for the swapping of gene segments.

Adaptive mutation is the second mechanism by which a pandemic virus can emerge. This mechanism involves stepwise changes in the virus, which occur during sequential infection

of humans or other mammals, whereby an avian virus gradually acquires the changes needed to improve its transmissibility among humans. Experts have postulated that the essential changes involve adaptation of receptors specific to binding sites in bird cells to receptors that bind more easily to human cells. Only a few changes are needed; once in a new mammalian host, avian influenza viruses evolve very rapidly.

As the deadly 1918 pandemic occurred before the advent of modern virology, knowledge about the virus has emerged slowly – pieced together from “seroarchaeology” – and remains incomplete. Efforts to characterize the virus have relied on stored tissue samples taken from United States soldiers and United Kingdom civilians who succumbed to the disease, and on samples retrieved from bodies of fatal cases preserved in the Alaskan permafrost. Evidence to date suggests that the virus may have evolved through adaptive mutation of an avian virus, though considerable debate centres on whether this happened fairly rapidly or took place over a number of years. Investigations have, however, failed to find the tell-tale sequence of amino acids that distinguish highly pathogenic avian viruses and are thought to confer their unique ability, at least in birds, to cause severe systemic disease in addition to severe respiratory illness. Studies to date have not been able to determine what made the virus so deadly or why it preferentially affected the young and healthy.

The 1918 virus – the H1N1 strain – was detected as a cause of severe disease in pigs during the second phase of the pandemic, which began in the autumn of 1918. It will probably never be known whether pigs played a role in emergence of the virus or – more likely – were merely the incidental victims of a virus already spreading rapidly and widely in humans.



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**EXPERT COMMITTEE  
ON RESPIRATORY  
VIRUS DISEASES**

WORLD HEALTH ORGANIZATION  
GENEVA

1959

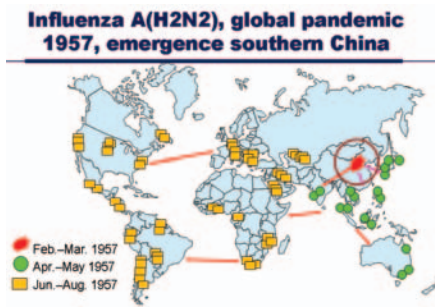
*WHO convened an expert panel in 1958 to consider lessons from the pandemic. The report of that meeting gives a good picture of the epidemiology of a pandemic.*

**During the first wave, cases were concentrated in school-aged children. This was attributed to their close contact in crowded settings, and not to a special vulnerability.**

This time, pathways of international spread were tracked by the network of laboratories, and the event was accompanied by a flurry of epidemiological, clinical, and virological studies. In 1958, WHO convened a panel of experts to discuss this work and assess what had been learned from the pandemic. The result is a good picture of how a pandemic – probably much more representative than that of 1918 – affected health, globally and within individual countries.

The speed of international spread was characteristically swift. Less than six months after the disease reached Hong Kong SAR, every part of the world had experienced cases. Within individual countries, however, the pattern of spread differed in striking ways. In tropical countries and Japan, introduction of the virus was followed almost immediately by a succession of outbreaks, quickly resulting in a general community-wide epidemic. In Japan, for example, influenza entered the country at the end of April, spread immediately, peaked in June, and disappeared after mid-July. In contrast, both Europe and the USA experienced a grace period of at least six weeks before epidemics occurred following the introduction of cases. Epidemiologists believe that an almost silent “seeding” of the population occurred during these weeks. The reasons for the delayed epidemics remain obscure but are thought to be associated with climate and the timing of school holidays. In Europe and the USA, for example, the epidemics exploded coincident with the opening of schools in September but peaked rapidly. By December, the worst was over, at least for the first wave.

Once epidemics began, patterns of morbidity were remarkably similar throughout the world. As with the initial wave in 1918, large numbers of cases occurred and the outbreaks were frequently explosive, but fatalities were much lower. Mortality showed a more characteristic pattern, similar to that seen in seasonal epidemics, with most excess deaths confined to infants and the elderly. During the first wave, cases of illness were concentrated in school-aged children; this was attributed to their close contact in crowded settings, and not to a particular age-related vulnerability. In general, close contact and crowding of persons together, as also seen in military barracks, favoured the spread of infection. In most countries, a second wave followed disappearance of the first from one to three months later, causing very high rates of illness and increased fatalities. Unlike the first wave, which affected mostly school-aged children, the second wave was concentrated in the elderly, which helps to explain the increased mortality.



