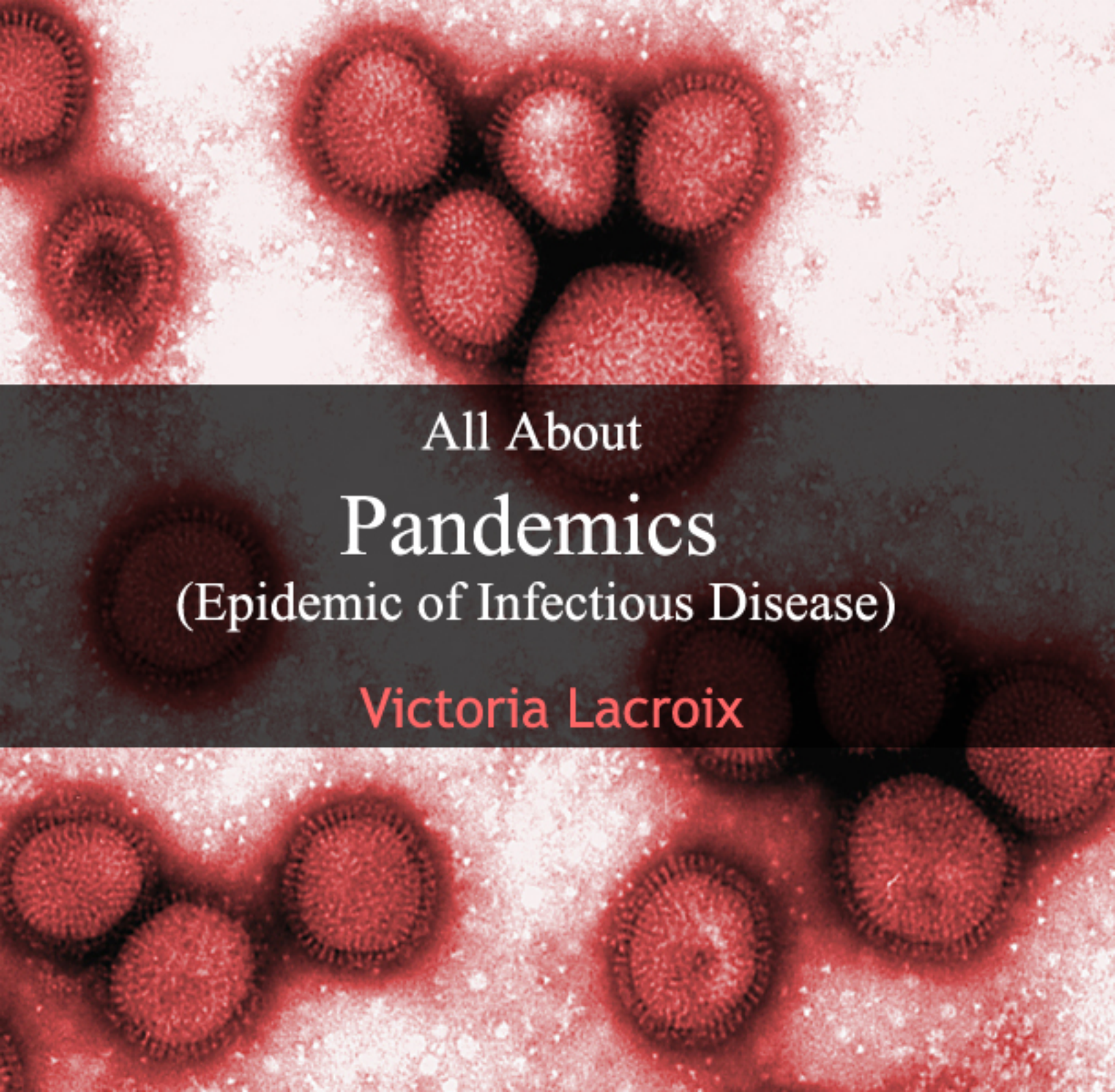
All About
Pandemics
(Epidemic of Infectious Disease)
Victoria Lacroix

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Introduction to Pandemic

A **pandemic** (from Greek πᾶν *pan* "all" + δῆμος *demos* "people") is an epidemic of infectious disease that is spreading through human populations across a large region; for instance a continent, or even worldwide. A widespread endemic disease that is stable in terms of how many people are getting sick from it is not a pandemic. Further, flu pandemics exclude seasonal flu, unless the flu of the season is a pandemic. Throughout history there have been a number of pandemics, such as smallpox and tuberculosis. More recent pandemics include the HIV pandemic and the 2009 flu pandemic.

Definition and stages

The World Health Organization (WHO) has produced a six-stage classification that describes the process by which a novel influenza virus moves from the first few infections in humans through to a pandemic. This starts with the virus mostly infecting animals, with a few cases where animals infect people, then moves through the stage where the virus begins to spread directly between people, and ends with a pandemic when infections from the new virus have spread worldwide.

A disease or condition is not a pandemic merely because it is widespread or kills many people; it must also be infectious. For instance, cancer is responsible for many deaths but is not considered a pandemic because the disease is not infectious or contagious.

In a virtual press conference in May 2009 on the influenza pandemic Dr Keiji Fukuda, Assistant Director-General ad Interim for Health Security and Environment, WHO said "An easy way to think about pandemic ... is to say: a pandemic is a global outbreak. Then you might ask yourself: “What is a global outbreak”? Global outbreak means that we see both spread of the agent ... and then we see disease activities in addition to the spread of the virus."

In planning for a possible influenza pandemic the WHO published a document on pandemic preparedness guidance in 1999, revised in 2005 and during the 2009 outbreak, defining phases and appropriate actions for each phase in an aide memoir entitled *WHO pandemic phase descriptions and main actions by phase*. All versions of this document refer to influenza. The phases are defined by the spread of the disease; virulence and mortality are not mentioned in the current WHO definition, although these factors have previously been included.

Current pandemics

2009 influenza A/H1N1

The 2009 outbreak of a new strain of Influenza A virus subtype H1N1 created concerns that a new pandemic was occurring. In the latter half of April 2009, the World Health Organization's pandemic alert level was sequentially increased from three to five until the announcement on 11 June 2009 that the pandemic level had been raised to its highest level, level six. This was the first pandemic on this level since 1968. Dr Margaret Chan, Director-General of the World Health Organization (WHO), gave a statement on 11 June 2009 confirming that the H1N1 strain was indeed a pandemic, having nearly 30,000 confirmed cases worldwide. The alleged pandemic, and the media attention, died out starting in November, with many critics soon claiming that the WHO hyped up the dangers, providing "fear and confusion" rather than "immediate information" about the pandemic. On August 10, 2010, the WHO announced that the pandemic was over.

HIV and AIDS

HIV spread to the United States and much of the rest of the world beginning around 1969. HIV, the virus that causes AIDS, is currently a pandemic, with infection rates as high as 25% in southern and eastern Africa. In 2006 the HIV prevalence rate among pregnant women in South Africa was 29.1%. Effective education about safer sexual practices and bloodborne infection precautions training have helped to slow down infection rates in several African countries sponsoring national education programs. Infection rates are rising again in Asia and the Americas. AIDS could kill 31 million people in India and 18 million in China by 2025, according to projections by U.N. population researchers. AIDS death toll in Africa may reach 90-100 million by 2025.

Pandemics and notable epidemics through history

There have been a number of significant pandemics recorded in human history, generally zoonoses which came about with domestication of animals, such as influenza and tuberculosis. There have been a number of particularly significant epidemics that deserve mention above the "mere" destruction of cities:

- Plague of Athens, 430 BC. Typhoid fever killed a quarter of the Athenian troops, and a quarter of the population over four years. This disease fatally weakened the dominance of Athens, but the sheer virulence of the disease prevented its wider spread; i.e. it killed off its hosts at a rate faster than they could spread it. The exact cause of the plague was unknown for many years. In January 2006, researchers from the University of Athens analyzed teeth recovered from a mass grave underneath the city, and confirmed the presence of bacteria responsible for typhoid.
- Antonine Plague, 165–180. Possibly smallpox brought to the Italian peninsula by soldiers returning from the Near East; it killed a quarter of those infected, and up

to five million in all. At the height of a second outbreak, the Plague of Cyprian (251–266), which may have been the same disease, 5,000 people a day were said to be dying in Rome.

- Plague of Justinian, from 541 to 750, was the first recorded outbreak of the bubonic plague. It started in Egypt, and reached Constantinople the following spring, killing (according to the Byzantine chronicler Procopius) 10,000 a day at its height, and perhaps 40% of the city's inhabitants. The plague went on to eliminate a quarter to a half of the human population that it struck throughout the known world. It caused Europe's population to drop by around 50% between 550 and 700.
- Black Death, started 14th century. The total number of deaths worldwide is estimated at 75 million people. Eight hundred years after the last outbreak, the plague returned to Europe. Starting in Asia, the disease reached Mediterranean and western Europe in 1348 (possibly from Italian merchants fleeing fighting in the Crimea), and killed an estimated 20 to 30 million Europeans in six years; a third of the total population, and up to a half in the worst-affected urban areas. It was the first of a cycle of European plague epidemics that continued until the 18th century. During this period, more than 100 plague epidemics swept across Europe. In England, for example, epidemics would continue in two to five-year cycles from 1361 to 1480. By the 1370s, England's population was reduced by 50%. The Great Plague of London of 1665–66 was the last major outbreak of the plague in England. The disease killed approximately 100,000 people, 20% of London's population.
- Third Pandemic, started in China in the middle of the 19th century, spreading plague to all inhabited continents and killing 10 million people in India alone. During this pandemic, the United States saw its first case of plague in 1900 in San Francisco. Today, isolated cases of plague are still found in the western United States.

Encounters between European explorers and populations in the rest of the world often introduced local epidemics of extraordinary virulence. Disease killed the entire native (Guanches) population of the Canary Islands in the 16th century. Half the native population of Hispaniola in 1518 was killed by smallpox. Smallpox also ravaged Mexico in the 1520s, killing 150,000 in Tenochtitlán alone, including the emperor, and Peru in the 1530s, aiding the European conquerors. Measles killed a further two million Mexican natives in the 17th century. In 1618–1619, smallpox wiped out 90% of the Massachusetts Bay Native Americans. During the 1770s, smallpox killed at least 30% of the Pacific Northwest Native Americans. Smallpox epidemics in 1780–1782 and 1837–1838 brought devastation and drastic depopulation among the Plains Indians. Some believe that the death of up to 95% of the Native American population of the New World was caused by Old World diseases such as smallpox, measles, and influenza. Over the centuries, the Europeans had developed high degrees of immunity to these diseases, while the indigenous peoples had no such immunity.

Smallpox devastated the native population of Australia, killing around 50% of Indigenous Australians in the early years of British colonisation. It also killed many New Zealand

Māori. As late as 1848–49, as many as 40,000 out of 150,000 Hawaiians are estimated to have died of measles, whooping cough and influenza. Introduced diseases, notably smallpox, nearly wiped out the native population of Easter Island. In 1875, measles killed over 40,000 Fijians, approximately one-third of the population. The disease devastated the Andamanese population. Ainu population decreased drastically in the 19th century, due in large part to infectious diseases brought by Japanese settlers pouring into Hokkaido.

Researchers concluded that syphilis was carried from the New World to Europe after Columbus' voyages. The findings suggested Europeans could have carried the nonvenereal tropical bacteria home, where the organisms may have mutated into a more deadly form in the different conditions of Europe. The disease was more frequently fatal than it is today. Syphilis was a major killer in Europe during the Renaissance. Between 1602 and 1796, the Dutch East India Company sent almost a million Europeans to work in the Asia. Ultimately, only less than one-third made their way back to Europe. The majority died of diseases. Disease killed more British soldiers in India than war. Between 1736 and 1834 only some 10% of East India Company's officers survived to take the final voyage home.

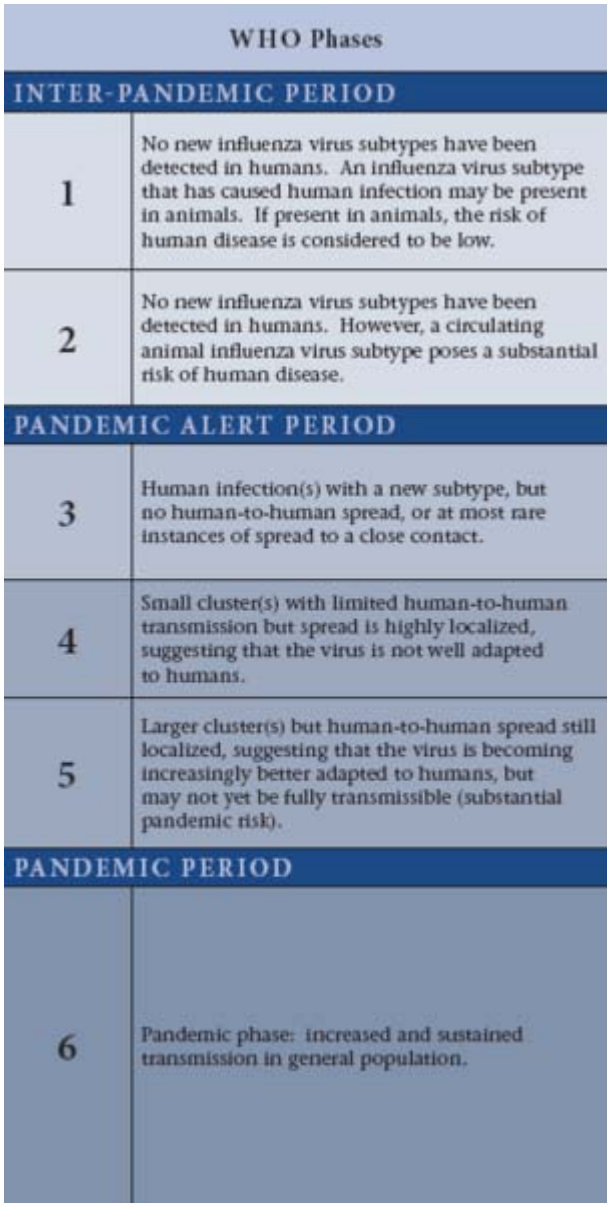
As early as 1803, the Spanish Crown organized a mission (the Balmis expedition) to transport the smallpox vaccine to the Spanish colonies, and establish mass vaccination programs there. By 1832, the federal government of the United States established a smallpox vaccination program for Native Americans. From the beginning of the 20th century onwards, the elimination or control of disease in tropical countries became a driving force for all colonial powers. The sleeping sickness epidemic in Africa was arrested due to mobile teams systematically screening millions of people at risk. In the 20th century, the world saw the biggest increase in its population in human history due to lessening of the mortality rate in many countries due to medical advances. The world population has grown from 1.6 billion in 1900 to an estimated 6.7 billion today.

Cholera

- First cholera pandemic 1816-1826. Previously restricted to the Indian subcontinent, the pandemic began in Bengal, then spread across India by 1820. 10,000 British troops and countless Indians died during this pandemic. It extended as far as China, Indonesia (where more than 100,000 people succumbed on the island of Java alone) and the Caspian Sea before receding. Deaths in India between 1817 and 1860 are estimated to have exceeded 15 million persons. Another 23 million died between 1865 and 1917. Russian deaths during a similar period exceeded 2 million.
- Second cholera pandemic 1829–1851. Reached Russia, Hungary (about 100,000 deaths) and Germany in 1831, London in 1832 (more than 55,000 persons died in the United Kingdom), France, Canada (Ontario), and United States (New York) in the same year, and the Pacific coast of North America by 1834. A two-year outbreak began in England and Wales in 1848 and claimed 52,000 lives. It is believed that over 150,000 Americans died of cholera between 1832 and 1849.

