

OCTOBER 2009

Big Picture

SPECIAL ISSUE

Flu

Your guide to H1N1
and other pandemics

- The origins of swine flu
- The history of flu pandemics
- Flu vaccines and drugs
- Swine flu and Spanish flu compared

FREE

'Swine Flu' sculpture by Luke Jerram

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Big Picture on influenza

A NOTE ON NOMENCLATURE

The name of the 2009 pandemic has been controversial (see page 7) and is referred to by the World Health Organization as 'pandemic (H1N1) 2009'. We have adopted the term 'H1N1 swine flu' for the 2009 pandemic and 'S-OIV' (swine-origin influenza virus) for the virus that causes it.

This special issue of *Big Picture* looks at what is known about H1N1 swine flu and how it compares with past pandemics, seasonal flu and H5N1 avian flu. H1N1 swine flu was first detected in Mexico in February 2009. It has since spread rapidly to become the first influenza pandemic of the 21st century.

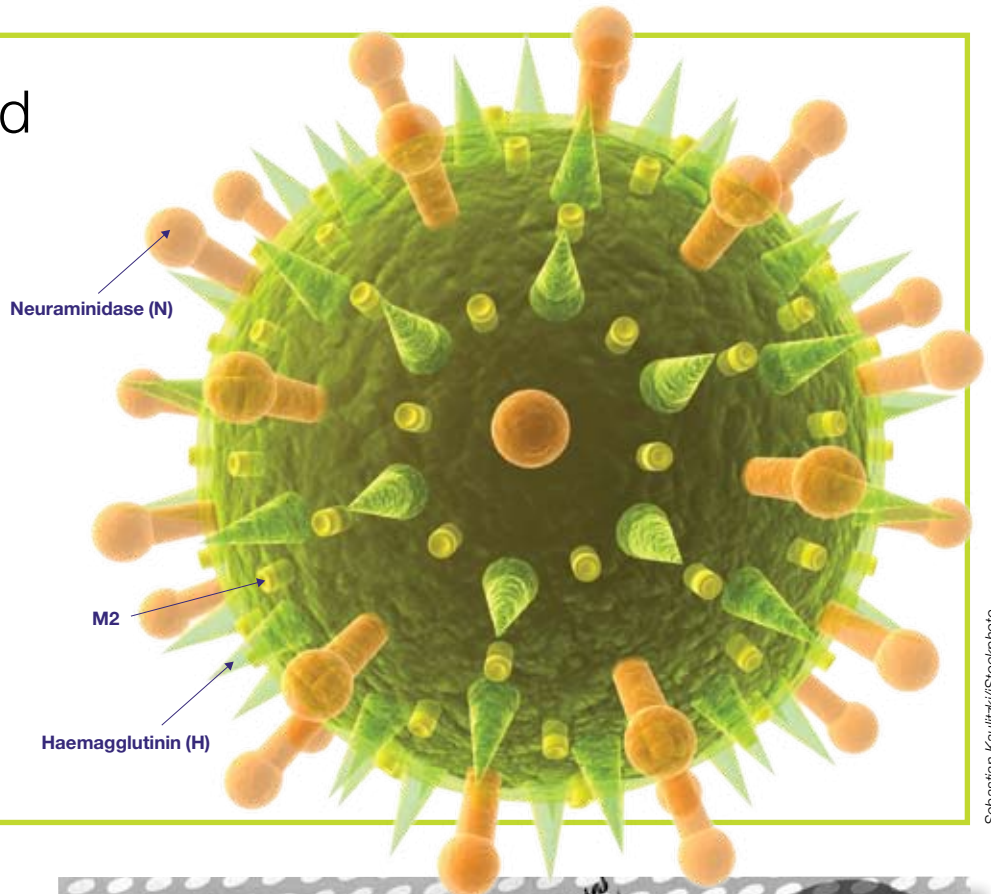
The virus unmasked

The influenza A virus is deceptively simple. At its core are eight short strands of RNA, the coding material for 11 proteins.