*Like other pandemics, the one in 1957 rapidly spread around the world.*

**Quarantine measures were applied in several countries and were generally found to be ineffective, managing at best to postpone the onset of an epidemic by a few weeks to two months.**

Total excess mortality globally has been estimated at more than 2 million deaths.

As in 1918, many countries observed a subset, though smaller, of fatal cases of pneumonia with no evidence of bacterial infection. At autopsy, examination of lung material indicated death resulting from primary viral pneumonia, with findings similar to those observed in 1918. In 1957, however, most such fatalities occurred in persons with underlying disease, and not in the previously healthy.

Vaccines were available in August in the USA, in October in the United Kingdom, and in November in Japan. The quantities, however, were too small for widescale use. Moreover, as the disease was so much milder than in 1918, health authorities decided against an expansion of vaccine production to the scale needed for population-wide vaccination. Then, as now, the greatest problem was inadequate manufacturing capacity. Countries with domestic capacity were able to produce enough vaccine, early enough, to protect priority groups only. No country had sufficient production capacity to cover its entire population, much less to export vaccines elsewhere.

Quarantine measures were applied in several countries and were generally found to be ineffective, managing at best to postpone the onset of an epidemic by a few weeks to two months. The WHO expert panel found that spread within some countries frequently followed public gatherings, such as conferences and festivals, with infection dispersed as participants returned home. The banning of public gatherings and the closing of schools were considered the only measures that could dampen the spread of pandemic influenza. Even the most extreme option – severe restrictions on international travel and trade – was thought to bring nothing more than a few weeks of freedom from a disease whose international spread might be forestalled, but never stopped.

For health authorities, the biggest challenge presented by the 1957 pandemic was the provision of adequate medical and hospital services. Measures to delay the speed of spread and thus flatten the peak occurrence of cases were considered justified if they allowed the maintenance of medical and other essential services.

Viruses causing  
past pandemics

1889–1891	H3N8
1918–1919	H1N1
1957–1958	H2N2
1968–1969	H3N2

Why was the 1968  
pandemic so mild?

The mildness of the 1968 pandemic, caused by the H3N2 strain, is thought to result, in part, from protection against severe disease conferred by the pandemic of 1957.

As that pandemic was caused – just 11 years previously – by the H2N2 strain, the N2 subtypes were the same. The short time between the two pandemics means that large populations exposed in 1957 would still be alive and protected from severe illness by their previous exposure. In addition, the fact that the 1889 pandemic, caused by the H3N8 strain, shared the same HA (H3) subtype may have protected a subgroup of the elderly from infection.

1968–1969

The pandemic that began in 1968 was even milder than that in 1957, but brought its own set of special epidemiological surprises. The first hint of a pandemic came from a newspaper story, published in the United Kingdom in mid-July, describing a widespread outbreak of acute respiratory disease in south-eastern China. That same month, the disease spread to Hong Kong SAR, where it reached maximum intensity within two weeks, causing half a million cases. Within days, Hong Kong SAR scientists isolated the virus and distributed it to network laboratories for analysis. The virus was rapidly identified as a novel subtype and, on 16 August, WHO issued a warning of possible worldwide spread, predicting a pattern similar to that seen in 1957, when the virus likewise spread from a focal point within mainland China.

Initial international spread did resemble that seen during 1957, but there the resemblance ended. Nearly everywhere, clinical symptoms were mild and mortality low. In most countries, the disease spread slowly rather than in the highly visible pattern of explosive outbreaks seen in previous pandemics. In some countries, the impact on absenteeism and on deaths rates was slight or absent altogether. The USA was the notable exception, and the epidemiology of the disease there was one of the most striking features of the pandemic.