- Third pandemic 1852–1860. Mainly affected Russia, with over a million deaths. In 1852, cholera spread east to Indonesia and later invaded China and Japan in 1854. The Philippines were infected in 1858 and Korea in 1859. In 1859, an outbreak in Bengal again led to the transmission of the disease to Iran, Iraq, Arabia and Russia.
- Fourth pandemic 1863–1875. Spread mostly in Europe and Africa. At least 30,000 of the 90,000 Mecca pilgrims fell victim to the disease. Cholera claimed 90,000 lives in Russia in 1866.
- In 1866, there was an outbreak in North America. It killed some 50,000 Americans.
- Fifth pandemic 1881-1896. The 1883-1887 epidemic cost 250,000 lives in Europe and at least 50,000 in Americas. Cholera claimed 267,890 lives in Russia (1892); 120,000 in Spain; 90,000 in Japan and 60,000 in Persia.
- In 1892, cholera contaminated the water supply of Hamburg, and caused 8606 deaths.
- Sixth pandemic 1899–1923. Had little effect in Europe because of advances in public health, but Russia was badly affected again (more than 500,000 people dying of cholera during the first quarter of the 20th century). The sixth pandemic killed more than 800,000 in India. The 1902-1904 cholera epidemic claimed over 200,000 lives in the Philippines. 27 epidemics were recorded during pilgrimages to Mecca from the 19th century to 1930, and more than 20,000 pilgrims died of cholera during the 1907–08 hajj.
- Seventh pandemic 1962-66. Began in Indonesia, called El Tor after the strain, and reached Bangladesh in 1963, India in 1964, and the USSR in 1966.
- Eighth pandemic 1991-2002,

Influenza



World Health Organization influenza pandemic alert phases

- The Greek physician Hippocrates, the "Father of Medicine", first described influenza in 412 BCE.
- The first influenza pandemic was recorded in 1580 and since then influenza pandemics occurred every 10 to 30 years.
- The "Asiatic Flu", 1889–1890, was first reported in May 1889 in Bukhara, Uzbekistan. By October, it had reached Tomsk and the Caucasus. It rapidly spread west and hit North America in December 1889, South America in February–April 1890, India in February–March 1890, and Australia in March–April 1890. It was purportedly caused by the H2N8 type of flu virus. It had a very high attack and mortality rate. About 1 million people died in this pandemic."

- The "Spanish flu", 1918–1919. First identified early in March 1918 in US troops training at Camp Funston, Kansas. By October 1918, it had spread to become a worldwide pandemic on all continents, and eventually infected about one-third of the world's population (or ≈500 million persons). Unusually deadly and virulent, it ended nearly as quickly as it began, vanishing completely within 18 months. In six months, some 50 million were dead; some estimates put the total of those killed worldwide at over twice that number. About 17 million died in India, 675,000 in the United States and 200,000 in the UK. The virus was recently reconstructed by scientists at the CDC studying remains preserved by the Alaskan permafrost. The H1N1 virus has a small, but crucial structure that that is similar to the Spanish Flu.
- The "Asian Flu", 1957–58. An H2N2 virus caused about 70,000 deaths in the United States. First identified in China in late February 1957, the Asian flu spread to the United States by June 1957. It caused about 2 million deaths globally.
- The "Hong Kong Flu", 1968–69. An H3N2 caused about 34,000 deaths in the United States. This virus was first detected in Hong Kong in early 1968, and spread to the United States later that year. This pandemic of 1968 and 1969 killed approximately one million people worldwide. Influenza A (H3N2) viruses still circulate today.

Typhus

Typhus is sometimes called "camp fever" because of its pattern of flaring up in times of strife. (It is also known as "gaol fever" and "ship fever", for its habits of spreading wildly in cramped quarters, such as jails and ships.) Emerging during the Crusades, it had its first impact in Europe in 1489, in Spain. During fighting between the Christian Spaniards and the Muslims in Granada, the Spanish lost 3,000 to war casualties, and 20,000 to typhus. In 1528, the French lost 18,000 troops in Italy, and lost supremacy in Italy to the Spanish. In 1542, 30,000 soldiers died of typhus while fighting the Ottomans in the Balkans.

During the Thirty Years' War (1618–1648), about 8 million Germans were wiped out by bubonic plague and typhus fever. The disease also played a major role in the destruction of Napoleon's *Grande Armée* in Russia in 1812. Felix Markham thinks that 450,000 soldiers crossed the Neman on 25 June 1812, of whom less than 40,000 recrossed in anything like a recognizable military formation. In early 1813 Napoleon raised a new army of 500,000 to replace his Russian losses. In the campaign of that year over 219,000 of Napoleon's soldiers were to die of typhus. Typhus played a major factor in the Irish Potato Famine. During the World War I, typhus epidemics have killed over 150,000 in Serbia. There were about 25 million infections and 3 million deaths from epidemic typhus in Russia from 1918 to 1922. Typhus also killed numerous prisoners in the Nazi concentration camps and Soviet prisoner of war camps during World War II. More than 3.5 million Soviet POWs died in the Nazi custody out of 5.7 million.

Smallpox

Smallpox is a highly contagious disease caused by the Variola virus. The disease killed an estimated 400,000 Europeans per year during the closing years of the 18th century. During the 20th century, it is estimated that smallpox was responsible for 300–500 million deaths. As recently as early 1950s an estimated 50 million cases of smallpox occurred in the world each year. After successful vaccination campaigns throughout the 19th and 20th centuries, the WHO certified the eradication of smallpox in December 1979. To this day, smallpox is the only human infectious disease to have been completely eradicated.

Measles

Historically, measles was prevalent throughout the world, as it is highly contagious. According to the National Immunization Program, 90% of people were infected with measles by age 15. Before the vaccine was introduced in 1963, there were an estimated 3-4 million cases in the U.S. each year. In roughly the last 150 years, measles has been estimated to have killed about 200 million people worldwide. In 2000 alone, measles killed some 777,000 worldwide. There were some 40 million cases of measles globally that year.

Measles is an endemic disease, meaning that it has been continually present in a community, and many people develop resistance. In populations that have not been exposed to measles, exposure to a new disease can be devastating. In 1529, a measles outbreak in Cuba killed two-thirds of the natives who had previously survived smallpox. The disease had ravaged Mexico, Central America, and the Inca civilization.

Tuberculosis

One–third of the world's current population has been infected with *Mycobacterium tuberculosis*, and new infections occur at a rate of one per second. About 5-10% of these latent infections will eventually progress to active disease, which, if left untreated, kills more than half of its victims. Annually, 8 million people become ill with tuberculosis, and 2 million people die from the disease worldwide. In the 19th century, tuberculosis killed an estimated one-quarter of the adult population of Europe; and by 1918 one in six deaths in France were still caused by TB. By the late 19th century, 70 to 90% of the urban populations of Europe and North America were infected with *M. tuberculosis*, and about 40% of working-class deaths in cities were from TB. During the 20th century, tuberculosis killed approximately 100 million people. TB is still one of the most important health problems in the developing world.

Leprosy

Leprosy, also known as Hansen's Disease, is caused by a bacillus, *Mycobacterium leprae*. It is a chronic disease with an incubation period of up to five years. Since 1985, 15 million people worldwide have been cured of leprosy. In 2002, 763,917 new cases were detected. It is estimated that there are between one and two million people permanently disabled because of leprosy.

Historically, leprosy has affected people since at least 600 BCE, and was well-recognized in the civilizations of ancient China, Egypt and India. During the High Middle Ages, Western Europe witnessed an unprecedented outbreak of leprosy. Numerous *leprosaria*, or leper hospitals, sprang up in the Middle Ages; Matthew Paris estimated that in the early 13th century there were 19,000 across Europe.

Malaria

Malaria is widespread in tropical and subtropical regions, including parts of the Americas, Asia, and Africa. Each year, there are approximately 350–500 million cases of malaria. Drug resistance poses a growing problem in the treatment of malaria in the 21st century, since resistance is now common against all classes of antimalarial drugs, except for the artemisinins.

Malaria was once common in most of Europe and North America, where it is now for all purposes non-existent. Malaria may have contributed to the decline of the Roman Empire. The disease became known as "Roman fever". *Plasmodium falciparum* became a real threat to colonists and indigenous people alike when it was introduced into the Americas along with the slave trade. Malaria devastated the Jamestown colony and regularly ravaged the South and Midwest. By 1830 it had reached the Pacific Northwest. During the American Civil War, there were over 1.2 million cases of malaria among soldiers of both sides. The southern U.S. continued to be afflicted with millions of cases of malaria into the 1930s.

Yellow fever

Yellow fever has been a source of several devastating epidemics. Cities as far north as New York, Philadelphia, and Boston were hit with epidemics. In 1793, one of the largest yellow fever epidemics in U.S. history killed as many as 5,000 people in Philadelphia—roughly 10% of the population. About half of the residents had fled the city, including President George Washington. Approximately 300,000 people are believed to have died from yellow fever in Spain during the 19th century. In colonial times, West Africa became known as "the white man's grave" because of malaria and yellow fever.

Unknown causes

There are also a number of unknown diseases that were extremely serious but have now vanished, so the etiology of these diseases cannot be established. The cause of *English Sweat* in 16th-century England, which struck people down in an instant and was more greatly feared than even the bubonic plague, is still unknown.

Concern about possible future pandemics

Viral hemorrhagic fevers

Some Viral Hemorrhagic Fever causing agents like Lassa fever, Rift Valley fever, Marburg virus, Ebola virus and Bolivian hemorrhagic fever are highly contagious and deadly diseases, with the theoretical potential to become pandemics. Their ability to spread efficiently enough to cause a pandemic is limited, however, as transmission of these viruses requires close contact with the infected vector, and the vector only has a short time before death or serious illness. Furthermore, the short time between a vector becoming infectious and the onset of symptoms allows medical professionals to quickly quarantine vectors, and prevent them from carrying the pathogen elsewhere. Genetic mutations could occur, which could elevate their potential for causing widespread harm; thus close observation by contagious disease specialists is merited.

Antibiotic resistance

Antibiotic-resistant microorganisms, sometimes referred to as "superbugs", may contribute to the re-emergence of diseases which are currently well-controlled. For example, cases of tuberculosis that are resistant to traditionally effective treatments remain a cause of great concern to health professionals. Every year, nearly half a million new cases of multidrug-resistant tuberculosis (MDR-TB) are estimated to occur worldwide. After India, China has the highest rate of multidrug-resistant TB. The World Health Organization (WHO) reports that approximately 50 million people worldwide are infected with MDR TB, with 79 percent of those cases resistant to three or more antibiotics. In 2005, 124 cases of MDR TB were reported in the United States. Extensively drug-resistant tuberculosis (XDR TB) was identified in Africa in 2006, and subsequently discovered to exist in 49 countries, including the United States. About 40,000 new cases of XDR-TB emerge every year, the WHO estimates.

The plague bacterium *Yersinia pestis* could develop drug-resistance and become a major health threat. Plague epidemics have occurred throughout human history, causing over 200 million deaths worldwide. The ability to resist many of the antibiotics used against plague has been found so far in only a single case of the disease in Madagascar.

In the past 20 years, common bacteria including *Staphylococcus aureus*, *Serratia marcescens* and Enterococcus, have developed resistance to various antibiotics such as vancomycin, as well as whole classes of antibiotics, such as the aminoglycosides and cephalosporins. Antibiotic-resistant organisms have become an important cause of healthcare-associated (nosocomial) infections (HAI). In addition, infections caused by community-acquired strains of methicillin-resistant *Staphylococcus aureus* (MRSA) in otherwise healthy individuals have become more frequent in recent years.

Inappropriate antibiotic treatment and overuse of antibiotics have been an element in the emergence of resistant bacteria. The problem is further exacerbated by self-prescribing of antibiotics by individuals without the guidelines of a qualified clinician and the non-therapeutic use of antibiotics as growth promoters in agriculture.

SARS

In 2003, there were concerns that Severe Acute Respiratory Syndrome (SARS), a new and highly contagious form of atypical pneumonia, might become pandemic. It is caused by a coronavirus dubbed SARS-CoV. Rapid action by national and international health authorities such as the World Health Organization helped to slow transmission and eventually broke the chain of transmission. That ended the localized epidemics before they could become a pandemic. However, the disease has not been eradicated. It could re-emerge. This warrants monitoring and reporting of suspicious cases of atypical pneumonia.

Influenza

Wild aquatic birds are the natural hosts for a range of influenza A viruses. Occasionally, viruses are transmitted from these species to other species, and may then cause outbreaks in domestic poultry or, rarely, in humans.

H5N1 (Avian Flu)

In February 2004, avian influenza virus was detected in birds in Vietnam, increasing fears of the emergence of new variant strains. It is feared that if the avian influenza virus combines with a human influenza virus (in a bird or a human), the new subtype created could be both highly contagious and highly lethal in humans. Such a subtype could cause a global influenza pandemic, similar to the Spanish Flu, or the lower mortality pandemics such as the Asian Flu and the Hong Kong Flu.

From October 2004 to February 2005, some 3,700 test kits of the 1957 Asian Flu virus were accidentally spread around the world from a lab in the US.

In May 2005, scientists urgently call nations to prepare for a global influenza pandemic that could strike as much as 20% of the world's population.

In October 2005, cases of the avian flu (the deadly strain H5N1) were identified in Turkey. EU Health Commissioner Markos Kyprianou said: "We have received now confirmation that the virus found in Turkey is an avian flu H5N1 virus. There is a direct relationship with viruses found in Russia, Mongolia and China." Cases of bird flu were also identified shortly thereafter in Romania, and then Greece. Possible cases of the virus have also been found in Croatia, Bulgaria and the United Kingdom.

By November 2007, numerous confirmed cases of the H5N1 strain had been identified across Europe. However, by the end of October only 59 people had died as a result of H5N1 which was atypical of previous influenza pandemics.

Avian flu cannot yet be categorized as a "pandemic", because the virus cannot yet cause sustained and efficient human-to-human transmission. Cases so far are recognized to have been transmitted from bird to human, but as of December 2006 there have been very few (if any) cases of proven human-to-human transmission. Regular influenza viruses establish infection by attaching to receptors in the throat and lungs, but the avian

influenza virus can only attach to receptors located deep in the lungs of humans, requiring close, prolonged contact with infected patients, and thus limiting person-to-person transmission.

Biological warfare

In 1346, the bodies of Mongol warriors who had died of plague were thrown over the walls of the besieged Crimean city of Kaffa (now Theodosia). After a protracted siege, during which the Mongol army under Jani Beg was suffering the disease, they catapulted the infected corpses over the city walls to infect the inhabitants. It has been speculated that this operation may have been responsible for the arrival of the Black Death in Europe.

The Native American population was devastated after contact with the Old World due to the introduction of many different fatal diseases. There is, however, only one documented case of germ warfare, involving British commander Jeffrey Amherst and Swiss-British officer Colonel Henry Bouquet, whose correspondence included a reference to the idea of giving smallpox-infected blankets to Indians as part of an incident known as Pontiac's Rebellion which occurred during the Siege of Fort Pitt (1763) late in the French and Indian War. It is uncertain whether this documented British attempt successfully infected the Indians.

During the Sino-Japanese War (1937–1945), Unit 731 of the Imperial Japanese Army conducted human experimentation on thousands, mostly Chinese. In military campaigns, the Japanese army used biological weapons on Chinese soldiers and civilians. Plague fleas, infected clothing, and infected supplies encased in bombs were dropped on various targets. The resulting cholera, anthrax, and plague were estimated to have killed around 400,000 Chinese civilians.

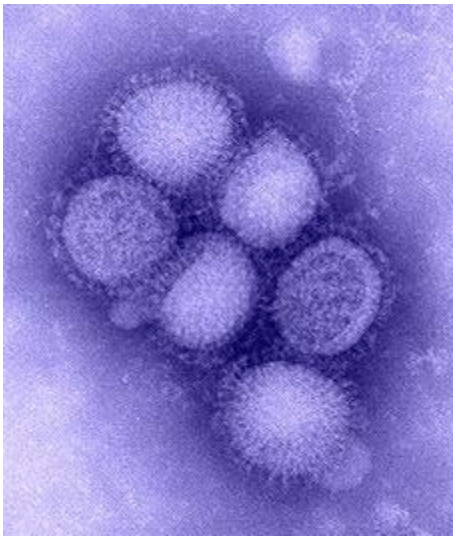
Diseases considered for or known to be used as a weapon include anthrax, ebola, Marburg virus, plague, cholera, typhus, Rocky Mountain spotted fever, tularemia, brucellosis, Q fever, machupo, Coccidioides mycosis, Glanders, Melioidosis, Shigella, Psittacosis, Japanese B encephalitis, Rift Valley fever, yellow fever, and smallpox.

Spores of weaponized anthrax were accidentally released from a military facility near the Soviet closed city of Sverdlovsk in 1979. The Sverdlovsk anthrax leak is sometimes called "biological Chernobyl". China possibly suffered a serious accident at one of its biological weapons plants in the late 1980s. The Soviets suspected that two separate epidemics of hemorrhagic fever that swept the region in the late 1980s were caused by an accident in a lab where Chinese scientists were weaponizing viral diseases. In January 2009, an Al-Qaeda training camp in Algeria had been wiped out by the plague, killing approximately 40 Islamic extremists. Experts said that the group was developing biological weapons. A couple of days later the Algerian Health Ministry flatly denied this rumour stating "No case of plague of any type has been recorded in any region of Algeria since 2003"

Chapter- 2

2009 Flu Pandemic

Pandemic H1N1/09 Influenza



Electron microscope image of the reassorted H1N1 influenza virus. The viruses are ~100 nanometres in diameter.