The surface of the virus particle is studded with proteins, notably haemagglutinin (the 'H' of H1N1) and neuraminidase (the 'N'). Haemagglutinin is the structure that sticks the virus to host cells; neuraminidase is an enzyme that clips off the sugars that haemagglutinin binds to, helping to release new virus particles on their way out of the cell.

There are at least 16 different types of haemagglutinin (H1–16) and nine types of neuraminidase. To date, only H1, H2 and H3 viruses have infected large numbers of people.

The M2 protein is an ion channel. The flow of ions through this channel enables the virus to uncoat inside the cell, freeing the strands of RNA to make new virus proteins.



Sebastian Kaulitzki/Stockphoto

Out of control?

Influenza epidemics are almost impossible to contain; the priority quickly becomes minimising their impact.

Stopping an epidemic before it can become established could save many lives. That was achieved with SARS (just) and has been the goal of H5N1 avian flu control, but has not been possible with H1N1 swine flu.

Initial containment calls for highly effective surveillance, so a new outbreak can be identified as rapidly as possible. Isolation measures can then be taken to contain infection and prevent escape of the virus. Mass culling of birds in the Hong Kong poultry markets helped to contain early bird flu outbreaks. Additional surveillance systems have been put in place to monitor for H5N1 outbreaks.

So why did S-OIV slip beneath the radar? Important factors include patchy monitoring of influenza in pigs and the mildness of illness in most people. Whereas a case of bird flu is likely to be picked up immediately, many cases of swine flu may have gone unnoticed. In addition, unlike the H5N1 virus, S-OIV readily transmits between people.

Within individual countries, health policy generally starts with **containment**: identifying and isolating cases, tracing contacts and treating with antivirals. More general hygiene measures are encouraged.



People with known infections are encouraged not to mix and affected schools may be shut.

Some countries monitor visitors for signs of fever, but this is likely to have little effect other than to delay an epidemic slightly.

Once cases become widespread, containment becomes impractical, and policy shifts to a **mitigation** phase: trying to minimise the impact of an epidemic. This may mean special protection for the vulnerable and preparing for the expected waves of new cases. At this point, special measures are likely to kick in, as the health service implements pandemic plans. For example, non-essential surgery may be put on hold.

Other public health measures could be considered, but much depends on the severity of the infection. Closing schools or banning large gatherings (such as football matches or concerts) would be difficult, disruptive and potentially economically costly. If S-OIV were to turn more virulent, however, such measures might be taken to protect public health.

Drugs and vaccines

Drugs

As S-OIV is a virus, antibiotics do not affect it. Antiviral drugs against influenza fall into two classes:

- neuraminidase inhibitors – such as oseltamivir (Tamiflu) and zanamivir (Relenza) – which target the neuraminidase enzyme
- adamantanes – such as amantadine – which act on M2.

Neuraminidase inhibitors have fewer side-effects and are more effective. They are not cures: they shorten flu episodes by a couple of days, reduce the risk of complications and possibly lower the likelihood that someone will pass on the virus. Ideally, they should be given as early as possible in an infection and can also be used prophylactically (to prevent infection).

Resistance to oseltamivir has been detected in seasonal H1N1 strains, and in most countries resistant strains now predominate. S-OIV is resistant to amantadine but usually susceptible to neuraminidase inhibitors; some cases of oseltamivir resistance have been seen. Oseltamivir resistance has been seen in some human cases of H5N1 avian flu.

Because of the risk of resistance, it is much better to use drugs in combination. Other flu drugs are in development but years away from human use.

Vaccines

Influenza viruses evolve rapidly, so new vaccines are frequently updated to match viral strains in circulation.

To deal with seasonal flu, the World Health Organization monitors strains circulating in the southern hemisphere and the tropics during its winter and predicts which are most likely to hit the northern hemisphere later in the year. Vaccine manufacturers take these predictions and, in a race against time, develop and test new vaccines. Each vaccine covers two influenza A strains and one B strain. Six months later, the process is repeated for the southern hemisphere.

Traditionally, vaccines have been grown in chicken eggs, but new, more efficient cell culture systems are now beginning to be used.