The epidemic in the USA began in September in California, carried there by troops returning from Viet Nam, and spread eastwards to affect the whole of the country by late December. A significant increase in deaths from influenza-related pneumonia occurred during the first two weeks of January, with deaths concentrated in the elderly. Altogether, around 34 000 excess deaths, mostly in the elderly, occurred in the USA. In striking contrast, Canada experienced a relatively slight increase in disease incidence and practically no excess deaths. A similar picture was seen in most parts of Europe, where symptoms were mild and excess deaths negligible. In the United Kingdom, for example, the epidemic began in December 1968, progressed at a leisurely pace until early April 1969, and was associated with no sudden or excessive demands on general medical practitioners or hospital services. Deaths from influenza-like illness and pneumonia were actually lower than the year before.



**Once again, vaccine arrived too late. Though vaccine manufacturing began within two months of virus isolation, only 20 million doses were ready when the epidemic peaked in the USA.**

Although good mortality estimates are not available, global excess mortality was probably around 1 million. Many efforts have been made to explain the relative mildness of this pandemic. As the virus was genetically similar to viruses from previous pandemics, including the one as recent as 1957, at least some segments of the world population probably had partial protection either against infection or from severe disease. The occurrence of major epidemics at different times in different parts of the world was another fortunate, but curious feature. Several tropical countries experienced epidemics only at the beginning of 1969. For unknown reasons, Japan experienced numerous imported cases at the start of the pandemic, but was spared a major epidemic until mid-January 1969. Once again, however, too little vaccine arrived too late. Though vaccine manufacturing began within two months of virus isolation, only 20 million doses were ready when the epidemic peaked in the USA.

## **Lessons from the three pandemics of the last century**

- 1** Pandemics behave as unpredictably as the viruses that cause them. During the previous century, great variations were seen in mortality, severity of illness, and patterns of spread.
- 2** One consistent feature important for preparedness planning is the rapid surge in the number of cases and their exponential increase over a very brief time, often measured in weeks. The severity of illness caused by the virus, which cannot be known in advance, will influence the capacity of health services, including hospitals, to cope, but a sudden sharp increase in the need for medical care will always occur.
- 3** Apart from the inherent lethality of the virus, its capacity to cause severe disease in non-traditional age groups, namely young adults, is a major determinant of a pandemic's overall impact. Milder pandemics are characterized by severe disease and excess deaths at the extremes of the lifespan (the very young and the elderly).

- 4 The epidemiological potential of a virus tends to unfold in waves. Age groups and geographical areas not affected initially are likely to prove vulnerable during the second wave. Subsequent waves have tended to be more severe, but for different reasons. In 1918, the virus mutated, within just a few months, into a far more virulent form. In 1957, schoolchildren were the primary vectors for spread into the general community during the first wave. The second wave reached the elderly, a group traditionally at risk of severe disease with fatal complications.
- 5 Virological surveillance, as conducted by the WHO laboratory network, has performed a vital function in rapidly confirming the onset of pandemics, alerting health services, isolating and characterizing the virus, and making it available to vaccine manufacturers.
- 6 Over the centuries, most pandemics have originated in parts of Asia where dense populations of humans live in close proximity to ducks and pigs. In this part of the world, surveillance for both animal influenza and clusters of unusual respiratory disease in humans performs an important early warning function.
- 7 Some public health interventions may have delayed the international spread of past pandemics, but could not stop them. Quarantine and travel restrictions have shown little effect. As spread within countries has been associated with close contact and crowding, the temporary banning of public gatherings and closure of schools are potentially effective measures. The speed with which pandemic influenza peaks and then disappears means that such measures would probably not need to be imposed for long.
- 8 Delaying spread is desirable, as it can flatten the epidemiological peak, thus distributing cases over a longer period of time. Having fewer people ill at a given time increases the likelihood that medical and other essential services can be maintained and improves capacity to cope with a sharp increase in demand for care.
- 9 The impact of vaccines on a pandemic, though potentially great, remains to be demonstrated. In 1957 and 1968, vaccine manufacturers responded rapidly, but limited production capacity resulted in the arrival of inadequate quantities too late to have an impact.

- 10 Countries with domestic manufacturing capacity will be the first to receive vaccines.
- 11 The tendency of pandemics to be most severe in later waves may extend the time before large supplies of vaccine are needed to prevent severe disease in high-risk populations. The interval between successive waves may, however, be as short as a month.
- 12 In the best-case scenario, a pandemic will cause excess mortality at the extremes of the lifespan and in persons with underlying chronic disease. As these risk groups are the same as during seasonal epidemics, countries with good programmes for yearly vaccination will have experience in the logistics of vaccine administration to at least some groups requiring priority protection during a pandemic. While such a strategy can reduce excess mortality, sudden and large increases in morbidity, and a correspondingly high demand for medical care, should nonetheless be anticipated.