MedlinePlus 007421

MeSH D053118

The **2009 flu pandemic** was a global outbreak of a new strain of H1N1 influenza virus, often referred to as "swine flu". First described in April 2009, the virus appeared to be a new strain of H1N1 which resulted when a previous triple reassortment of bird, pig and human flu viruses further combined with a Eurasian pig flu virus. Unlike most strains of influenza, H1N1 does not disproportionately infect adults older than 60 years; this was an unusual and characteristic feature of the H1N1 pandemic. Even in the case of previously very healthy persons, a small percentage will develop pneumonia or acute respiratory

distress syndrome. This manifests itself as increased breathing difficulty and typically occurs 3–6 days after initial onset of flu symptoms. The pneumonia caused by flu can be either direct viral pneumonia or a secondary bacterial pneumonia. In fact, a November 2009 *New England Journal of Medicine* article recommends that flu patients whose chest X-ray indicates pneumonia receive both antivirals and antibiotics. In particular, it is a warning sign if a child (and presumably an adult) seems to be getting better and then relapses with high fever, as this relapse may be bacterial pneumonia.

The outbreak began in the state of Veracruz, Mexico, with evidence that there had been an ongoing epidemic for months before it was officially recognized as such. The Mexican government closed most of Mexico City's public and private facilities in an attempt to contain the spread of the virus; however, it continued to spread globally, and clinics in some areas were overwhelmed by infected people. In June, the World Health Organization (WHO) and US Centers for Disease Control (CDC) stopped counting cases and declared the outbreak a pandemic.

Despite being informally called "swine flu", the H1N1 flu virus cannot be spread by eating pork or pork products; similar to other influenza viruses, it is typically contracted by person to person transmission through respiratory droplets. Symptoms usually last 4–6 days. Antivirals (oseltamivir or zanamivir) were recommended for those with more severe symptoms or those in an at-risk group. Currently, there are 14,286 confirmed deaths worldwide. This figure is a sum of confirmed deaths reported by national authorities; the WHO states that total mortality (including deaths unconfirmed or unreported) from the new H1N1 strain is "unquestionably higher".

The pandemic began to taper off in November 2009, and by May 2010, the number of cases was in steep decline. On 10 August 2010, the Director-General of the World Health Organization, Margaret Chan, announced the end of the H1N1 pandemic. Chan noted that the H1N1 pandemic could have been much worse. According to the latest WHO statistics, the virus has killed more than 18,000 people since it appeared in April 2009, approximately 4% of the 250,000 to 500,000 annual influenza deaths. Research released in September 2010 disclosed that children with the pandemic flu were less likely to develop complications than those sick with seasonal flu strains, contradicting early reports on the severity of the pandemic. Critics claimed the WHO had exaggerated the danger, spreading "fear and confusion" rather than "immediate information". The WHO began an investigation to determine whether it had "frightened people unnecessarily".

Classification

The initial outbreak was called the "H1N1 influenza", or "Swine Flu" by American media. It is called pandemic H1N1/09 virus by the World Health Organization, while the U.S. Centers for Disease Control refer to it as "novel influenza A (H1N1)" or "2009 H1N1 flu". In the Netherlands, it was originally called "Pig Flu", but is now called "New Influenza A (H1N1)" by the national health institute, although the media and general population use the name "Mexican Flu". South Korea and Israel briefly considered calling it the "Mexican virus". Later, the South Korean press used "SI", short for "swine

influenza". Taiwan suggested the names "H1N1 flu" or "new flu", which most local media adopted. The World Organization for Animal Health proposed the name "North American influenza". The European Commission adopted the term "novel flu virus".

Signs and symptoms

The symptoms of H1N1 flu are similar to those of other influenzas, and may include a fever, cough (typically a "dry cough"), headache, muscle or joint pain, sore throat, chills, fatigue, and runny nose. Diarrhoea, vomiting, and neurological problems have also been reported in some cases. People at higher risk of serious complications include those aged over 65, children younger than 5, children with neurodevelopmental conditions, pregnant women (especially during the third trimester), and those of any age with underlying medical conditions, such as asthma, diabetes, obesity, heart disease, or a weakened immune system (e.g., taking immunosuppressive medications or infected with HIV). More than 70% of hospitalizations in the U.S. have been people with such underlying conditions, according to the CDC.

In September 2009, the CDC reported that the H1N1 flu "seems to be taking a heavier toll among chronically ill children than the seasonal flu usually does." Through 8 August 2009, the CDC had received 36 reports of paediatric deaths with associated influenza symptoms and laboratory-confirmed pandemic H1N1 from state and local health authorities within the United States, with 22 of these children having neurodevelopmental conditions such as cerebral palsy, muscular dystrophy, or developmental delays. "Children with nerve and muscle problems may be at especially high risk for complications because they cannot cough hard enough to clear their airways". From 26 April 2009, to 13 February 2010, the CDC had received reports of the deaths of 277 children with laboratory-confirmed 2009 influenza A (H1N1) within the United States.

Symptoms in severe cases

The World Health Organization reports that the clinical picture in severe cases is strikingly different from the disease pattern seen during epidemics of seasonal influenza. While people with certain underlying medical conditions are known to be at increased risk, many severe cases occur in previously healthy people. In severe cases, patients generally begin to deteriorate around three to five days after symptom onset. Deterioration is rapid, with many patients progressing to respiratory failure within 24 hours, requiring immediate admission to an intensive care unit. Upon admission, most patients need immediate respiratory support with mechanical ventilation.

A November 2009 CDC recommendation stated that the following constitute "emergency warning signs" and advised seeking immediate care if a person experiences any one of these signs:

In adults:

- Difficulty breathing or shortness of breath

- Pain or pressure in the chest or abdomen
- Sudden dizziness
- Confusion
- Severe or persistent vomiting
- Low temperature

In children:

- Fast breathing or working hard to breathe
- Bluish skin color
- Not drinking enough fluids
- Not waking up or not interacting
- Being so irritable that the child does not want to be held
- Flu-like symptoms which improve but then return with fever and worse cough
- Fever with a rash
- Being unable to eat
- Having no tears when crying

Research later indicated that the severe flu effects in healthy young and middle-aged adults are caused by an excessive immune response.

Complications

Most complications have occurred among previously healthy individuals, with obesity and respiratory disease as the strongest risk factors. Pulmonary complications are common. Primary influenza pneumonia occurs most commonly in adults and may progress rapidly to acute lung injury requiring mechanical ventilation. Secondary bacterial infection is more common in children. *Staphylococcus aureus*, including methicillin-resistant strains, is an important cause of secondary bacterial pneumonia with a high mortality rate. Neuromuscular and cardiac complications are unusual but may occur.

A United Kingdom investigation of risk factors for hospitalisation and poor outcome with pandemic A/H1N1 influenza looked at 631 patients from 55 hospitals admitted with confirmed infection from May through September 2009. 13% were admitted to a high dependency or intensive care unit and 5% died; 36% were aged <16 years and 5% were aged ≥65 years. Non-white and pregnant patients were over-represented. 45% of patients had at least one underlying condition, mainly asthma, and 13% received antiviral drugs before admission. Of 349 with documented chest x-rays on admission, 29% had evidence of pneumonia, but bacterial co-infection was uncommon. Multivariate analyses showed that physician-recorded obesity on admission and pulmonary conditions other than asthma or chronic obstructive pulmonary disease (COPD) were associated with a severe outcome, as were radiologically confirmed pneumonia and a raised C-reactive protein (CRP) level (≥100 mg/l). 59% of all in-hospital deaths occurred in previously healthy people.

Fulminant (sudden-onset) myocarditis has been linked to infection with H1N1, with at least four cases of myocarditis confirmed in patients also infected with A/H1N1. Three out of the four cases of H1N1-associated myocarditis were classified as fulminant, and one of the patients died. Also, there appears to be a link between severe A/H1N1 influenza infection and pulmonary embolism. In one report, 5 out of 14 patients admitted to the intensive care unit with severe A/H1N1 infection were found to have pulmonary emboli.

An article published in *JAMA* in September 2010 challenged previous reports and stated that children infected in the 2009 flu pandemic were no more likely to be hospitalised with complications or get pneumonia than those who catch seasonal strains. Researchers found that about 1.5 percent of children with the H1N1 swine flu strain were hospitalised within 30 days, compared with 3.7 percent of those sick with a seasonal strain of H1N1 and 3.1 percent with an H3N2 virus.

Diagnosis

Confirmed diagnosis of pandemic H1N1 flu requires testing of a nasopharyngeal, nasal or oropharyngeal tissue swab from the patient. Real-time RT-PCR is the recommended test as others are unable to differentiate between pandemic H1N1 and regular seasonal flu. However, most people with flu symptoms do not need a test for pandemic H1N1 flu specifically, because the test results usually do not affect the recommended course of treatment. The U.S. CDC recommend testing only for people who are hospitalised with suspected flu, pregnant women and people with weakened immune systems. For the mere diagnosis of influenza and not pandemic H1N1 flu specifically, more widely available tests include rapid influenza diagnostic tests (RIDT), which yield results in about 30 minutes, and direct and indirect immunofluorescence assays (DFA and IFA), which take 2–4 hours. Due to the high rate of RIDT false negatives, the CDC advise that patients with illnesses compatible with novel influenza A (H1N1) virus infection but with negative RIDT results should be treated empirically based on the level of clinical suspicion, underlying medical conditions, severity of illness and risk for complications, and if a more definitive determination of infection with influenza virus is required, testing with rRT-PCR or virus isolation should be performed. Dr. Rhonda Medows of the Georgia Department of Community Health states that the rapid tests are incorrect anywhere from 30 to 90% of the time and warns doctors in her state not to use them because they are wrong so often. The use of RIDTs has also been questioned by researcher Paul Schreckenberger of the Loyola University Health System, who suggests that rapid tests may actually pose a dangerous public health risk. Dr. Nikki Shindo of the WHO has expressed regret at reports of treatment being delayed by waiting for H1N1 test results and suggests, "[D]octors should not wait for the laboratory confirmation but make diagnosis based on clinical and epidemiological backgrounds and start treatment early".

On 22 June 2010, the CDC announced a new test called the "CDC Influenza 2009 A (H1N1)pdm Real-Time RT-PCR Panel (IVD)". It uses a molecular biology technique to detect influenza A viruses and specifically the 2009 H1N1 virus. The new test will replace the previous real-time RT-PCR diagnostic test used during the 2009 H1N1

pandemic, which received an emergency use authorisation from the U.S. Food and Drug Administration in April 2009. Tests results are available in 4 hours and are 96% accurate.

Virus characteristics

The virus was found to be a novel strain of influenza for which extant vaccines against seasonal flu provided little protection. A study at the U.S. Centers for Disease Control and Prevention published in May 2009 found that children had no preexisting immunity to the new strain but that adults, particularly those over 60, had some degree of immunity. Children showed no cross-reactive antibody reaction to the new strain, adults aged 18 to 64 had 6–9%, and older adults 33%. While it has been thought that these findings suggest the partial immunity in older adults may be due to previous exposure to similar seasonal influenza viruses, a November 2009 study of a rural unvaccinated population in China found only a 0.3% cross-reactive antibody reaction to the H1N1 strain, suggesting that previous vaccinations for seasonal flu and not exposure may have resulted in the immunity found in the older U.S. population.

It has been determined that the strain contains genes from five different flu viruses: North American swine influenza, North American avian influenza, human influenza and two swine influenza viruses typically found in Asia and Europe. Further analysis has shown that several proteins of the virus are most similar to strains that cause mild symptoms in humans, leading virologist Wendy Barclay to suggest on 1 May 2009 that the initial indications are that the virus was unlikely to cause severe symptoms for most people.

The virus is currently less lethal than previous pandemic strains and kills about 0.01–0.03% of those infected; the 1918 influenza was about one hundred times more lethal and had a case fatality rate of 2–3%. By 14 November 2009, the virus had infected one in 6 Americans with 200,000 hospitalisations and 10,000 deaths – as many hospitalizations and fewer deaths than in an average flu season overall, but with much higher risk for those under 50. With deaths of 1,100 children and 7,500 adults 18 to 64, these figures "are much higher than in a usual flu season".

In June 2010, scientists from Hong Kong reported discovery of a new swine flu virus which is a hybrid of the pandemic H1N1 virus and viruses previously found in pigs. It is the first report of a reassortment of the pandemic virus, which in humans has been slow to evolve. Nancy Cox, head of the influenza division at the U.S. Centers for Disease Control, has said, "This particular paper is extremely interesting because it demonstrates for the first time what we had worried about at the very onset of the pandemic, and that is that this particular virus, when introduced into pigs, could reassort with the resident viruses in pigs and we would have new gene constellations. And bingo, here we are." Pigs have been termed the mixing vessel of flu because they can be infected both by avian flu viruses, which rarely directly infect people, and by human viruses. When pigs become simultaneously infected with more than one virus, the viruses can swap genes, producing new variants which can pass to humans and sometimes spread amongst them. "Unlike the situation with birds and humans, we have a situation with pigs and humans

where there's a two-way street of exchange of viruses. With pigs it's very much a two-way street".

Transmission

Spread of the H1N1 virus is thought to occur in the same way that seasonal flu spreads. Flu viruses are spread mainly from person to person through coughing or sneezing by people with influenza. Sometimes people may become infected by touching something – such as a surface or object – with flu viruses on it and then touching their face. "Avoid touching your eyes, nose or mouth. Germs spread this way".

The basic reproduction number (the average number of other individuals whom each infected individual will infect, in a population which has no immunity to the disease) for the 2009 novel H1N1 is estimated to be 1.75. A December 2009 study found that the transmissibility of the H1N1 influenza virus in households is lower than that seen in past pandemics. Most transmissions occur soon before or after the onset of symptoms.

The H1N1 virus has been transmitted to animals, including swine, turkeys, ferrets, household cats, at least one dog and a cheetah.

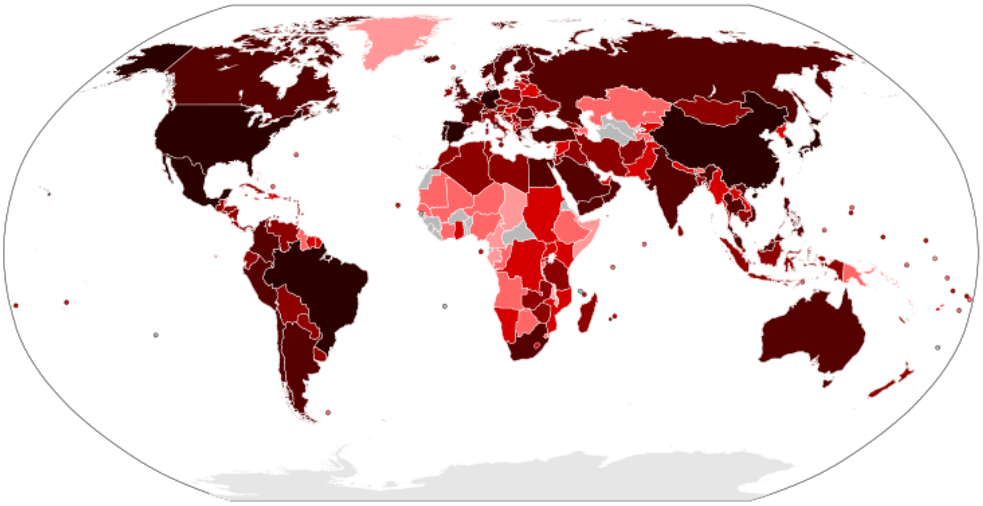
Prevention

The H1N1 vaccine was initially in short supply and in the U.S., the CDC recommended that initial doses should go to priority groups such as pregnant women, people who live with or care for babies under six months old, children 6 months to 4 years old and health-care workers. In the UK, the NHS recommended vaccine priority go to people over 6 months old who were clinically at risk for seasonal flu, pregnant women and households of people with compromised immunity.

Although it was initially thought that two injections would be required, clinical trials showed that the new vaccine protected adults "with only one dose instead of two", and so the limited vaccine supplies would go twice as far as had been predicted. Health officials worldwide were also concerned because the virus was new and could easily mutate and become more virulent, even though most flu symptoms were mild and lasted only a few days without treatment. Officials also urged communities, businesses and individuals to make contingency plans for possible school closures, multiple employee absences for illness, surges of patients in hospitals and other effects of potentially widespread outbreaks.

In February 2010, the CDC's Advisory Committee on Immunization Practices voted for "universal" flu vaccination in the U.S. to include all people over six months of age. The 2010-2011 vaccine will protect against the 2009 H1N1 pandemic virus and two other flu viruses.