If a vaccine is a close match for the strains that eventually dominate, it will give better protection. If the circulating virus changes more than expected, or a minor strain becomes unexpectedly common, the vaccine will be less effective. Protection is typically effective in 60–80 per cent of cases (lower in elderly people, who tend to have weaker immune systems).

Vaccine responses can be enhanced by **adjuvants** – chemicals that ‘turbocharge’ immune responses. This is a way to eke out vaccine supplies, as lower doses of the viral haemagglutinin could be used (‘antigen sparing’).

Most valuable would be a vaccine that recognised all influenza strains. One such ‘universal’ vaccine, targeted at the less rapidly evolving M2 protein, has been successfully tested in animals. ‘Virus-like particles’ containing a mix of flu proteins have also shown promising results in animal studies.

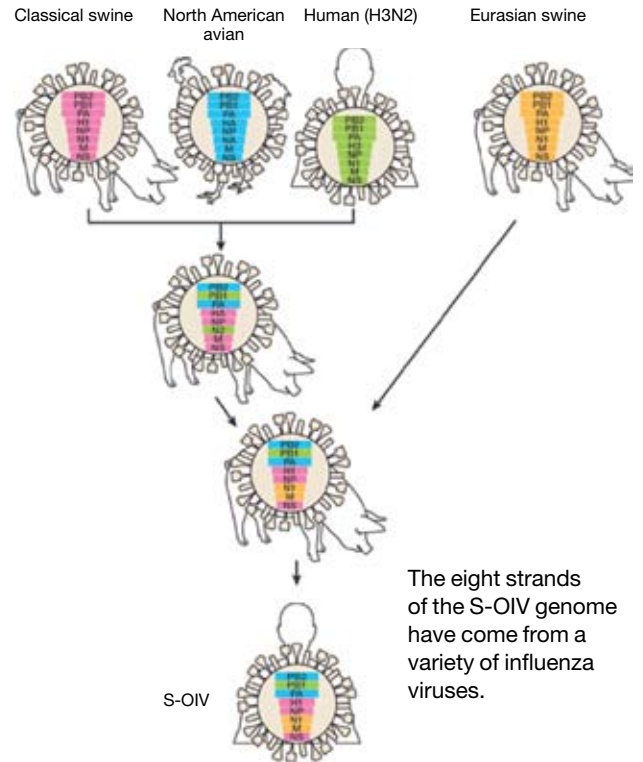
Researchers are working on new types of vaccine, including those that recognise all strains of influenza. These are several years away from human use, however.

The merits of ferrets

In 1933, ferrets being used in work on a distemper vaccine contracted influenza from a researcher (and also managed to pass it on to another). The researchers identified influenza virus and since then the ferret has been used as a model of human flu – they show similar symptoms and a similar pattern of virus receptors along their respiratory tract (unlike mice). They have been used to understand more about flu and to test new vaccines.



Eric Isselée/Stockphoto



From Neumann G et al. Nature 2009;459:931–9.

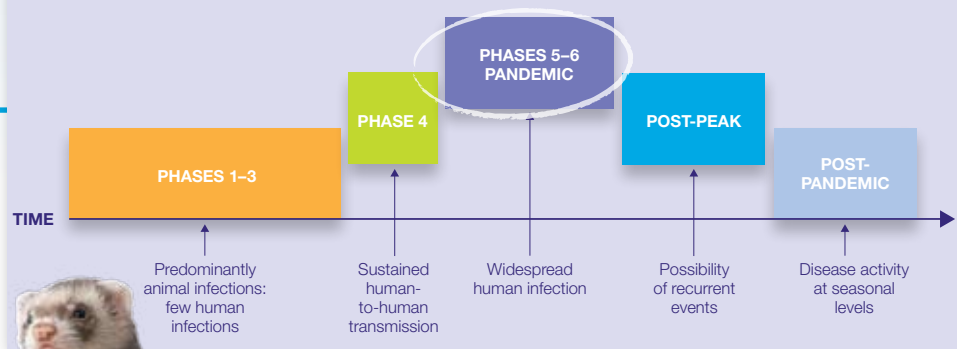
Where has it come from?