#### **Box 4. The WHO global influenza programme: a network of flu “detectives”**

Influenza surveillance is the oldest disease control programme at WHO. It was established in 1947 because of two concerns: the inevitable recurrence, at unpredictable intervals, of highly disruptive pandemics, and the significant health and economic impact of seasonal epidemics, which occur nearly every year. The objective at the outset was to obtain an ongoing representative picture, at the global level, of how the virus is changing and what these changes mean for human health. The programme was set up as a network of laboratories commissioned to study circulating influenza viruses, collected from around the world, and document changes in the viruses’ genetic make-up.

Within four years, the network included 60 laboratories in 40 countries. At that time, when the world was far less mobile and interdependent than now, public health authorities recognized influenza as a disease that cannot be mitigated without an international collaborative effort having a broad geographical scope. From its earliest years on, the network has operated as a model of international scientific collaboration to safeguard public health: virus strains are made freely available to other laboratories and to manufacturers the moment any unusual characteristics are detected.

Today, the WHO Global Influenza Surveillance Network consists of 113 national influenza centres located in 84 countries, and four WHO collaborating centres for influenza reference and research, located in London (England), Atlanta (USA), Melbourne (Australia), and Tokyo (Japan). A fifth collaborating centre, located in Memphis, USA, performs specialized work on influenza viruses in animals. The national centres collect influenza viruses circulating in different parts of the world. These are then sent to the four collaborating laboratories for

in-depth investigations. Apart from providing a composite global picture of changing influenza activity, this work allows WHO to issue advice, twice each year, on the composition of influenza vaccines considered most likely to confer protection against seasonal epidemics in both the northern and southern hemispheres. The WHO network has thus contributed greatly to the understanding of influenza epidemiology and assists manufacturers both by ensuring that influenza vaccines contain the most appropriate viruses and by providing them with high-yielding “seed” virus for vaccine production.

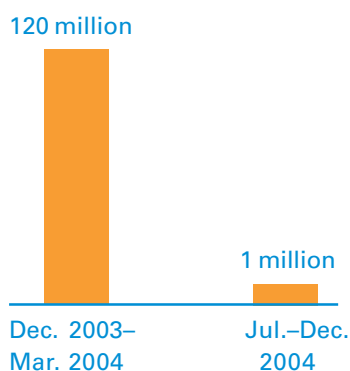
In a given year, around 200 000 samples are collected by the national centres, of which some 6 500 are sent to the four collaborating centres for in-depth analysis. Each year, the United States Centers for Disease Control and Prevention (CDC) prepares a kit of reagents to assist the global network in determining the types of viruses in circulation. The results are reported directly to WHO. The four collaborating centres also store virus samples for historical comparisons and provide diagnostic support for countries experiencing unusual influenza cases, such as those caused by H5N1. At present, eight network laboratories perform confirmatory diagnostic work on H5N1 viruses. Sequencing of 2004 viruses and comparisons with historical samples from previous outbreaks have yielded valuable clues about the evolution of the virus and the significance of possible instances of human-to-human transmission. Although all this work takes place quietly behind the scenes and receives little attention, it is universally regarded as a model of efficient surveillance and of effective international collaboration.

In responding to the H5N1 outbreaks, WHO has also drawn considerable support from a second network of laboratories and scientists conducting work on animal influenza.

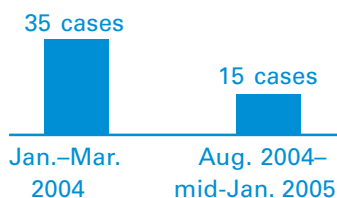
# 3

## Understanding the outbreaks in poultry

### Outbreaks in poultry



### Human cases, Thailand and Viet Nam combined



**O**pportunities for both the occurrence of further human cases and the emergence of a pandemic virus are intrinsically linked to the presence of the H5N1 virus in poultry. Hopes that a potentially explosive situation might be defused by elimination of the virus – as was done in Hong Kong SAR in 1997 – have dwindled. As 2004 progressed, evidence mounted that the virus has become firmly entrenched in parts of Asia. Time and time again, countries on the verge of declaring outbreaks over have been set back by detection of the disease in yet another farm or flock.