Public health response

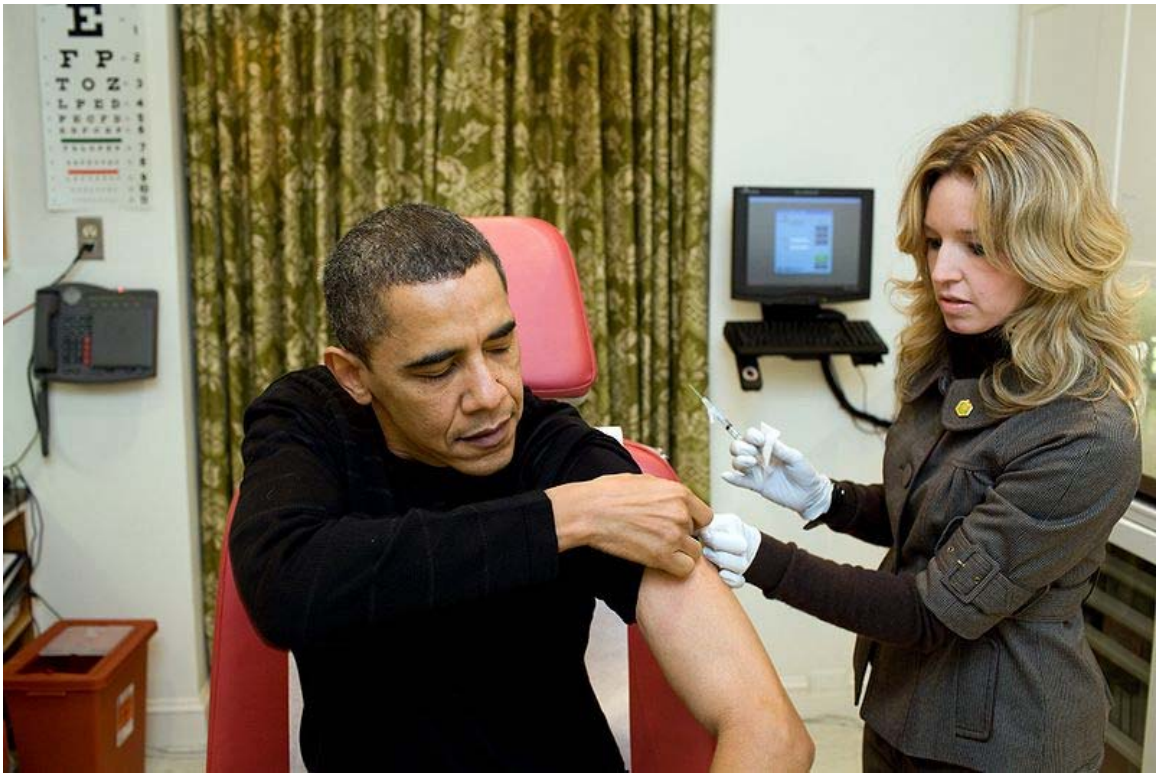


5,000+ confirmed cases
500+ confirmed cases
50+ confirmed cases
5+ confirmed cases
1+ confirmed cases

On 27 April 2009, the European Union health commissioner advised Europeans to postpone nonessential travel to the United States or Mexico. This followed the discovery of the first confirmed case in Spain. On 6 May 2009, the Public Health Agency of Canada announced that their National Microbiology Laboratory (NML) had mapped the genetic code of the swine flu virus, the first time that had been done. In the U.K., the National Health Service launched a website, the National Pandemic Flu Service, allowing patients to self-assess and get an authorisation number for antiviral medication. The system was expected to reduce the burden on general practitioners.

U.S. officials observed that 6 years of concern about H5N1 avian flu did much to prepare for the current H1N1 flu outbreak, noting that after H5N1 emerged in Asia, ultimately killing about 60% of the few hundred people infected by it over the years, many countries took steps to try to prevent any similar crisis from spreading further. The CDC and other American governmental agencies used the summer lull to take stock of the United States' response to H1N1 flu and attempt to patch any gaps in the public health safety net before flu season started in early autumn. Preparations included planning a second influenza vaccination program in addition to that for seasonal influenza, and improving coordination between federal, state and local governments and private health providers. On 24 October 2009, U.S. President Obama declared swine flu a national emergency, giving Secretary of Health and Human Services Kathleen Sebelius authority to grant waivers to requesting hospitals from usual federal requirements.

Vaccines



U.S. President Barack Obama being vaccinated against H1N1 flu onDecember 20, 2009, long after the pandemic had subsided in the U.S.

As of 19 November 2009, over 65 million doses of vaccine had been administered in over 16 countries; the vaccine seems safe and effective, producing a strong immune response that should protect against infection. Whereas the 2009 trivalent seasonal influenza vaccine neither increases nor decreases the risk of infection with H1N1, the vaccines rushed to combat the new strain are effective against H1N1, although they are manufactured similarly. Overall the safety profile of the new H1N1 vaccine is similar to that of the seasonal flu vaccine, and as of November 2009 fewer than a dozen cases of Guillain-Barre syndrome had been reported post-vaccination. Only a few of these were suspected to be actually related to the H1N1 vaccination, and only temporary illness had been observed. This is in strong contrast to the 1976 swine flu outbreak, when mass vaccinations in the United States caused over 500 cases of Guillain-Barre syndrome and led to 25 deaths. Although the vaccines were effective, many industrialised nations were giving away, selling, canceling orders for and destroying excess doses of the vaccine.

There are safety concerns for people who are allergic to eggs because the viruses for the vaccine are grown in chicken-egg-based cultures. People with egg allergies may be able to receive the vaccine, after consultation with their physician, in graded doses in a careful and controlled environment. A vaccine manufactured by Baxter is made without using eggs, but requires 2 doses 3 weeks apart to produce immunity.

As of late November 2009, in Canada there had been 24 confirmed cases of anaphylactic shock following vaccination, including one death. The estimated rate is one anaphylactic

reaction per 312,000 persons receiving the vaccine; however, 6 persons had suffered anaphylaxis out of 157,000 doses given from one batch of vaccine. Dr. David Butler-Jones, Canada's chief public health officer, stated that even though this was an adjuvanted vaccine, that did not appear to be the cause of this severe allergic reaction in these 6 patients.

Accusations of conflict of interest

In January 2010, Wolfgang Wodarg, a German Social Democrat deputy who trained as a doctor and now chairs the health committee at the Council of Europe, claimed major firms had organised a "campaign of panic" to put pressure on the World Health Organisation (WHO) to declare a "false pandemic" to sell vaccines. Dr. Wodarg said the WHO's "false pandemic" flu campaign is "one of the greatest medicine scandals of the century". He said that the "false pandemic" campaign began last May in Mexico City, when a hundred or so "normal" reported influenza cases were declared to be the beginning of a threatening new pandemic, although he said there was little scientific evidence for this. Nevertheless he argued that the WHO, "in cooperation with some big pharmaceutical companies and their scientists, re-defined pandemics", removing the statement that "an enormous amount of people have contracted the illness or died" from its existing definition and replacing it by stating simply that there has to be a virus, spreading beyond borders and to which people have no immunity. The WHO responded by stating that they take their duty to provide independent advice seriously and guarded against interference from outside interests. Announcing a review of the WHO's actions, spokeswoman Fadela Chaib stated: "Criticism is part of an outbreak cycle. We expect and indeed welcome criticism and the chance to discuss it". In March 2010, the Council of Europe launched an enquiry into 'the influence of the pharmaceutical companies on the global swine flu campaign', and a preliminary report is in preparation.

On April 12, 2010, Keiji Fukuda, the WHO's top influenza expert, stated that the system leading to the declaration of a pandemic led to confusion about H1N1 circulating around the world, and he expressed concern that there was a failure to communicate in regard to uncertainties about the new virus, which turned out to be not as deadly as feared. WHO Director-General Margaret Chan has appointed 29 flu experts from outside the organization to conduct a review of WHO's handling of the H1N1 flu pandemic. She has told them, "We want a frank, critical, transparent, credible and independent review of our performance".

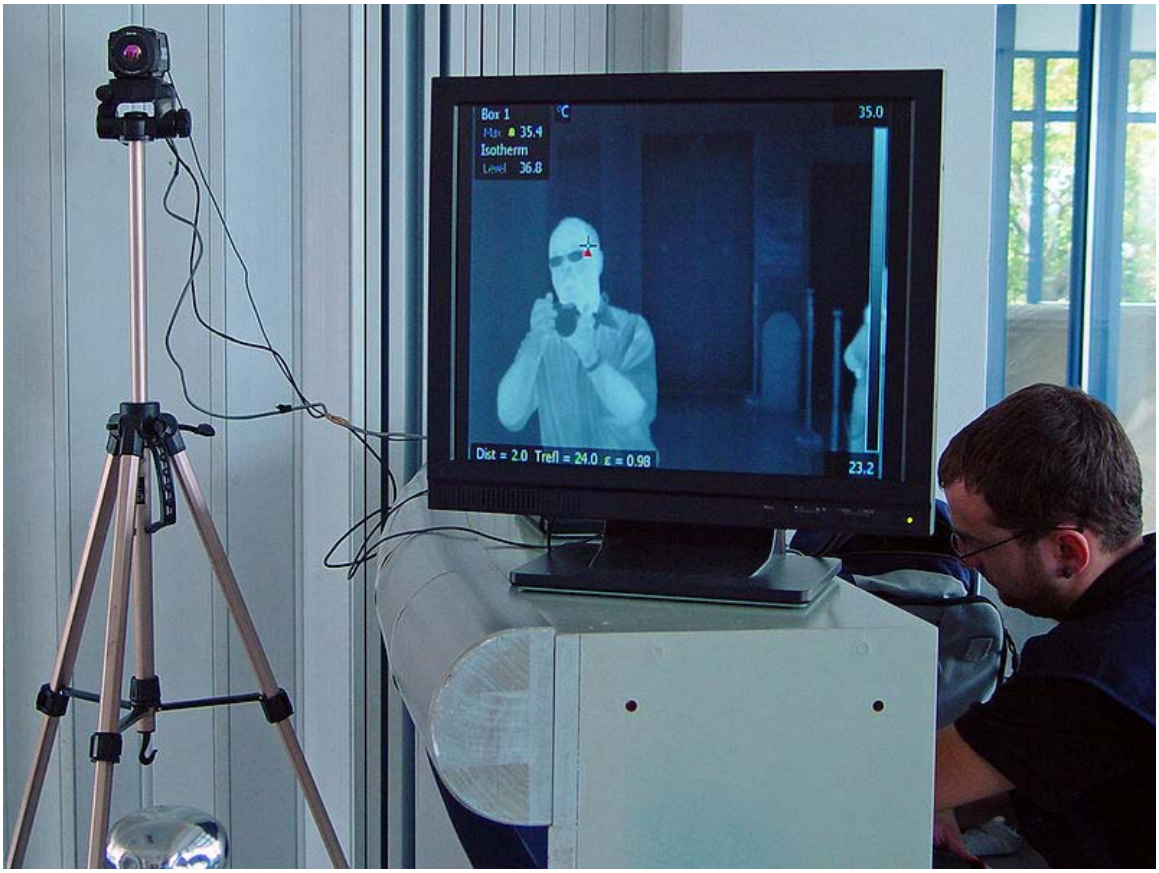
In June 2010, Fiona Godlee, editor in chief of the British medical journal *BMJ*, published an editorial which criticised the WHO, saying that an investigation had disclosed that some of the experts advising WHO on the pandemic had financial ties with drug companies which were producing antivirals and vaccines. Margaret Chan, Director-General of the WHO, replied stating, "Without question, the BMJ feature and editorial will leave many readers with the impression that WHO's decision to declare a pandemic was at least partially influenced by a desire to boost the profits of the pharmaceutical industry. The bottom line, however, is that decisions to raise the level of pandemic alert were based on clearly defined virological and epidemiological criteria. It is hard to bend

these criteria, no matter what the motive". In August 2010, the *Daily Mail* printed an article stating that "a third of the experts advising the World Health Organisation about the swine flu pandemic had ties to drugs firms" and that of the 20 members of the Scientific Advisory Group for Emergencies, which advised the British Government on swine flu, 11 had done work for the pharmaceutical industry or were linked to it through their universities.

Infection control

Travel precautions

Flu inspection on a flight arriving in China



Thermal imaging camera and screen, photographed in an airport terminal in Greece. Thermal imaging can detect elevated body temperature, one of the signs of swine flu.

On 7 May 2009, the WHO stated that containment was not feasible and that countries should focus on mitigating the effect of the virus. They did not recommend closing borders or restricting travel. On 26 April 2009, the Chinese government announced that visitors returning from flu-affected areas who experienced flu-like symptoms within 2 weeks would be quarantined.

U.S. airlines had made no major changes as of the beginning of June 2009, but continued standing practices which include looking for passengers with symptoms of flu, measles or other infections, and relying on in-flight air filters to ensure that aircraft were sanitised. Masks were not generally provided by airlines and the CDC did not recommend that airline crews wear them. Some non-U.S. airlines, mostly Asian, including Singapore Airlines, China Eastern Airlines, China Southern Airlines, Cathay Pacific and Mexicana Airlines, took measures such as stepping up cabin cleaning, installing state-of-the-art air filters and allowing in-flight staff to wear face masks.

Schools

U.S. government officials have been especially concerned about schools because the H1N1 flu virus appears to disproportionately affect young and school-age people,

between 6 months and 24 years of age. The H1N1 outbreak led to numerous precautionary school closures in some areas. Rather than closing schools, the CDC recommended that students and school workers with flu symptoms should stay home for either 7 days total, or until 24 hours after symptoms subsided, whichever was longer. The CDC also recommended that colleges should consider suspending fall 2009 classes if the virus began to cause severe illness in a significantly larger share of students than the previous spring. They also urged schools to suspend rules, such as penalties for late papers or missed classes or requirements for a doctor's note, to enforce "self-isolation" and prevent students from venturing out while ill; schools were advised to set aside a room for people developing flu-like symptoms while they waited to go home and to have ill students or staff and those caring for them use face masks.

In California, school districts and universities were on alert and working with health officials to launch education campaigns. Many planned to stockpile medical supplies and discuss worst-case scenarios, including plans to provide lessons and meals for low-income children in case elementary and secondary schools closed. University of California campuses stockpiled supplies, from paper masks and hand sanitizer to food and water. To help prepare for contingencies, University of Maryland School of Medicine professor of pediatrics James C. King Jr. suggested that every county should create an "influenza action team" to be run by the local health department, parents and school administrators. As of 28 October 2009, about 600 schools in the United States had been temporarily closed, affecting over 126,000 students in 19 states.

Workplace

Fearing a worst-case scenario, the U.S. Department of Health and Human Services (HHS), the Centers for Disease Control and Prevention and the Department of Homeland Security (DHS) developed updated guidance and a video for employers to use as they developed plans to respond to the H1N1 outbreak. The guidance suggested that employers consider and communicate their objectives, such as reducing transmission among staff, protecting people who are at increased risk of influenza-related complications from becoming infected, maintaining business operations, and minimising adverse effects on other entities in their supply chains.

The CDC estimated that as much as 40% of the workforce might be unable to work at the peak of the pandemic due to the need for many healthy adults to stay home and care for an ill family member, and advised that individuals should have steps in place should a workplace close down or a situation arise that requires working from home. The CDC further advised that persons in the workplace should stay home sick for 7 days after getting the flu, or 24 hours after symptoms end, whichever is longer.

In the UK, the Health and Safety Executive (HSE) also issued general guidance for employers.

Facial masks

Mexico City Metro

The U.S. CDC does not recommend use of face masks or respirators in non-health care settings, such as schools, workplaces, or public places, with a few exceptions: people who are ill with the virus when around other people, and people who are at risk for severe illness while caring for someone with the flu. There has been some disagreement about the value of wearing facial masks, some experts fearing that masks may give people a false sense of security and should not replace other standard precautions. Masks may benefit people in close contact with infected persons, but it is unknown whether they prevent H1N1 flu infection. Yukihiro Nishiyama, professor of virology at Nagoya University's School of Medicine, commented that the masks are "better than nothing, but it's hard to completely block out an airborne virus since it can easily slip through the gaps".

According to mask manufacturer 3M, masks will filter out particles in industrial settings, but "there are no established exposure limits for biological agents such as swine flu virus". However, despite the lack of evidence of effectiveness, the use of such masks is common in Asia. They are particularly popular in Japan, where cleanliness and hygiene are highly valued and where etiquette obligates those who are sick to wear masks to avoid spreading disease.