H1N1 flu viruses are in constant circulation, but S-OIV is different: it contains bits of bird, pig and human influenza viruses.

Analysis of its genetic make-up suggests that it first appeared sometime between autumn and Christmas 2008, so was almost certainly circulating before it was first detected in Mexico.

Where it first made the leap from pigs to humans is unclear; its closest relative in pigs is a Hong Kong sample from 2004. However, this is a ‘cousin’, distantly related to S-OIV, so it cannot be said with certainty where S-OIV emerged. Asia may be a ‘hotspot’ for jumps across species as large numbers of people live close to livestock such as pigs and poultry. China, for example, accounts for half the world’s pig consumption – around 1.2 million pigs every day.

Pandemic influenza phases



World Health Organization

Pandemic: A pandemic is a worldwide epidemic of a disease. The World Health Organization formally categorises outbreaks into different phases. A global pandemic of H1N1 swine flu was announced on 11 June 2009.

The past and present

H1N1 swine flu shares features with seasonal flu and past pandemics. Flu viruses spread quickest in cool, dry conditions typical of winter (when people are also more likely to be close together indoors). Other than the likelihood that swine flu will strike hard during winter 2009–10, little can be said with certainty about its future impact.



1918 flu virus

The 1918 flu virus has been revived – and is helping to explain why flu can be so deadly.

The Spanish flu virus disappeared from circulation many years ago, leaving unexplained the reasons for its severity. In 2005, however, a US team tracked down an Alaskan flu victim who had been buried in permafrost since November 1918, then reconstructed from scratch the 1918 virus.

The reborn virus is lethal to mice, and grows rapidly in human cells; it infects but does not kill pigs. Although re-creating a lethal virus might seem risky, studies of the 1918 virus have told us much about the effects of different flu proteins and how the virus spreads (see page 6). Studies are carried out in specialised containment facilities to prevent the virus escaping.

With the 1918 virus available, systematic studies can be done, with artificial viruses containing different combinations of 1918 and ‘modern’ genes. Such studies have helped to reveal the key role of the *HA*, *NA* and *PB1* genes from the 1918 virus. *HA* conferred the ability to infect human cells with high efficiency. Because *NA* and *HA* come from an avian virus, they are more compatible and work well together. *PB1* and other genes contributed to the severity of infection.

Flu through history

- 1890:** Russian flu (H3?) kills 1 million
- 1918:** Spanish flu (H1N1) kills 40–50 million
- 1957:** Asian flu (H2N2) kills 100 000–2 million
- 1959:** H5N1 bird flu kills two flocks of chickens in Scotland (but does not infect people)
- 1968:** Hong Kong flu (H3N2) kills 700 000–1 million
- 1976:** Fort Dix swine flu outbreak; one death, 40 million Americans inoculated
- 1997:** Hong Kong H5N1 outbreak; six human deaths
- 2003:** First post-Hong Kong H5N1 deaths
- 2009:** H1N1 swine flu detected in Mexico

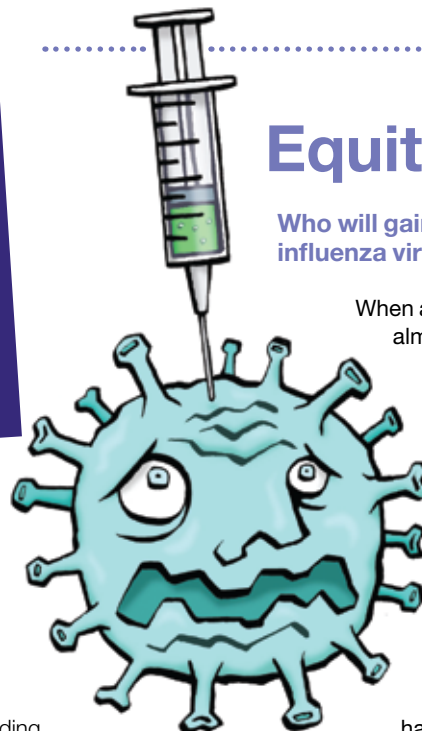
Where next?