Though far fewer outbreaks, affecting far fewer birds, were detected in the second half of the year, the threat to humans has actually become more dangerous. The virus is no longer causing large and highly conspicuous outbreaks on commercial farms. Nor have poultry workers or cullers turned out to be an important risk group that could be targeted for protection. Instead, the virus has become stealthier: human cases are now occurring with no discernible exposure to H5N1 through contact with diseased or dead birds. This change has created a community-wide risk for large numbers of rural households and – for unknown reasons – most especially for children and young adults. The true magnitude of the threat may well be masked in rural areas where surveillance is poor and respiratory illness, including pneumonia, is common.

True to the nature of influenza A viruses, H5N1 is certain to continue to mutate, though the direction these changes will take cannot be predicted. If the virus continues to expand its avian and mammalian host range, the prospects for eliminating the disease in animals will become even grimmer. An understanding of the H5N1 outbreaks in poultry, and of their unique features when compared with previous outbreaks, adds to the total fund of information useful in assessing the severity of the present situation and its implications for public health.



## Previous outbreaks of highly pathogenic avian influenza worldwide

1959	Scotland	H5N1
1963	England	H7N3
1966	Ontario (Canada)	H5N9
1976	Victoria (Australia)	H7N7
1979	Germany	H7N7
1979	England	H7N7
1983–1985	Pennsylvania (USA) <sup>a</sup>	H5N2
1983	Ireland	H5N8
1985	Victoria (Australia)	H7N7
1991	England	H5N1
1992	Victoria (Australia)	H7N3
1994	Queensland (Australia)	H7N3
1994–1995	Mexico <sup>a</sup>	H5N2
1994	Pakistan <sup>a</sup>	H7N3
1997	New S. Wales (Australia)	H7N4
1997	Hong Kong SAR <sup>a</sup>	H5N1
1997	Italy	H5N2
1999–2000	Italy <sup>a</sup>	H7N1
2002	Hong Kong SAR	H5N1
2002	Chile	H7N3
2003	Netherlands <sup>a</sup>	H7N7
2004	Pakistan	H7N3
2004	Texas (USA)	H5N2
2004	British Col. (Canada) <sup>a</sup>	H7N3
2004	South Africa	H5N2

<sup>a</sup> Outbreaks with significant spread to numerous farms, resulting in great economic losses.

## The disease in birds: from ruffled feathers to “chicken Ebola”

Avian influenza, previously known as “fowl plague”, was first recognized as a serious disease of chickens in Italy in 1878. Decades later, in 1955, studies demonstrated that the disease was caused by influenza A viruses. Since then, influenza A viruses of all subtypes have been detected in more than 90 species of apparently healthy wild birds.

Wild waterfowl, most notably ducks, are by far the most frequent carriers of the largest variety of viruses. It is now recognized that wild waterfowl, gulls, and shorebirds are the natural reservoir of all influenza A viruses. These birds have carried the viruses without developing symptoms – presumably for thousands of years – in a relationship thought to represent optimal adaptation of a virus to its host. This huge, stable, benign, and perpetual reservoir of viruses is also highly mobile. Wild waterfowl can carry viruses over great distances and excrete large quantities in their faeces, yet remain perfectly healthy.

Other bird species, including domestic poultry, are less fortunate. In poultry, avian influenza causes two distinctly different forms of disease – one common and mild, the other rare and highly lethal. Considerable circumstantial evidence indicates that the viruses, in their low-pathogenic form, are introduced into poultry by wild waterfowl. This evidence is further substantiated by the fact that outbreaks are seen most often in poultry having contact with feral birds, often sharing the same water sources.

In the mild form of avian influenza, signs of illness range from ruffled feathers and reduced egg production to typical respiratory symptoms. Outbreaks can be so mild they escape detection unless regular testing for the virus is in place. In contrast, the second and far less common highly pathogenic form is difficult to miss, characterized as it is by sudden onset of severe disease, rapid contagion and a mortality that can approach 100% within 48 hours. In this form, the virus not only affects the respiratory tract, as in the mild form of disease, but also invades multiple organs and tissues, causing massive internal haemorrhaging that has earned it the lay name of “chicken Ebola”.