Quarantine

During the height of the fear of a pandemic, some countries initiated or threatened to initiate quarantines of foreign visitors suspected of having or being in contact with others who may have been infected. In May 2009, the Chinese government confined 21 U.S. students and 3 teachers to their hotel rooms. As a result, the US State Department issued a travel alert about China's anti-flu measures and warned travellers against travelling to China if ill. In Hong Kong, an entire hotel was quarantined with 240 guests; Australia ordered a cruise ship with 2,000 passengers to stay at sea because of a swine flu threat. Egyptian Muslims who went on the annual pilgrimage to Mecca risked being quarantined upon their return. Russia and Taiwan said they would quarantine visitors with fevers who come from areas where the flu was present. Japan quarantined 47 airline passengers in a hotel for a week in mid-May, then in mid-June India suggested pre-screening "outbound" passengers from countries thought to have a high rate of infection.

Pigs and food safety

The pandemic virus is a type of swine influenza, derived originally from a strain which lived in pigs, and this origin gave rise to the common name of "swine flu". This term is widely used by mass media. The virus has been found in American hogs, and Canadian as well as in hogs in Northern Ireland, Argentina, and Norway. Leading health agencies and the United States Secretary of Agriculture have stressed that eating properly cooked pork or other food products derived from pigs will not cause flu. Nevertheless, on April 27, Azerbaijan imposed a ban on the importation of animal husbandry products from America. The Indonesian government also halted the importation of pigs and initiated the examination of 9 million pigs in Indonesia. The Egyptian government ordered the slaughter of all pigs in Egypt on April 29, 2009.

Treatment

A number of methods have been recommended to help ease symptoms, including adequate liquid intake and rest. Over-the-counter pain medications such as acetaminophen and ibuprofen do not kill the virus; however, they may be useful to reduce symptoms. Aspirin and other salicylate products should not be used by people under 19 with any flu-type symptoms because of the risk of developing Reye's Syndrome.

If the fever is mild and there are no other complications, fever medication is not recommended. Most people recover without medical attention, although those with pre-existing or underlying medical conditions are more prone to complications and may benefit from further treatments.

People in at-risk groups should be treated with antivirals (oseltamivir or zanamivir) as soon as possible when they first experience flu symptoms. The at-risk groups include pregnant and post partum women, children under 2 years old, and people with underlying conditions such as respiratory problems. People who are not in an at-risk group who have persistent or rapidly worsening symptoms should also be treated with antivirals. People who have developed pneumonia should be given both antivirals and antibiotics, as in many severe cases of H1N1-caused illness, bacterial infection develops. Antivirals are

most useful if given within 48 hours of the start of symptoms and may improve outcomes in hospitalised patients. In those beyond 48 hours who are moderately or severely ill, antivirals may still be beneficial. If oseltamivir (Tamiflu) is unavailable or cannot be used, zanamivir (Relenza) is recommended as a substitute. Peramivir is an experimental antiviral drug approved for hospitalised patients in cases where the other available methods of treatment are ineffective or unavailable.

To help avoid shortages of these drugs, the U.S. CDC recommended oseltamivir treatment primarily for people hospitalised with pandemic flu; people at risk of serious flu complications due to underlying medical conditions; and patients at risk of serious flu complications. The CDC warned that the indiscriminate use of antiviral medications to prevent and treat influenza could ease the way for drug-resistant strains to emerge, which would make the fight against the pandemic that much harder. In addition, a British report found that people often failed to complete a full course of the drug or took the medication when not needed.

Side effects

Both medications have known side effects, including lightheadedness, chills, nausea, vomiting, loss of appetite and trouble breathing. Children were reported to be at increased risk of self-injury and confusion after taking oseltamivir. The WHO warn against buying antiviral medications from online sources, and estimate that half the drugs sold by online pharmacies without a physical address are counterfeit.

Resistance

As of August 2010, the World Health Organization (WHO) reported 302 out of over 15,000 samples of the prevalent 2009 pandemic H1N1 flu tested worldwide have shown resistance to oseltamivir (Tamiflu). This is not totally unexpected as 99.6% of the seasonal H1N1 flu strains tested have developed resistance to oseltamivir. No circulating flu has yet shown any resistance to zanamivir (Relenza), the other available anti-viral.

Effectiveness of antivirals questioned

On 8 December 2009, the Cochrane Collaboration, which reviews medical evidence, announced in a review published in *BMJ* that it had reversed its previous findings that the antiviral drugs oseltamivir (Tamiflu) and zanamivir (Relenza) can ward off pneumonia and other serious conditions linked to influenza. They reported that an analysis of 20 studies showed oseltamivir offered mild benefits for healthy adults if taken within 24 hours of onset of symptoms, but found no clear evidence it prevented lower respiratory tract infections or other complications of influenza. Their published finding relates only to its use in healthy adults with influenza; they say nothing about its use in patients judged to be at high risk of complications (pregnant women, children under 5 and those with underlying medical conditions), and uncertainty over its role in reducing complications in healthy adults may still leave it as a useful drug for reducing the duration of symptoms. The drugs might eventually be demonstrated to be effective

against flu-related complications; in general, the Cochrane Collaboration concluded "Paucity of good data".

Some specific results from the *BMJ* article include: "The efficacy of oral oseltamivir against symptomatic laboratory confirmed influenza was 61% (risk ratio 0.39, 95% confidence interval 0.18 to 0.85) at 75 mg daily ... The remaining evidence suggests oseltamivir did not reduce influenza related lower respiratory tract complications (risk ratio 0.55, 95% confidence interval 0.22 to 1.35)". Notice especially the wide range for this second result.

Epidemiology

2009 flu pandemic data	
Area	Confirmed deaths
Worldwide (total)	**14,286**
European Union and EFTA	2,290
Other European countries and Central Asia	457
Mediterranean and Middle East	1,450
Africa	116
North America	3,642
Central America and Caribbean	237
South America	3,190
Northeast Asia and South Asia	2,294
Southeast Asia	393
Australia and Pacific	217

While it is not known precisely where or when the virus originated, analyses in scientific journals have suggested that the H1N1 strain responsible for the current outbreak first

evolved in September 2008 and circulated amongst humans for several months before being formally recognised and identified as a novel strain of influenza.

Mexico

The virus was first reported in two U.S. children in March 2009, but health officials have reported that it apparently infected people as early as January 2009 in Mexico. The outbreak was first detected in Mexico City on 18 March 2009; immediately after the outbreak was officially announced, Mexico notified the U.S. and World Health Organization, and within days of the outbreak Mexico City was "effectively shut down". Some countries cancelled flights to Mexico while others halted trade. Calls to close the border to contain the spread were rejected. Mexico already had hundreds of non-lethal cases before the outbreak was officially discovered, and was therefore in the midst of a "silent epidemic". As a result, Mexico was reporting only the most serious cases which showed more severe signs different from those of normal flu, possibly leading to a skewed initial estimate of the case fatality rate.

United States

The new strain was first identified by the CDC in two children, neither of whom had been in contact with pigs. The first case, from San Diego County, California, was confirmed from clinical specimens (nasopharyngeal swab) examined by the CDC on 14 April 2009. A second case, from nearby Imperial County, California, was confirmed on 17 April. The patient in the first confirmed case had flu symptoms including fever and cough on clinical examination on 30 March, and the second on 28 March.

The first confirmed H1N1/09 pandemic flu death, which occurred at Texas Children's Hospital in Houston, Texas, was of a toddler from Mexico City who was visiting family in Brownsville, Texas, before being air-lifted to Houston for treatment.

Data reporting and accuracy

Influenza surveillance information "answers the questions of where, when, and what influenza viruses are circulating. It can be used to determine if influenza activity is increasing or decreasing, but cannot be used to ascertain how many people have become ill with influenza". For example, as of late June 2009, influenza surveillance information showed the U.S. had nearly 28,000 laboratory-confirmed cases including 3,065 hospitalisations and 127 deaths; but mathematical modelling showed an estimated 1 million Americans currently had the 2009 pandemic flu, according to Lyn Finelli, a flu surveillance official with the CDC. Estimating deaths from influenza is also a complicated process. In 2005, influenza only appeared on the death certificates of 1,812 people in the US. The average annual US death toll from flu is, however, estimated to be 36,000. The CDC explains: "[I]nfluenza is infrequently listed on death certificates of people who die from flu-related complications" and hence, "Only counting deaths where influenza was included on a death certificate would be a gross underestimation of influenza's true impact".

With respect to the current H1N1 flu pandemic, influenza surveillance information is available but almost no studies have attempted to estimate the total number of deaths attributable to H1N1 flu. Two studies have been performed by the CDC, however; the most recent estimates that there were 9,820 deaths (range 7,070–13,930) attributable to H1N1 flu from April to 14 November 2009. During the same period, 1642 deaths were officially confirmed as caused by H1N1 flu. The WHO state that total mortality (including deaths unconfirmed or unreported) from H1N1 flu is "unquestionably higher" than their own confirmed death statistics.

The initial outbreak received a week of near-constant media attention. Epidemiologists cautioned that the number of cases reported in the early days of an outbreak can be very inaccurate and deceptive due to several causes, among them selection bias, media bias and incorrect reporting by governments. Inaccuracies could also be caused by authorities in different countries looking at differing population groups. Furthermore, countries with poor health care systems and older laboratory facilities may take longer to identify or report cases. "[E]ven in developed countries the [numbers of flu deaths] are uncertain, because medical authorities don't usually verify who actually died of influenza and who died of a flu-like illness". Dr. Joseph S. Bresee (the CDC flu division's epidemiology chief) and Dr. Michael T. Osterholm (director of the Center for Infectious Disease Research) have pointed out that millions of people have had H1N1 flu, usually in a mild form, so the numbers of laboratory-confirmed cases were actually meaningless, and in July 2009 the WHO stopped keeping count of individual cases and focussed more on major outbreaks.

History of influenza epidemics

Annual influenza epidemics are estimated to affect 5–15% of the global population. Although most cases are mild, these epidemics still cause severe illness in 3–5 million people and 250,000–500,000 deaths worldwide. On average 41,400 people die of influenza each year in the United States, based on data collected between 1979 and 2001. In industrialised countries, severe illness and deaths occur mainly in the high-risk populations of infants, the elderly and chronically ill patients, although the H1N1 flu outbreak (like the 1918 Spanish flu) differs in its tendency to affect younger, healthier people.

In addition to these annual epidemics, Influenza A virus strains caused 3 global pandemics during the 20th century: the Spanish flu in 1918, Asian flu in 1957, and Hong Kong flu in 1968–69. These virus strains had undergone major genetic changes for which the population did not possess significant immunity. Recent genetic analysis has revealed that three-quarters, or six out of the eight genetic segments, of the 2009 flu pandemic strain arose from the North American swine flu strains circulating since 1998, when a new strain was first identified on a factory farm in North Carolina, and which was the first-ever reported triple-hybrid flu virus.

The 1918 flu epidemic began with a wave of mild cases in the spring, followed by more deadly waves in the autumn, eventually killing hundreds of thousands in the United

States. The great majority of deaths in the 1918 flu pandemic were the result of secondary bacterial pneumonia. The influenza virus damaged the lining of the bronchial tubes and lungs of victims, allowing common bacteria from the nose and throat to infect their lungs. Subsequent pandemics have had many fewer fatalities due to the development of antibiotic medicines which can treat pneumonia.

20th century flu pandemics

Pandemic	Year	Influenza virus type	People infected (approximate)	Estimated deaths worldwide	Case fatality rate
Spanish flu	1918–1919	A/H1N1	33% (500 million)	20–100 million	>2.5%
Asian flu	1956–1958	A/H2N2	?	2 million	<0.1%
Hong Kong flu	1968–1969	A/H3N2	?	1 million	<0.1%
Seasonal flu	Every year	mainly A/H3N2, A/H1N1, and B	5–15% (340 million – 1 billion)	250,000–500,000 per year	<0.1%
Swine flu	2009–2010	Pandemic H1N1/09	> 622,482 (lab-confirmed)	14,286 (lab-confirmed;ECDC) ≥8,768 (lab-confirmed; WHO)	0.03%

1. ^ Not necessarily pandemic, but included for comparison purposes.
2. ^ [a] [b] The ratio of confirmed deaths to total deaths due to pandemic H1N1/09 flu is unknown. For more information, see "Data reporting and accuracy".

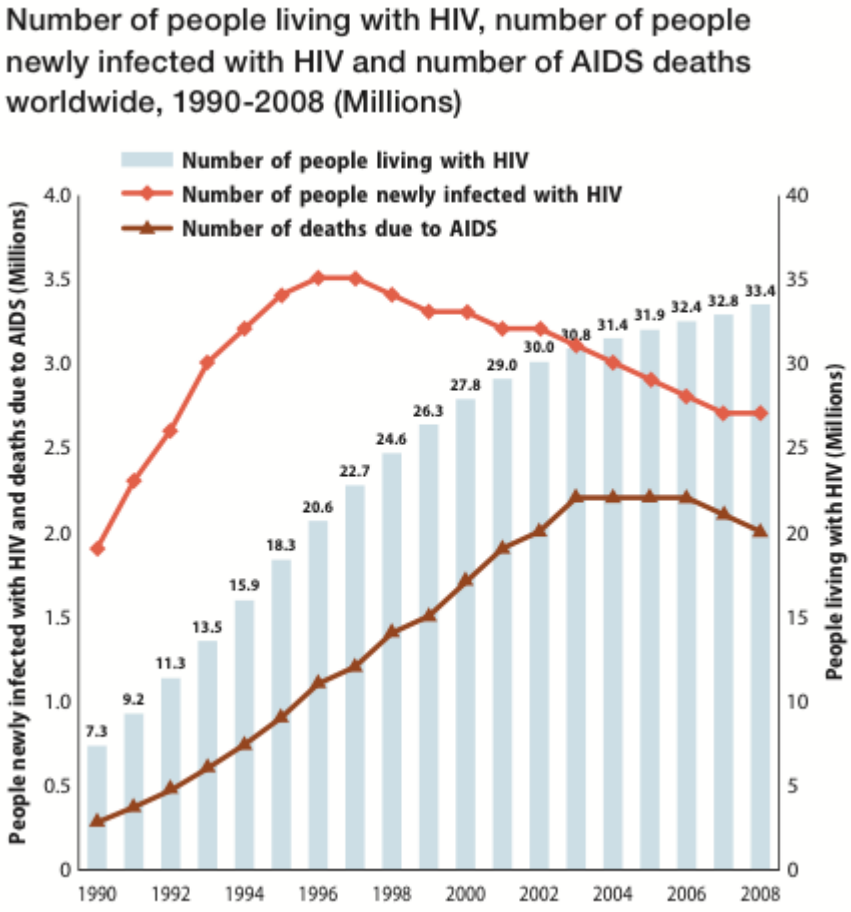
The influenza virus has also caused several pandemic threats over the past century, including the pseudo-pandemic of 1947 (thought of as mild because although globally distributed, it caused relatively few deaths), the 1976 swine flu outbreak and the 1977 Russian flu, all caused by the H1N1 subtype. The world has been at an increased level of alert since the SARS epidemic in Southeast Asia (caused by the SARS coronavirus). The level of preparedness was further increased and sustained with the advent of the H5N1 bird flu outbreaks because of H5N1's high fatality rate, although the strains currently prevalent have limited human-to-human transmission (anthroponotic) capability, or epidemicity.

People who contracted flu before 1957 appeared to have some immunity to H1N1 flu. Dr. Daniel Jernigan, head of flu epidemiology for the the U.S. CDC, has stated: "Tests on blood serum from older people showed that they had antibodies that attacked the new

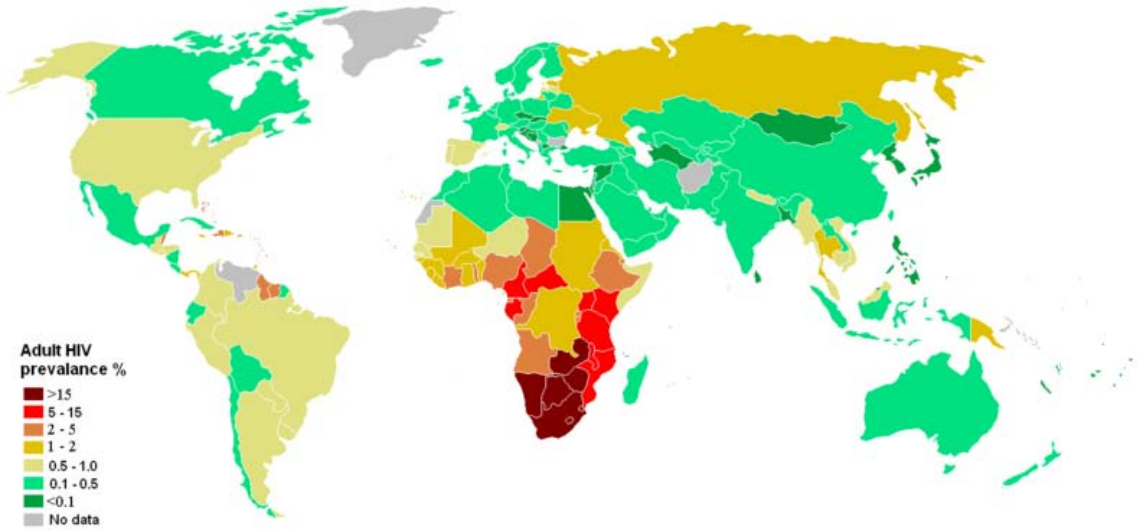
virus ... That does not mean that everyone over 52 is immune, since Americans and Mexicans older than that have died of the new flu".