What might be the next step in the swine flu pandemic?

It is unnerving that most of the previous flu pandemics, including Spanish flu, have occurred in waves, sometimes with later waves being more severe than earlier ones.

However, this is not necessarily an inherent feature of flu pandemics. Since S-OIV is new to human hosts, it is likely to change as it circulates, but in ways that are hard to predict.

The success of a virus lies in its ability to make more copies of itself and spread. Mutations that increase these abilities will be selected for and thrive. A mutation that increases the severity of infection may not actually help the virus in the long run: if it rapidly kills its host, it may reduce its chances of being passed on (see page 6).



Equitable access

Who will gain access to an influenza virus vaccine?

When a swine flu vaccine becomes available, almost everyone in the UK is likely to be offered a vaccine. In less developed countries, people may not be so lucky.

Amid the rush to order and make an H1N1 swine flu vaccine, the World Health Organization (WHO) has urged manufacturers to consider the plight of developing countries. The largest manufacturer, Sanofi-Aventis, has pledged to donate 10 per cent of vaccine output (100 million doses) to the WHO, while GlaxoSmithKline has offered 50m doses. A third key producer, Novartis, has declined to donate for free but has offered to supply vaccine at a discount.

The WHO is also encouraging countries to donate vaccine and funds to support distribution.

Because of other health problems, such as HIV, malaria, TB and malnutrition, H1N1 swine flu could have a substantially greater impact on poor countries.

In reality, gaining access to vaccines is not the only obstacle to mass vaccination. Many developing countries have little medical infrastructure through which to deliver vaccines. The likelihood is that they will be available only for key groups such as healthcare workers.

Flu (seasonal, swine, avian and Spanish) and SARS compared

	SEASONAL FLU	2009 SWINE FLU	AVIAN FLU	1918 SPANISH FLU	SARS
Virus type	Influenza A and B	Influenza A	Influenza A	Influenza A	Coronavirus
Influenza subtype	H1N1/H3N2	H1N1	H5N1	H1N1	–
Route to humans	Humans	Pigs	Wild birds via domesticated birds	Birds, possibly via pigs or directly	Bats via small mammals
Transmissibility	Moderate	High	Human-to-human transmission rare	High	Moderate
Symptoms	Fever, cough, aching, tiredness, sore throat, runny nose	As seasonal flu, sometimes with diarrhoea or stomach upset	As seasonal flu, plus fluid build-up in the lungs, severe breathing problems, chest pains	As avian flu, plus lung problems and pneumonia	As avian flu, plus pneumonia
Estimated death rate	0.1%	0.1% or less	60%	2–20%	10%
Deaths (global)	250 000–500 000 (annual)	3555 (as at 10/9/09)	262 (as at 31/8/09)	50–100 million (total)	447 (total)
Deaths (UK)	Typically 3000–4000; in severe years, up to 30 000	75 (as at 10/9/09)	0	250 000	0
At-risk groups	Elderly, frail, those with heart and lung problems or diabetes	Infants, those with underlying health problems, pregnant women; could change as virus evolves	All	Unusual peak in deaths of young adults	Older adults, those with underlying health problems
SUMMARY	Underappreciated annual killer	Watch this space...	Extremely nasty, but not yet spreading in people	Killed more people than World War I	'We got lucky': low transmissibility and draconian public health clampdown stamped it out before it could spread widely



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From astrology to chills

The word influenza is derived from the Italian for 'influence' – it was originally thought to have astrological origins. This was later modified to *influenza del freddo*, 'influence of the cold'. The anglicised term influenza was first used in 1743.



A very peculiar pandemic

The 1976 swine flu outbreak: the pandemic that never was.

On 5 February 1976, Private David Lewis at Fort Dix barracks in New Jersey, USA, began to feel unwell. Within 24 hours he was dead, victim of a virus last seen 58 years before: highly pathogenic H1N1 swine flu.