## **Testing for highly pathogenic avian influenza**

The standard method used to determine whether an avian influenza virus is highly pathogenic takes time. The method involves the inoculation of a minimum of eight susceptible 4- to 8-week old chickens with infectious virus. If 75% of the chickens (six of the eight) die within 8 days, the virus strain is considered to be highly pathogenic. Because work with a highly lethal virus is involved, testing must be done in a high-security laboratory.

Some highly pathogenic avian influenza viruses will kill six or more chickens within 48 hours or less. In such cases, conclusive test results become available quickly.

An additional test involves sequencing of the virus. All highly pathogenic avian influenza viruses will show a distinctive sequence of amino acids, located at the so-called HA "cleavage site", known to be associated with high lethality.

**Viruses of the H5 and H7 subtypes can rapidly mutate from a mild to a highly lethal form. Their detection in poultry is always of great concern.**

## **H5 and H7 viruses: always cause for alarm**

Viruses that can cause highly pathogenic avian influenza are currently restricted to the H5 and H7 subtypes. Some variants within these two subtypes are capable of causing highly lethal disease, but not all will do so, as an intermediate step is required. Highly pathogenic viruses have no natural reservoir. Instead, they emerge by mutation when a virus, carried in its mild form by a wild bird, is introduced to poultry. Once in poultry, the previously stable virus begins to evolve rapidly, and can mutate, over an unpredictable period of time, into a highly lethal version of the same initially mild strain. It is this propensity for rapid mutation from a mild into a lethal form that always makes detection of any H5 or H7 infection in poultry of great concern. If the disease is detected early enough, and aggressive control measures are undertaken, the mild virus can be eliminated before it has an opportunity to mutate into the highly pathogenic form.

Outbreaks of low pathogenic avian influenza have been reported in poultry throughout the world, but the frequency and size of outbreaks have varied with individual countries, regions, and agricultural systems. Prior to 2004, outbreaks of highly pathogenic avian influenza were considered rare. While the 1878 outbreak in Italy, which caused extremely high mortality in chickens, was almost certainly of the highly pathogenic form, the first confirmed outbreak of highly pathogenic avian influenza was reported in 1959. Since then, 24 outbreaks have been recorded worldwide, of which 14 have occurred in the past 10 years. The majority have shown limited geographical spread, a few remained confined to a single farm or flock, and only one spread internationally. All of the larger outbreaks proved notoriously difficult to control, typically requiring two to three years to eliminate the virus. Since 1959, none of the outbreaks has approached the size of the Asian outbreaks of H5N1 in 2004.

The most important control measures are rapid culling of all infected or exposed birds, proper disposal of carcasses, and the quarantining and rigorous disinfection of farms. Restrictions on the movement of live poultry, both within and between countries, are another important control measure. Strict application of these



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measures, while feasible on commercial farms, is virtually impossible in rural areas where chickens and ducks roam freely and mingle with wild birds or share water sources with them. Faecal contamination of water supplies is considered a very efficient way for waterfowl to transmit the virus. Moreover, domestic ducks attract wild ducks and provide a significant link in the chain of transmission from wild birds to domestic flocks.

Highly pathogenic avian influenza viruses were probably endemic in Europe and Asia from 1900 to the mid-1930s. Endemicity of these viruses has not been reported since that time. Even in areas where outbreaks have tended to recur, differences in the causative viruses have suggested independent introductions from wild birds, especially as many areas with recurring outbreaks are located along the flight paths of migratory birds.

## **The 2004 outbreaks: the largest – and most ominous – on record**

Viewed against this historical background, the 2004 outbreaks of highly pathogenic H5N1 avian influenza in Asia are clearly unprecedented in their geographical scale and the endemicity of the virus, which now appears firmly entrenched in parts of Asia. Other unique features of the outbreaks suggest that the complex ecology of influenza viruses may be changing in ominous ways. Domestic ducks are now known to be excreting H5N1 in its highly pathogenic form yet – like wild ducks – appear to be perfectly healthy. They may thus be silently perpetuating transmission of the virus to chickens and other poultry and possibly also to humans. The recent detection of highly pathogenic H5N1 in dead migratory birds – long considered asymptomatic carriers – may suggest another ominous change, but more research is needed before any conclusions can be reached.