Chapter- 3

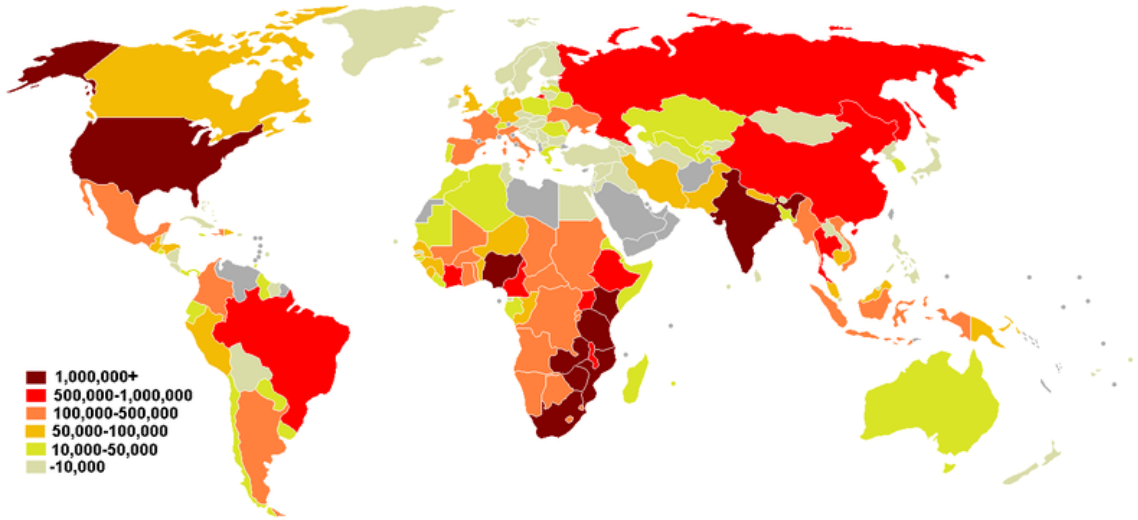
AIDS Pandemic



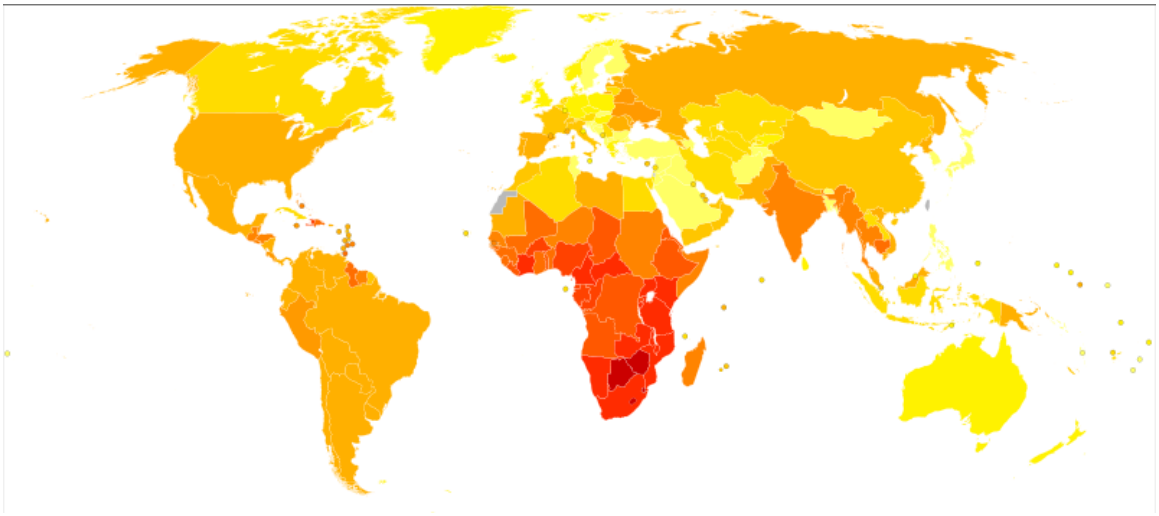
Numbers of people living with, newly infected with and killed by HIV



Estimated prevalence of HIV among young adults (15–49) per country at the end of 2005



Estimated number of people living with HIV/AIDS by country



Disability-adjusted life year for HIV and AIDS per 100,000 inhabitants
no data
≤ 10
10–25
25–50
50–100
100–500
500–1000
1000–2500
2500–5000
5000–7500
7500-10000
10000-50000
≥ 50000

The **acquired immune deficiency syndrome** (**AIDS**) pandemic is a widespread disease caused by human immunodeficiency virus (HIV).

Since AIDS was first recognized in 1981, it has led to the deaths of more than 25 million people, making it one of the most destructive diseases in recorded history.

Despite recent improved access to antiretroviral treatment and care in many regions of the world, in 2007 the AIDS pandemic killed an estimated 2.1 million people, including 330,000 children. In 2007, an estimated 33.2 million people lived with the disease worldwide, with an estimated 2.5 million people newly infected in 2007. This has been attributed to lack of access to antiretroviral treatment in huge areas such as the continent of Africa, where (according to French researcher Olivier Schwarz), less than 10 percent of infected are reported to have access to it.

Origins

The origin of HIV/AIDS has been elucidated by studies of the HIV genome, which indicate that the most common type of HIV (HIV-1) originated in chimpanzees.

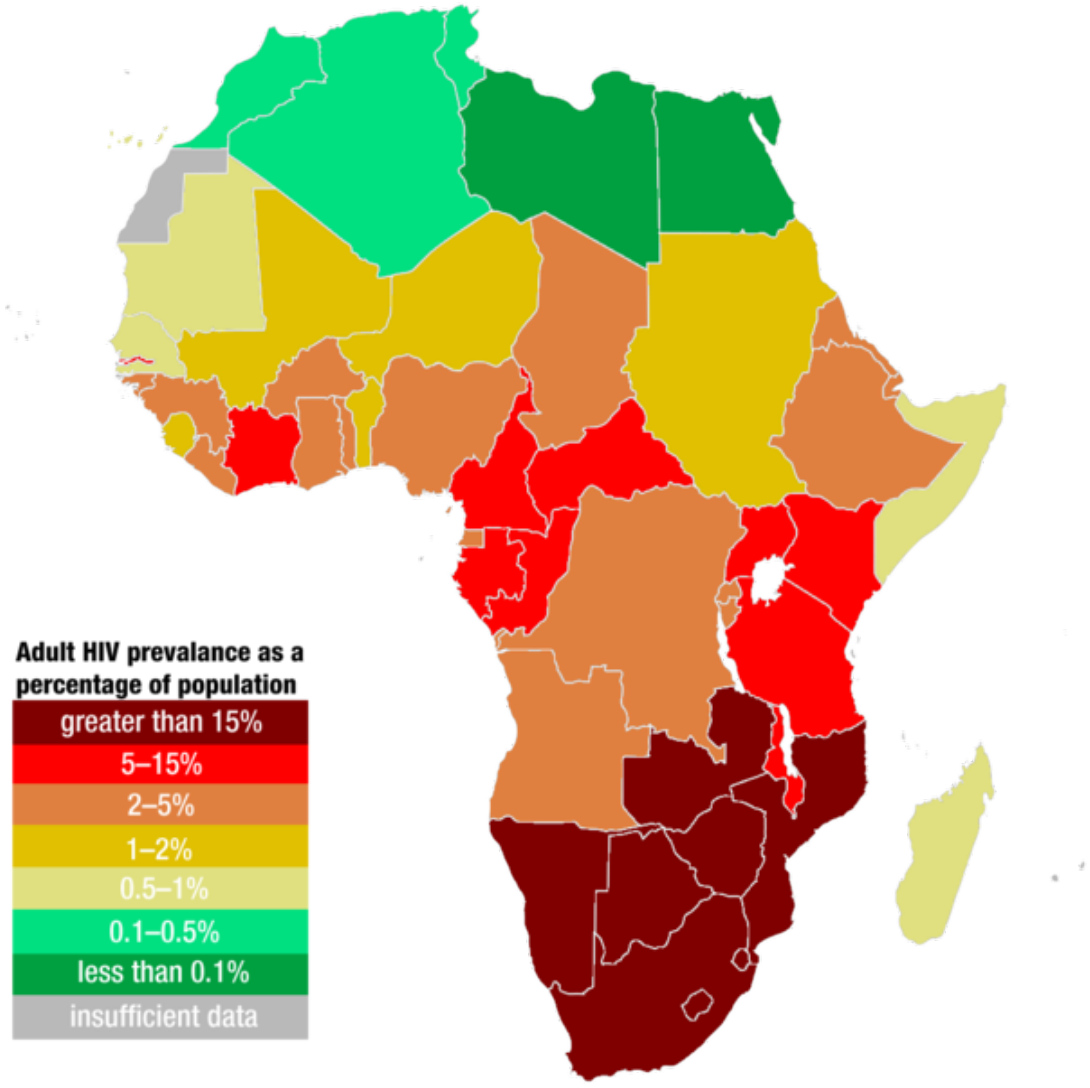
Regions with large infected populations

The pandemic is not homogeneous within regions, with some countries more afflicted than others. Even at the country level, there are wide variations in infection levels between different areas. The number of people infected with HIV continues to rise in most parts of the world, despite the implementation of prevention strategies, Sub-Saharan Africa being by far the worst-affected region, with an estimated 22.5 million at the end of 2007, 68% of the global total. South & South East Asia have an estimated 12% of the global total.

World region	Estimated adult prevalence of HIV infection (ages 15–49)	Estimated adult and child deaths during 2007	Adult prevalence (%)
Worldwide	30.6 million – 36.1 million	1.9 to 2.4 million	0.8%
Sub-Saharan Africa	20.9 million – 24.3 million	1.6 million	5.0%
South and South-East Asia	3.3 million – 5.1 million	270,000	0.3%
Eastern Europe and Central Asia	1.2 million – 2.1 million	55,000	0.9%
Central and South America	1.4 million – 1.9 million	58,000	0.5%
North America	480,000 – 1.9 million	21,000	0.6%
Western and Central Europe	600,000 – 1.1 million	12,000	0.3%
East Asia	620,000 – 960,000	32,000	0.1%

Source: UNAIDS 2007 estimates. The ranges define the boundaries within which the actual numbers lie, based on the best available information.

Sub-Saharan Africa



Estimated HIV infection in Africa in 2007.

Sub-Saharan Africa remains the hardest-hit region. HIV infection is becoming endemic in sub-Saharan Africa, which is home to just over 10% of the world's population but more than 60% of all people infected with HIV. The adult (ages 15–49) HIV prevalence rate is 7.2% (range: 6.6–8.0%) with between 20.9 million and 24.3 million. However, the actual prevalence varies between regions. Presently, Southern Africa is the hardest hit region, with adult prevalence rates exceeding 20% in most countries in the region, and 30% in Swaziland and Botswana.

Eastern Africa also experiences relatively high levels of prevalence with estimates above 10% in some countries, although there are signs that the pandemic is declining in this region, notably in Uganda, which previously recorded one of the highest prevalence rates on the continent. West Africa on the other hand has been much less affected by the pandemic. Several countries reportedly have prevalence rates around 2 to 3%, and no

country has rates above 10%. In Nigeria and Côte d'Ivoire, two of the region's most populous countries, between 5 and 7% of adults are reported to carry the virus.

Across Sub-Saharan Africa, more women are infected with HIV than men, with 13 women infected for every 10 infected men. This gender gap continues to grow. Throughout the region, women are being infected with HIV at earlier ages than men. The differences in infection levels between women and men are most pronounced among young people (aged 15–24 years). In this age group, there are 36 women infected with HIV for every 10 men. The widespread prevalence of sexually transmitted diseases, the practice of scarification, unsafe blood transfusions, and the poor state of hygiene and nutrition in some areas may all be facilitating factors in the transmission of HIV-1 (Bentwich et al., 1995).

Mother-to-child transmission is another contributing factor in the transmission of HIV-1 in developing nations. Due to a lack of testing, a shortage in antenatal therapies and through the feeding of contaminated breast milk, 590 000 infants born in developing countries are infected with HIV-1 per year. In 2000, the World Health Organization estimated that 25% of the units of blood transfused in Africa were not tested for HIV, and that 10% of HIV infections in Africa were transmitted via blood.

Poor economic conditions (leading to the use of dirty needles in healthcare clinics) and lack of sex education contribute to high rates of infection. In some African countries, 25% or more of the working adult population is HIV-positive. Poor economic conditions caused by slow onset-emergencies, such as drought, or rapid onset natural disasters and conflict can result in young women and girls being forced into using sex as a survival strategy. Worse still, research indicates that as emergencies, such as drought, take their toll and the number of potential 'clients' decreases, women are forced by clients to accept greater risks, such as not using contraceptives.

Former South African President Thabo Mbeki and some of his political allies notably questioned the connection between HIV and AIDS, stating instead that factors such as undernourishment caused AIDS. Critics charge that the AIDS denialist policies of Mbeki's administration impeded the creation of effective programs for distribution of antiretroviral drugs, causing thousands of unnecessary deaths. UNAIDS estimates that in 2005 there were 5.5 million people in South Africa infected with HIV — 12.4% of the population. This was an increase of 200,000 people since 2003.

Although HIV infection rates are much lower in Nigeria than in other African countries, the size of Nigeria's population meant that by the end of 2003, there were an estimated 3.6 million people infected. On the other hand, Uganda, Zambia, Senegal, and most recently Botswana have begun intervention and educational measures to slow the spread of HIV, and Uganda has succeeded in actually reducing its HIV infection rate.

Middle East and North Africa

HIV/AIDS prevalence in the Middle East and North Africa is around 0.2% (0.1–0.7%), with between 230,000 and 1.4 million people infected. Among young people 15–24 years of age, 0.3% of women [0.1–0.8%] and 0.1% of men [0.1–0.3%] were living with HIV infection by the end of 2004.

South and South-East Asia

The HIV prevalence rate in South and South-East Asia is less than 0.35 percent, with total of 4.2 – 4.7 million adults and children infected. More AIDS deaths (480,000) occur in this region than in any other except sub-Saharan Africa. The geographical size and human diversity of South and South-East Asia have resulted in HIV epidemics differing across the region. The AIDS picture in South Asia is dominated by the epidemic in India. In South and Southeast Asia, the HIV epidemic remains largely concentrated in injecting drug users, men who have sex with men, sex workers, and clients of sex workers and their immediate sexual partners.

East Asia

The national HIV prevalence levels in East Asia is 0.1% in the adult (15–49) group. However, due to the large populations of many East Asian nations, this low national HIV prevalence still means that large numbers of people are infected with HIV. The picture in this region is dominated by China. Much of the current spread of HIV in China is through injecting drug use and paid sex. In China, the number was estimated at between 430,000 and 1.5 million by independent researchers, with some estimates going much higher. In the rural areas of China, where large numbers of farmers, especially in Henan province, participated in unclean blood transfusions; estimates of those infected are in the tens of thousands. In Japan, just over half of HIV/AIDS cases are officially recorded as occurring amongst homosexual men, with the remainder occurring amongst heterosexuals and also via drug abuse, in the womb or unknown means.

Americas

Caribbean

The Caribbean is the second-most affected region in the world. Among adults aged 15–44, AIDS has become the leading cause of death. The region's adult prevalence rate is 1.6% with national rates ranging from 0.2% to 2.7%. HIV transmission occurs largely through heterosexual intercourse, with two thirds of AIDS cases in this region attributed to this route. Sex between men is also a significant route of transmission, even though it is heavily stigmatised and illegal in many areas. HIV transmission through injecting drug use remains rare, except in Bermuda and Puerto Rico.