Decisions had to be made fast. Could this be the birth of another pandemic, capable of devastating the US population? With the support of the medical community, by March President Gerald Ford (above) ordered a nationwide vaccination campaign, which Congress approved in August.

By October, a new vaccine was ready. Almost immediately there were problems. Three elderly people in the Pittsburgh area suffered heart attacks soon after vaccination. A surge of cases of Guillain-Barré syndrome also raised safety fears. In December the programme was halted, after 40 million doses had been given. No other cases of swine flu were detected.

Rights and wrongs

The story has provoked heated debate. Were the medical establishment and government wrong to run with the programme? Yet if they had done nothing, and a pandemic had taken hold, the effects would have been catastrophic.

Nowadays, decision-making processes are different. More tools are available, for example for surveillance and modelling. And more phased approaches are used, allowing for escalation or fall-back as circumstances change.

By stimulating interest in swine flu, the 1976 episode may have had one other legacy. Soon afterwards, a human H1N1 virus reappeared – possibly an accidental laboratory release.

It's good to talk

Swine flu has been characterised by open communication – unlike previous pandemics.

In 1918, US President Woodrow Wilson held an iron fist on government communications, which he believed were vital to maintain morale.

His adviser, Arthur Bullard, told him: "Truth and falsehood are arbitrary terms...There is nothing in experience to tell us one is always preferable to the other...The force of an idea lies in its inspirational value. It matters very little if it is true or false."

Ignorance isn't bliss

So when the Spanish flu pandemic hit the USA in September 1918, Wilson said nothing and public officials did little but utter reassuring words. Chicago's director of public health concluded: "It is our job to keep people from fear. Worry kills more than the disease." Newspapers toed the line, rarely questioning official pronouncements.

In the absence of realistic information, wild theories took off. And people were scared. Communication systems came close to collapse.

According to the Red Cross, people "were starving to death not for lack of food but because the well were too panic stricken to bring food to the sick".

The current swine flu pandemic, by contrast, has been played out in a remarkably public way. The outbreak in Mexico was world news almost immediately. International and national agencies have generally attempted to communicate rapidly and openly with the public. Media reporting has, by and large, been responsible. In the days of the internet, blogs and twittering, information cannot be easily contained.

So far, there have been few signs of public panic. Another of Woodrow Wilson's advisers, Walter Lippman, told him that most citizens were "mentally children". Perhaps the first pandemic of the information age has proved him wholly wrong.

- For more information, see 'Pandemics', by John Barry (*Nature*, 21 May 2009).

Hit and run

A flu infection can be unpleasant or deadly. The difference depends on both the virus and the person infected.

Virus genomes

The influenza genome is in constant flux.

The influenza virus can survive and spread so well because of its ever-changing genome. Two key processes shape its genome: reassortment (gene swapping) and mutation (gene change).

Reassortment refers to the mixing of RNA in the virus genome, which can occur if more than one type of influenza virus infects a single cell, as seen in the emergence of S-OIV from a mix of different ancestors. In effect, influenza viruses have an enormous global pool of genetic material that can come together in different combinations. Changes in the genome by reassortment may change significantly the proteins on the surface of the virus, a process known as antigenic shift.

Mutations are smaller-scale changes that occur in the genetic material of an individual virus. However, these mutations can lead to changes in the surface-protein-encoding genes, resulting in new variants through the process of 'antigenic drift'. Changes may arise because of selective pressures (e.g. from the host's immune system) or the accumulation of random changes over time.

Shifts can be the earthquakes that unleash new pandemics, but drift is a constant nuisance, as new variants evade immune responses and render vaccines ineffective within a year or so.

Body of evidence

What happens when the influenza virus invades?

The impact of an influenza virus depends on viral and host factors. Previous infection or vaccination should provide some protection. If the virus is novel, the severity of an infection will depend on its haemagglutinin and neuraminidase, and other viral proteins, which enable the virus to reproduce better in human cells.