The history of all known human infections with avian influenza viruses readily reveals the significance of the 2004 outbreaks for human health (Table 3). They have caused the largest number of severe cases of avian influenza in humans on record. Compared with the Hong Kong SAR outbreak in 1997, the 2004 H5N1 outbreak in humans has also been far more deadly.



## **WHO advice on the preparation of poultry for consumption**

### **1. Avoid contamination**

Separate raw meat from cooked or ready-to-eat foods. Do not use the same chopping board or the same knife for preparing raw meat and cooked or ready-to-eat foods. Do not handle both raw and cooked foods without washing your hands in between and do not place cooked meat back on the same plate or surface it was on before it was cooked.

### **2. Cook thoroughly**

Thorough cooking will inactivate influenza viruses. Either ensure that the poultry meat reaches 70 °C or that the meat is not pink and there are no pink juices.

### **3. Be careful with eggs**

Eggs, too, may carry pathogens, such as the bird-flu virus inside or on their shells. Care must be taken in handling raw eggs and shells. Wash shells in soapy water and wash hands afterwards. Egg yolks should not be runny or liquid. Do not use raw or soft-boiled eggs in foods that will not be cooked.

### **4. Keep clean**

After handling raw or thawed raw poultry or eggs, wash your hands and all surfaces and utensils thoroughly with soap and water.

## **Chicken and eggs: is there a risk from poultry products?**

As a general rule, WHO recommends that all meats, including that from poultry, be thoroughly cooked, so that all parts of the meat reach an internal temperature of 70 °C. This temperature will kill an influenza virus and thus render safe any raw poultry meat contaminated with H5N1 virus.

In countries affected by H5N1 outbreaks, eggs should also be thoroughly cooked, as some studies have detected virus in raw eggs.

To date, epidemiological investigations have not linked any human cases to the consumption of poultry products. Strong evidence does, however, point to a far greater risk: exposure to the virus during the slaughter of infected birds and their preparation for cooking. This risk is compounded by the practice, common among rural subsistence farmers, of killing and eating poultry – even those showing obvious signs of illness – once birds within a flock start to die. In several such instances, the person who slaughtered or prepared an ill bird for consumption developed fatal illness, while family members who participated in the meal did not.

The large outbreak in captive tigers, which occurred in October in Thailand, is thought to be linked to the feeding of contaminated whole chicken carcasses. If this hypothesis is substantiated, it will provide further evidence that contact with raw poultry carcasses can be a significant source of exposure to the virus.

**Table 3. Documented human infections with avian influenza viruses**

<b>Date</b>	<b>Country/ area</b>	<b>Strain</b>	<b>Cases</b>	<b>Deaths</b>	<b>Symptoms</b>	<b>Source</b>
1959	USA	H7N7 <sup>a</sup>	1 (46-year-old man)	0	respiratory	overseas travel
1995	United Kingdom	H7N7	1 (43-year-old woman)	0	conjunctivitis	pet ducks (shared lake with migratorybirds)
1997	Hong Kong SAR	H5N1 <sup>a</sup>	18	6	respiratory, pneumonia	poultry
1998	China (Guangdong)	H9N2	5	0	unknown	unknown
1999	Hong Kong SAR	H9N2	2 girls (4 years, 13 months)	0	respiratory	poultry for 4-year-old; unknown for 13-month-old
2003 (Feb.)	Hong Kong SAR <sup>b</sup>	H5N1 <sup>a</sup>	2 (9-year-old boy, 33-year-old father)	1	respiratory	unknown
2003 (Mar.)	Netherlands	H7N7 <sup>a</sup>	89	1 (57-year-old veterinarian)	conjunctivitis (pneumonia, respiratory insufficiency in fatal case)	poultry
2003 (Dec.)	Hong Kong SAR	H9N2	1 boy (5-year-old)	0	respiratory	unknown
2004	Viet Nam	H5N1 <sup>a</sup>	33	25	respiratory	poultry
2004	Thailand	H5N1 <sup>a</sup>	17	12	respiratory	poultry
2004	Canada	H7N3 <sup>a</sup>	2	0	conjunctivitis	poultry

<sup>a</sup> Highly pathogenic for poultry.

<sup>b</sup> Possibly acquired in mainland China.