Central and South America

In these regions of the American continent, only Guatemala and Honduras have national HIV prevalence of over 1%. In these countries, HIV-infected men outnumber HIV-infected women by roughly 3:1.

United States and Canada

The adult prevalence rate in this region is 0.7% with over 1 million people currently infected with HIV. In the United States from 2001–2005, the highest transmission risk behaviors were sex between men (40–49% of new cases) and high risk heterosexual sex (32–35% of new cases). Currently, rates of HIV infection in the US are highest in the eastern and southern regions, with the exception of California. Currently, 35,000–40,000 new infections occur in the USA every year. AIDS is one of the top three causes of death for African American men aged 25–54 and for African American women aged 35–44 years in the United States of America. In the United States, African Americans make up about 48% of the total HIV-positive population and make up more than half of new HIV cases, despite making up only 12% of the population. The main route of transmission for women is through unprotected heterosexual sex. African American women are 19 times more likely to contract HIV than other women. Experts attribute this to "AIDS fatigue" among younger people who have no memory of the worst phase of the epidemic in the 1980s and early 1990s, as well as "condom fatigue" among those who have grown tired of and disillusioned with the unrelenting safer sex message. This trend is of major concern to public health workers.

In the United States in particular, a new wave of infection is being blamed on the use of methamphetamine, known as crystal meth. Research presented at the 12th Annual Retrovirus Conference in Boston in February 2005 concluded that using crystal meth or cocaine is the biggest single risk factor for becoming HIV+ among US gay men, contributing 29% of the overall risk of becoming positive and 28% of the overall risk of being the receptive partner in anal sex. In addition, several renowned clinical psychologists now cite methamphetamine as the biggest problem facing gay men today, including Michael Majeski, who reckons meth is the catalyst for at least 80% of seroconversions currently occurring across the United States, and Tony Zimbardi, who calls methamphetamine the number one cause of HIV transmission, and says that high rates of new HIV infection are not being found among non-crystal users. In addition, various HIV and STD clinics across the United States report anecdotal evidence that 75% of new HIV seroconversions they deal with are methamphetamine-related; indeed, in Los Angeles, methamphetamine is regarded as the main cause of HIV seroconversion among gay men in their late thirties. The First National Conference on Methamphetamine, HIV and Hepatitis took place in Salt Lake City in August 2005.

In Canada, nearly 60,000 people were living with HIV/AIDS in 2005. The HIV-positive population continues to increase in Canada, with the greatest increases amongst aboriginal Canadians.

As in Western Europe, the death rate from AIDS in North America fell sharply with the introduction of combination AIDS therapies (HAART).

Eastern Europe and Central Asia

There is also growing concern about a rapidly growing epidemic in Eastern Europe and Central Asia, where an estimated 0.99–2.3 million people were infected in December 2005, though the adult (15–49) prevalence rate is low (0.9%). The rate of HIV infections began to grow rapidly from the mid-1990s, due to social and economic collapse, increased levels of intravenous drug use and increased numbers of prostitutes. By 2004 the number of reported cases in Russia was over 257,000, according to the World Health Organization, up from 15,000 in 1995 and 190,000 in 2002; some estimates claim the real number is up to five times higher, over 1 million. There are predictions that the infection rate in Russia will continue to rise quickly, since education there about AIDS is almost non-existent. Ukraine and Estonia also had growing numbers of infected people, with estimates of 500,000 and 3,700 respectively in 2004. The epidemic is still in its early stages in this region, which means that prevention strategies may be able to halt and reverse this epidemic. However, transmission of HIV is increasing through sexual contact and drug use among the young (<30 years). Indeed, over 80% of current infections occur in this region in people less than 30 years of age.

Western Europe

In most countries of Western Europe, AIDS cases have fallen to levels not seen since the original outbreak; many attribute this trend to aggressive educational campaigns, screening of blood transfusions and increased use of condoms. Also, the death rate from AIDS in Western Europe has fallen sharply, as new AIDS therapies have proven to be an effective (though expensive) means of suppressing HIV.

In this area, the routes of transmission of HIV is diverse, including paid sex, injecting drug use, mother to child, male with male sex and heterosexual sex. However, many new infections in this region occur through contact with HIV-infected individuals from other regions. The adult (15–49) prevalence in this region is 0.3% with between 570,000 and 890,000 people currently infected with HIV infection. Due to the availability of antiretroviral therapy, AIDS deaths have stayed low since the lows of the late 1990s. However, in some countries, a large share of HIV infections remain undiagnosed and there is worrying evidence of antiretroviral drug resistance among some newly HIV-infected individuals in this region.

Oceania

There is a very large range of national situations regarding AIDS and HIV in this region. This is due, in part, to the large distances between the islands of Oceania. The wide range of development in the region also plays an important role. The prevalence is estimated at between 0.2% and 0.7%, with between 45,000 and 120,000 adults and children currently infected with HIV.

Papua New Guinea has one of the most serious AIDS epidemics in the region. According to UNAIDS, HIV cases in the country have been increasing at a rate of 30 percent annually since 1997, and the country's HIV prevalence rate in late 2006 was 1.3%.

AIDS and society

Regarding the social effects of the HIV/AIDS pandemic, some sociologists suggest that AIDS has caused a "profound re-medicalization of sexuality".

Social factors also influence HIV/AIDS. A 2003 study states that HIV and AIDS are less prevalent in Muslim populations and speculates that this may be due to the effect of several Islamic tenets, such as the avoidance of extramarital affairs and the "benefits arising from circumcision".

Chapter- 4

Cholera Pandemics

First cholera pandemic

The **first cholera pandemic**, also known as the **first Asiatic cholera pandemic** or **Asiatic cholera**, lasted from 1817 to 1824. While cholera had spread across India many times previously, this outbreak went further; it reached as far as China and the Caspian Sea before receding. Thousands of people died as a result of this pandemic, including many British soldiers, drawing European attention. This was the first of several cholera pandemics to sweep through Asia and Europe during the 19th and 20th centuries. This first pandemic spread over an unprecedented territory, affecting almost every country in Asia.

Origin and initial spread

Cholera was endemic to the Lower Ganges River (Ganges-rich, wealthy, abundant) with its prime headwaters at Rishikesh, Uttar Pradesh and subsequent rivers feeding into it from Nepal. At festival times, pilgrims brought the disease back to other parts of India, where it would spread, then subside. The first cholera pandemic started similarly, as an outbreak that was suspected to have begun at a Hindu pilgrimage, Kumbh Mela, on the upper Ganges River, in the town of Jessore in 1817. There were earlier outbreaks of Cholera near Purnia in Bihar but these are thought to be unrelated. In 1817, Cholera began spreading outside of the Ganges delta. In September 1817, the disease had moved to Calcutta and quickly spread to the rest of the subcontinent. In 1818 the disease broke out in Bombay.

Spread beyond India

In March 1820 the disease was found in Siam, in May 1820 the disease had spread as far as Bangkok and Manila, in spring of 1821 the disease reached Java, Oman, and Anhai in China, in 1822 the disease was found in Japan, in the Persian Gulf, in Baghdad, in Syria, and in the Transcaucacus, and in 1823 cholera reached Astrakhan, Zanzibar, and Mauritius.

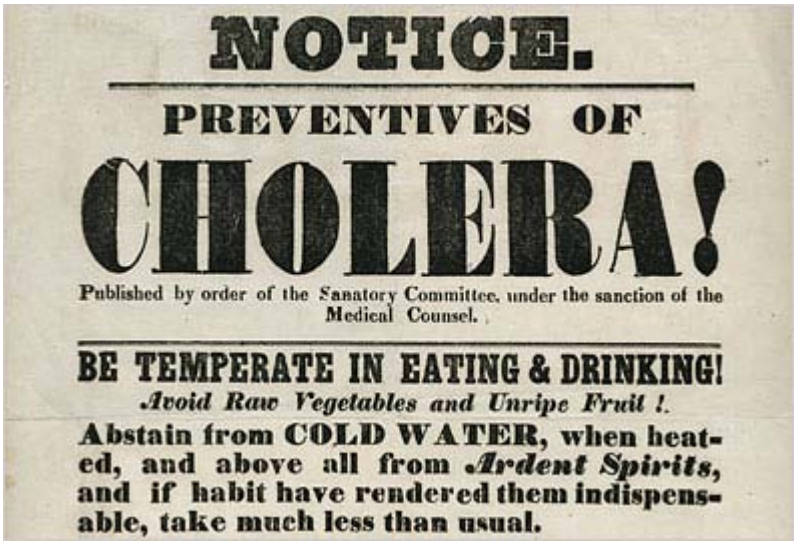
In 1824, the disease halted its expansion; some believe that it might have been due in part to the cold winter of 1823-24.

The movement of the British Army and Navy account for the vast distances that this pandemic covered. Hindu pilgrims carried cholera within the subcontinent, as had happened many times previous, but British troops carried it overland to Nepal and Afghanistan, and the navy and merchant ships brought it the shores of the Indian Ocean, from Africa to Indonesia, and north to China and Japan.

Total deaths

The total deaths from the epidemic remain unknown although there are some estimates of death tolls in specific areas. Some estimate that Bangkok might have suffered 30,000 deaths from the disease. In Semarang, Java, 1,225 people died in eleven days in April 1821.

Second cholera pandemic


NOTICE.

PREVENTIVES OF

CHOLERA!

Published by order of the Sanatory Committee, under the sanction of the Medical Counsel.

BE TEMPERATE IN EATING & DRINKING!

Avoid Raw Vegetables and Unripe Fruit !.

Abstain from COLD WATER, when heated, and above all from *Ardent Spirits*, and if habit have rendered them indispensable, take much less than usual.

Hand bill from the New York City Board of Health, 1832. The outdated public health advice demonstrates the lack of understanding of the disease and its actual causative factors.

The **second cholera pandemic** also known as the **Asiatic Cholera Pandemic** was a Cholera pandemic from 1829-1849.

This pandemic began, like the first, with outbreaks along the Ganges River delta. From there the disease spread along trade routes to cover most of India. By 1828 the disease had traveled to China and was at the southern tips of the Ural Mountains in 1829. In London, the disease claimed 6,536 victims; in Paris, 20,000 succumbed (out of a population of 650,000) with about 100,000 deaths in all of France. The epidemic reached Russia, Quebec, Ontario and New York in the same year and the Pacific coast of North America between 1832 and 1834.

Norwegian Poet Henrik Wergeland wrote a stage-play inspired by the pandemic, as it reached as far as Norway. *The Indian Cholera*, as he called it, criticized British colonialism for spreading the pandemic.

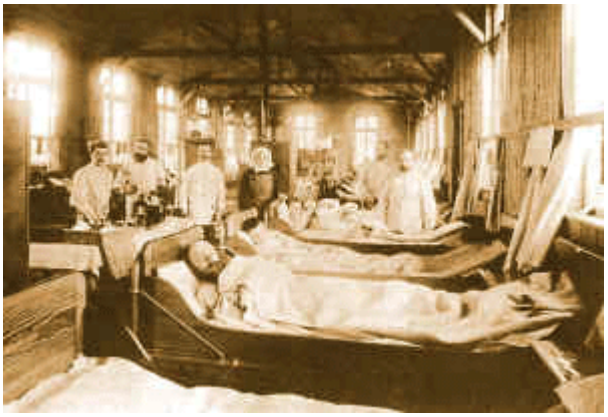
Third cholera pandemic

The **third cholera pandemic** was an outbreak of cholera that occurred from 1852-1860, and mainly affected Russia, with over a million deaths. In 1853-1854, London's epidemic claimed over 10,000 lives with 23,000 deaths for all of Britain.

Fourth cholera pandemic

The **fourth cholera pandemic** was the fourth major pandemic of cholera that spread from 1863 to 1879. It began in the Bengal region, and Indian Muslim pilgrims visiting Mecca spread the disease through the Middle East.

Fifth cholera pandemic



1892 Cholera outbreak in Hamburg, Germany, hospital ward

1892 Cholera outbreak in Hamburg, Germany, disinfection team

The **fifth cholera pandemic** was the fifth major outbreak of cholera that occurred in the years 1881-1896 starting in India. The 1892 outbreak in Hamburg, Germany was the only major European outbreak; about 8,600 people died in Hamburg. Although generally held responsible for the virulence of the epidemic, the city government went largely unchanged. This was the last serious European cholera outbreak.

The epidemic was serious enough in Rome that Pope Leo XIII built a hospice for afflicted residents inside the Vatican. That building would be torn down in 1996 to make way for construction of the Domus Sanctae Marthae.

Sixth cholera pandemic

Drawing of Death bringing the cholera, in *Le Petit Journal*

The **sixth cholera pandemic** was a major outbreak of cholera from the years 1899 to 1923. It killed more than 800,000 in India then erupted in the Middle East, northern Africa, Russia and Eastern Europe.

The last outbreak in the United States was in 1910-1911 when the steamship Moltke brought infected people to New York City. Vigilant health authorities isolated the infected on Swinburne Island. Eleven people died, including a health care worker at Swinburne Island.

Seventh cholera pandemic

The **seventh cholera pandemic** was the seventh major outbreak of cholera and occurred from the years 1961 to the 1970s and has continued (though much diminished) to the present. The outbreak began in Indonesia, called El Tor after the strain, and reached Bangladesh in 1963, India in 1964, and the USSR in 1966. From North Africa it spread into Italy by 1973. In the late 1970s, there were small outbreaks in Japan and in the South Pacific. There were also many reports of a cholera outbreak near Baku in 1972, but information about it was suppressed in the USSR.

In 1971, the number of reported cases reported worldwide was 155,000. In 1991, it reached 570,000.

The spread of the disease was helped by modern transportation and mass migrations. Mortality rates, however, dropped markedly as governments began modern curative and preventative measures. The usual mortality rate of 50% dropped to 10% by the 1980s and less than 3% by the 1990s.

Chapter- 5

Influenza Pandemic

Influenza ward at Walter Reed Hospital, in Washington, D.C. during the Spanish flu pandemic of 1918–1919.

An **influenza pandemic** is an epidemic of an influenza virus that spreads on a worldwide scale and infects a large proportion of the human population. In contrast to the regular seasonal epidemics of influenza, these pandemics occur irregularly, with the 1918 Spanish flu the most serious pandemic in recent history. Pandemics can cause high levels of mortality, with the Spanish influenza estimated as being responsible for the deaths of

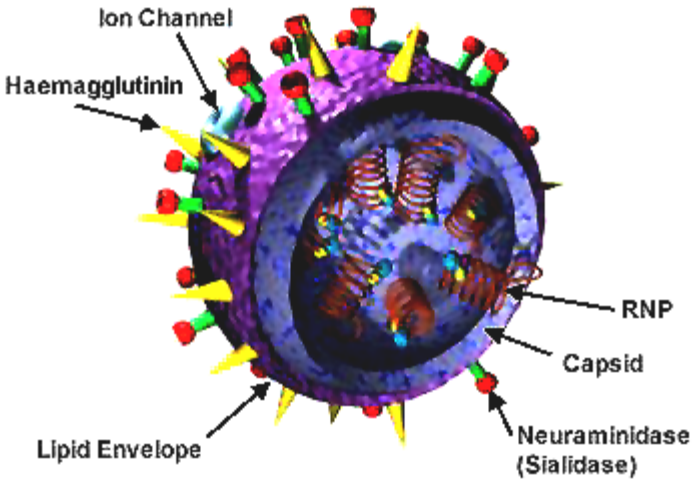
over 50 million people. There have been about three influenza pandemics in each century for the last 300 years. The most recent one was the 2009 flu pandemic.

Influenza pandemics occur when a new strain of the influenza virus is transmitted to humans from another animal species. Species that are thought to be important in the emergence of new human strains are pigs, chickens and ducks. These novel strains are unaffected by any immunity people may have to older strains of human influenza and can therefore spread extremely rapidly and infect very large numbers of people. Influenza A viruses can occasionally be transmitted from wild birds to other species causing outbreaks in domestic poultry and may give rise to human influenza pandemics.

The World Health Organization (WHO) has produced a six-stage classification that describes the process by which a novel influenza virus moves from the first few infections in humans through to a pandemic. This starts with the virus mostly infecting animals, with a few cases where animals infect people, then moves through the stage where the virus begins to spread directly between people, and ends with a pandemic when infections from the new virus have spread worldwide.

One strain of virus that may produce a pandemic in the future is a highly pathogenic variation of the H5N1 subtype of Influenza A virus. On 11 June 2009, a new strain of H1N1 influenza was declared to be a global pandemic (Stage 6) by the World Health Organization after evidence of spreading in the southern hemisphere. 8 November 2009 worldwide update by the UN's World Health Organization (WHO) states that "206 countries and overseas territories/communities have officially reported over 503,536 laboratory confirmed cases of the influenza pandemic H1N1 infection, including 6,250 deaths."