In fact, tissue damage has two origins – cells killed by the virus and the damage caused to the body's own cells by the immune system. Both Spanish flu and H5N1 avian flu replicate to high levels and provoke exceptionally powerful immune responses, which run away out of control in the lungs. Influenza viruses also leave patients at risk of secondary bacterial infections.

To date, S-OIV has caused comparatively mild symptoms in most people. Those who have died have usually but not always had underlying health problems, such as asthma or other respiratory ailments, morbid obesity or diabetes. Pregnant women are also at higher risk.

Flu pandemics typically affect younger age groups than seasonal flu. To date, H1N1 swine flu has had less impact on older groups, possibly because they retain immunity from earlier H1N1 epidemics or benefit from some crossover immunity from vaccination.

Infants and young children may be at risk because their immune systems are immature. Paradoxically, young adults may be at risk because they have the strongest immune systems.



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Civil liberties

Do human rights go out of the window when a pandemic strikes?

When a group of Mexicans landed in China shortly after the start of the H1N1 swine flu pandemic they were in for a surprise. They were immediately placed in quarantine.

However, preventing a disease such as flu from entering a country is almost impossible: in early stages of infection, people may show few if any symptoms. The number of places that an infection can enter a country is so large that control would be next to impossible without bringing the country to a virtual standstill.

To date, public health has focused on encouraging good infection control practices among the public. Is there a case for a more coercive approach? Certainly, if swine flu were to

become more severe, more draconian measures might be considered, such as preventing certain large gatherings, restricting the movement of infected people or enforcing vaccination.

Given the political consequences of such actions, they are likely to be made only after very careful consideration and when there is a substantial threat to public health.

It has been argued that part of the success in controlling SARS was because governments in the East were able to impose public restrictions rapidly and effectively. However, this virus has a different pattern of spread from influenza.

Politicians have the unenviable task of safeguarding public liberties and public health, and a country's economic wellbeing, in situations characterised by considerable uncertainty.

Who is doing what?

International and national bodies are implementing pandemic plans.

The international response to swine flu is coordinated by the **World Health Organization**, which decides pandemic levels (see page 3) and can act as a global coordinating body, particularly to support less developed countries. It has limited enforcement powers, however, so usually can only recommend particular courses of action.

The UK's response to swine flu is led by the **Department of Health** (in partnership with the devolved administrations), which receives input from a wide range of experts. Coordination across government and other key services is achieved through the high-level 'COBR' emergencies committee. The Department of Health has a pandemic plan, which has been adapted and implemented for swine flu; it includes stockpiling of drugs and commitments to purchase vaccines.

Monitoring of the pandemic has been the responsibility of the UK's **Health Protection Agency**, which has collected and disseminated data on the prevalence and spread of S-OIV.

The way in

Why are S-OIV and seasonal influenza viruses able to transmit so easily between people while H5N1 is still restricted mainly to birds?

One contributing factor is the structure of sugar molecules on the surface of cells, which affects the viruses' ability to infect and spread.

Influenza viruses bind to galactose-sialic acid disaccharides on the ends of long carbohydrate polymers, but they are sensitive to the way the two are chemically linked together. Some like $\alpha 2-3$ linkages; others prefer $\alpha 2-6$. In humans, $\alpha 2-6$ linkages predominate, while birds tend to have more $\alpha 2-3$ linkages. Pigs have both, so can act as mixing vessels for bird and human viruses.

So far, H5N1 has retained its preference for $\alpha 2-3$ linkages. However, an artificial H5 virus with a preference for $\alpha 2-6$ is viable, so would in theory be able to spread between people.

People, pigs and poultry have different sugar structures on the surface of their cells.

Influenza viruses bind to galactose-sialic acid disaccharides, which can be joined via positions 3 or 6 on galactose's carbon backbone. The resulting disaccharides differ slightly in their conformations, which affects their binding to different haemagglutinins: those from avian viruses prefer to stick to $\alpha 2-3$ -linked sugars; those from human viruses prefer $\alpha 2-6$ -linked sugars. As pig cells have both forms, they can be infected by both avian and human viruses.

Scientific input

Are we better off than we were during previous flu pandemics?

When Spanish flu hit in 1918, its cause was not known with certainty. The finger of blame was pointed at a bacterium, *Haemophilus influenzae*, often found in the lungs of people with flu. In fact, *H. influenzae* is an opportunistic pathogen, thriving as a patient succumbs to influenza virus. The virus causing human flu was not finally identified until 1933.

A flu **vaccine** came soon after – the US Army used vaccines during World War II. Flu vaccine production was insufficient for the pandemics of the 1950s and 1960s, but capacity is significantly greater now.

Antivirals were slower to arrive, first developed in the 1960s. Oseltamivir and zanamivir were approved in 1999. Neuraminidase inhibitors were rationally designed (built to bind to a specific site in the enzyme), so the emergence of resistance can be understood in molecular terms and (in theory) alternatives developed.

Another relatively new tool is **genome sequencing**. Viral genomes are short and can be sequenced rapidly. With many genome sequences available, the evolution of the virus can be mapped in fine detail. In conjunction with clinical information, such data may reveal genetic features responsible for enhanced virulence or other important traits, as well as patterns of gene swapping and virus spread.

Modelling is another new tool feeding into decision making. Computer simulations can be used to test the effects of outbreaks and various control measures, on scales ranging from the global to the local. Although inevitably simplifications, they can be refined as more is discovered about the virus and disease. While not the only factor influencing decision making, they can help to identify useful (or useless) interventions.

- To find out more about computer modelling, see 'Further info' at www.wellcome.ac.uk/bigpicture/influenza

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What's in a name?

Curiously, the name of the 2009 flu pandemic has proven controversial.

The name of a pandemic might seem like a trivial matter. Far from it.

Conventionally, pandemics have been named after the place they were first seen – so logically the 2009 pandemic should be known as 'Mexican flu'. However, Mexico has been understandably keen to avoid stigmatisation.

'Swine flu' rapidly gained ground as an acceptable alternative – despite a rearguard action from the pig livestock industry, fearful of anti-pig

sentiments leading to a consumer boycott of pig food products or mass slaughter, as seen in Egypt (an action with little scientific justification).

The World Health Organization first used 'influenza A(H1N1)' – hardly ideal as a strain of seasonal flu is also an H1N1 influenza (as was Spanish flu). It has now gone for 'pandemic (H1N1) 2009'.

Swine flu may have stuck, even though it is something of a misnomer – it is a disease of humans not of pigs.



Swine flu: Five key questions

● **Is H1N1 swine flu going to become more severe?**

It is not possible to say. Previous pandemics have sometimes come in waves of increasing severity, but there is no reason to believe that the virus will automatically become more severe over time.

● **Who is at risk?**

So far swine flu has been relatively mild for most people. Individuals with an underlying health problem (a respiratory condition such as asthma or diabetes) and pregnant women are at particular risk. Unlike seasonal flu, swine flu preferentially infects young adults rather than older people.

● **How many people are likely to be affected?**

It is difficult to say, but it could be up to 30 per cent of the population. This could translate to 19 000 deaths. This is fewer than first feared, and is similar to a bad year for seasonal flu.

● **Will a vaccine be ready in time for winter?**

Vaccines are due to be delivered in autumn and around half the population could be vaccinated this year. Priority will be given to at-risk individuals and groups such as healthcare workers.

● **Can we expect another pandemic in the future?**

Almost certainly. The influenza virus evolves rapidly and genetic mixing of human, pig and bird viruses is probably happening all the time in pigs. It is highly likely that a novel virus will find its way into humans in the future – emphasising the importance of ongoing surveillance. An H5N1 pandemic is a possibility, if the virus becomes able to transmit between people.

Online extras

Find out how viruses spread through populations in 'Sneeze'. This online game demonstrates that the likelihood of infection and speed of virus transmission varies depending on people's age and shows you how quickly a virus can spread.

Plus further information about flu, links to other resources and curriculum matching are all available:

www.wellcome.ac.uk/bigpicture/influenza



'Swine Flu' glass sculpture by Luke Jerram, acquired by Wellcome Collection. www.wellcomecollection.org



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