Influenza



Structure of the influenza viron. The hemagglutinin (HA) and neuraminidase (NA) proteins are shown on the surface of the particle. The viral RNAs that make up the

genome are shown as red coils inside the particle and bound to Ribonuclear Proteins (RNPs).

Influenza, commonly known as flu, is an infectious disease of birds and mammals caused by an RNA virus of the family Orthomyxoviridae (the influenza viruses). In humans, common symptoms of influenza infection are fever, sore throat, muscle pains, severe headache, coughing, and weakness and fatigue. In more serious cases, influenza causes pneumonia, which can be fatal, particularly in young children and the elderly. While sometimes confused with the common cold, influenza is a much more severe disease and is caused by a different type of virus. Although nausea and vomiting can be produced, especially in children, these symptoms are more characteristic of the unrelated gastroenteritis, which is sometimes called "stomach flu" or "24-hour flu."

Typically, influenza is transmitted from infected mammals through the air by coughs or sneezes, creating aerosols containing the virus, and from infected birds through their droppings. Influenza can also be transmitted by saliva, nasal secretions, feces and blood. Healthy individuals can become infected if they breathe in a virus-laden aerosol directly, or if they touch their eyes, nose or mouth after touching any of the aforementioned bodily fluids (or surfaces contaminated with those fluids). Flu viruses can remain infectious for about one week at human body temperature, over 30 days at 0 °C (32 °F), and indefinitely at very low temperatures (such as lakes in northeast Siberia). Most influenza strains can be inactivated easily by disinfectants and detergents.

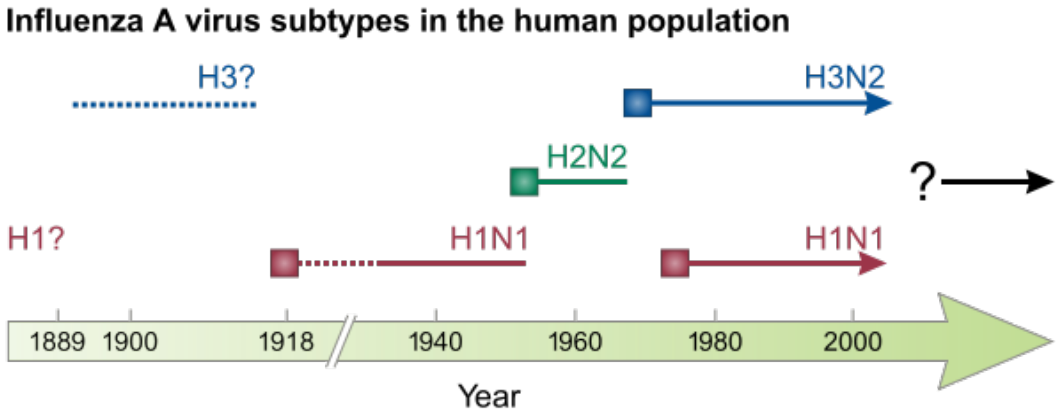
Flu spreads around the world in seasonal epidemics. Three influenza pandemics occurred in the 20th century and killed tens of millions of people, with each of these pandemics being caused by the appearance of a new strain of the virus in humans. Often, these new strains result from the spread of an existing flu virus to humans from other animal species. When it first killed humans in Asia in the 1990s, a deadly avian strain of H5N1 posed a great risk for a new influenza pandemic; however, this virus did not mutate to spread easily between people.

Vaccinations against influenza are most commonly given to high-risk humans in industrialized countries and to farmed poultry. The most common human vaccine is the trivalent influenza vaccine that contains purified and inactivated material from three viral strains. Typically this vaccine includes material from two influenza A virus subtypes and one influenza B virus strain. A vaccine formulated for one year may be ineffective in the following year, since the influenza virus changes rapidly over time and different strains become dominant. Antiviral drugs can be used to treat influenza, with neuraminidase inhibitors being particularly effective.

Variants and subtypes of Influenzavirus A

Variants of Influenzavirus A are identified and named according to the isolate that they are like and thus are presumed to share lineage (example Fujian flu virus like); according to their typical host (example Human flu virus); according to their subtype (example

H3N2); and according to their deadliness (example LP). So a flu from a virus similar to the isolate A/Fujian/411/2002(H3N2) is called Fujian flu, human flu, and H3N2 flu.



The various types of influenza viruses in humans. Solid squares show the appearance of a new strain, causing recurring influenza pandemics. Broken lines indicate uncertain strain identifications.

Variants are sometimes named according to the species (host) the strain is endemic in or adapted to. Some variants named using this convention are:

- Bird Flu
- Human Flu
- Swine Flu
- Horse Flu
- Dog Flu

Avian variants have also sometimes been named according to their deadliness in poultry, especially chickens:

- Low Pathogenic Avian Influenza (LPAI)
- Highly Pathogenic Avian Influenza (HPAI), also called: deadly flu or death flu

The Influenza A virus subtypes are labeled according to an H number (for hemagglutinin) and an N number (for neuraminidase). Each subtype virus has mutated into a variety of strains with differing pathogenic profiles; some pathogenic to one species but not others, some pathogenic to multiple species. Most known strains are extinct strains. For example, the annual flu subtype H3N2 no longer contains the strain that caused the Hong Kong Flu.

Influenza A viruses are negative sense, single-stranded, segmented RNA viruses. "There are 16 different HA antigens (H1 to H16) and nine different NA antigens (N1 to N9) for influenza A. Until recently, 15 HA types had been recognized, but a new type (H16) was

isolated from black-headed gulls caught in Sweden and the Netherlands in 1999 and reported in the literature in 2005."

Nature of a flu pandemic

Some pandemics are relatively minor such as the one in 1957 called "Asian flu" (1 – 4 million dead, depending on source). Others have a higher Pandemic Severity Index whose severity warrants more comprehensive social isolation measures.

The 1918 pandemic killed tens of millions and sickened hundreds of millions; the loss of this many people in the population caused upheaval and psychological damage to many people. There were not enough doctors, hospital rooms, or medical supplies for the living as they contacted the disease. Dead bodies were often left unburied as few people were available to deal with them. There can be great social disruption as well as a sense of fear. Efforts to deal with pandemics can leave a great deal to be desired because of human selfishness, lack of trust, illegal behavior, and ignorance. For example in the 1918 pandemic: "This horrific disconnect between reassurances and reality destroyed the credibility of those in authority. People felt they had no one to turn to, no one to rely on, no one to trust."

A letter from a physician at one U.S. Army camp in the 1918 pandemic said:

> It is only a matter of a few hours then until death comes [...]. It is horrible. One can stand it to see one, two or twenty men die, but to see these poor devils dropping like flies [...]. We have been averaging about 100 deaths per day [...]. Pneumonia means in about all cases death [...]. We have lost an outrageous number of Nurses and Drs. It takes special trains to carry away the dead. For several days there were no coffins and the bodies piled up something fierce [...].

Wave nature

Flu pandemics typically come in waves. The 1889–1890 and 1918–1919 flu pandemics each came in three or four waves of increasing lethality. But within a wave, mortality was greater at the beginning of the wave.

Variable mortality

Mortality varies widely in a pandemic. In the 1918 pandemic:

> In U.S. Army camps where reasonably reliable statistics were kept, case mortality often exceeded 5 percent, and in some circumstances exceeded 10 percent. In the British Army in India, case mortality for white troops was 9.6 percent, for Indian troops 21.9 percent. In isolated human populations, the virus killed at even higher rates. In the Fiji islands, it killed 14 percent of the entire population in 16 days. In Labrador and Alaska, it killed at least one-third of the entire native population.

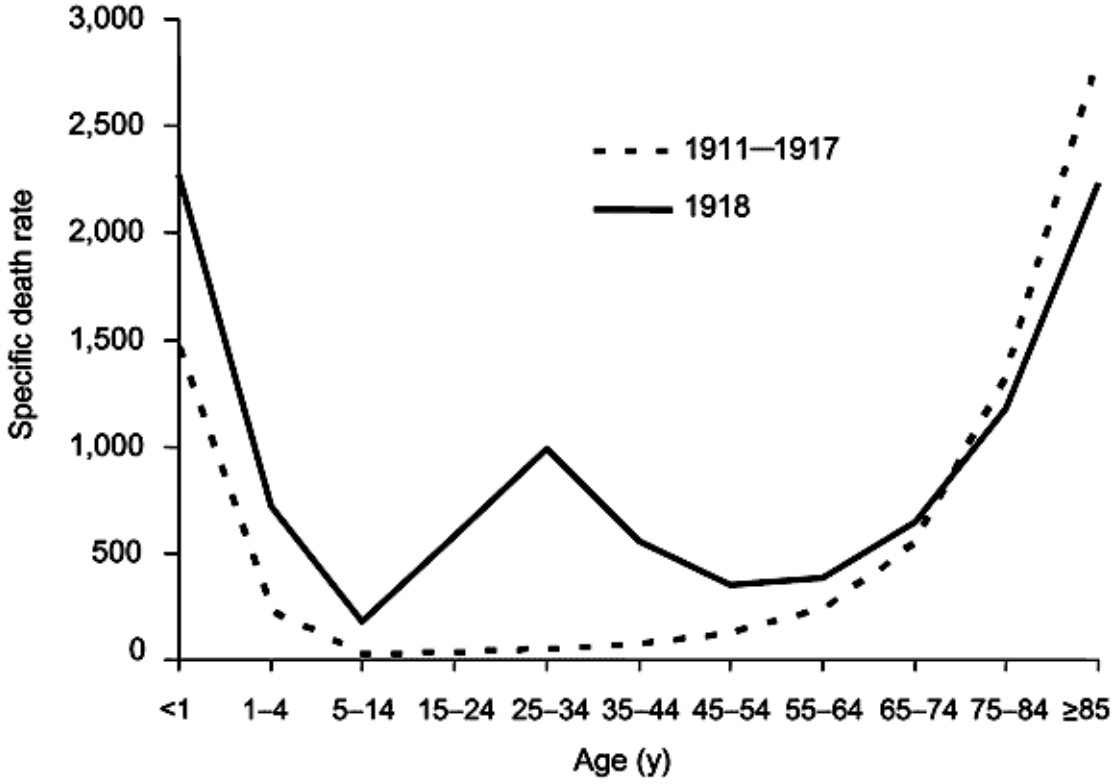
influenza pandemics

Latest flu pandemics

Name of pandemic	Date	Deaths	Subtype involved
Asiatic (Russian) Flu	1889–90	1 million	possibly H2N2
Spanish Flu	1918–20	50 million	H1N1
Asian Flu	1957–58	1.5 to 2 million	H2N2
Hong Kong Flu	1968–69	1 million	H3N2
Swine Flu	As of 25 June 2010	over 18,209	novel H1N1

Spanish Flu (1918–1920)

The 1918 flu pandemic, commonly referred to as the Spanish flu, was a category 5 influenza pandemic caused by an unusually severe and deadly Influenza A virus strain of subtype H1N1.



The difference between the influenza mortality age-distributions of the 1918 epidemic and normal epidemics. Deaths per 100,000 persons in each age group, United States, for the interpandemic years 1911–1917 (dashed line) and the pandemic year 1918 (solid line).

The Spanish flu pandemic lasted from 1918 to 1919, although Price-Smith's data suggest it may have begun in Austria in the Spring of 1917. Older estimates say it killed 40–50 million people while current estimates say 50 million to 100 million people worldwide were killed. This pandemic has been described as "the greatest medical holocaust in history" and may have killed as many people as the Black Death, although the Black Death is estimated to have killed over a fifth of the world's population at the time, a significantly higher proportion. This huge death toll was caused by an extremely high infection rate of up to 50% and the extreme severity of the symptoms, suspected to be caused by cytokine storms. Indeed, symptoms in 1918 were so unusual that initially influenza was misdiagnosed as dengue, cholera, or typhoid. One observer wrote, "One of the most striking of the complications was hemorrhage from mucous membranes, especially from the nose, stomach, and intestine. Bleeding from the ears and petechial hemorrhages in the skin also occurred." The majority of deaths were from bacterial pneumonia, a secondary infection caused by influenza, but the virus also killed people directly, causing massive hemorrhages and edema in the lung.

The Spanish flu pandemic was truly global, spreading even to the Arctic and remote Pacific islands. The unusually severe disease killed between 2 and 20% of those infected, as opposed to the more usual flu epidemic mortality rate of 0.1%. Another unusual feature of this pandemic was that it mostly killed young adults, with 99% of pandemic influenza deaths occurring in people under 65, and more than half in young adults 20 to 40 years old. This is unusual since influenza is normally most deadly to the very young (under age 2) and the very old (over age 70). The total mortality of the 1918–1919 pandemic is not known, but it is estimated that up to 1% of the world's population was killed. As many as 25 million may have been killed in the first 25 weeks; in contrast, HIV/AIDS has killed 25 million in its first 25 years.

The Manchester Influenza Epidemic of 1937

The Epidemic that never escalated to Pandemic This is an example of an interwar epidemic that public health controls did not allow to develop into a full blown pandemic because of what was already known from 1918, as well as employing very strict patient, contact and family isolation. In 1937 there were 620 claims for sickness benefits made to various insurance companies.

Asian Flu (1957–1958)

The "Asian Flu" was a category 2 flu pandemic outbreak of avian influenza that originated in China in early 1956 lasting until 1958. It originated from mutation in wild ducks combining with a pre-existing human strain. The virus was first identified in Guizhou. It spread to Singapore in February 1957, reached Hong Kong by April, and US by June. Death toll in the US was approximately 69,800. The elderly were particularly vulnerable. Estimates of worldwide deaths vary widely depending on source, ranging from 1 million to 4 million.

Hong Kong Flu (1968–1969)

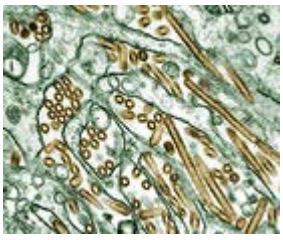
The Hong Kong Flu was a category 2 flu pandemic caused by a strain of H3N2 descended from H2N2 by antigenic shift, in which genes from multiple subtypes reassorted to form a new virus. The Hong Kong Flu pandemic of 1968 and 1969 killed an estimated one million people worldwide. Those over 65 had the greatest death rates. In the US, there were about 33,800 deaths.

2009 Flu Pandemic (Since 2009)

An epidemic of influenza-like illness of unknown causation occurred in Mexico in March–April 2009. On 24 April 2009, following the isolation of an A/H1N1 influenza in 7 ill patients in the southwest US. The WHO issued a statement on the outbreak of "influenza like illness" in the confirmed cases of A/H1N1 influenza had been reported in Mexico, and that 20 confirmed cases of the disease had been reported in the US.The next day, the number of confirmed cases rose to 40 in the US, 26 in Mexico, 6 in Canada, and 1 in Spain. The disease spread rapidly through the rest the spring, and by 3 May, a total of 787 confirmed cases had been reported worldwide. On 11 June 2009, the ongoing outbreak of Influenza A/H1N1, commonly referred to as "swine flu", was officially declared by the WHO to be the first influenza pandemic of the 21st century and a new strain of Influenza A virus subtype H1N1 first identified in April 2009. It is thought to be a mutation (reassortment) of four known strains of influenza A virus subtype H1N1: one endemic in humans, one endemic in birds, and two endemic in pigs (swine).

In 1 November 2009 a worldwide update by the UN's World Health Organization (WHO) stated that "199 countries and overseas territories/communities have officially reported a total of over 482,300 laboratory confirmed cases of the influenza pandemic H1N1 infection, that included 6,071 deaths."

H5N1



Influenza A virus subtype H5N1, also known as A(H5N1) or simply H5N1, is a subtype of the Influenza A virus which can cause illness in humans and many other animal species. A bird-adapted strain of H5N1, called HPAI A(H5N1) for "highly pathogenic avian influenza virus of type A of subtype H5N1", is the causative agent of H5N1 flu, commonly known as "avian influenza" or "bird flu". It is endemic in many bird populations, especially in Southeast Asia. One strain of HPAI A(H5N1) is spreading globally after first appearing in Asia. It is epizootic (an epidemic in nonhumans) and panzootic (affecting animals of many species, especially over a wide area), killing tens of millions of birds and spurring the culling of hundreds of millions of others to stem its spread. Most mentions of "bird flu" and H5N1 in the media refer to this strain.

HPAI A(H5N1) is an avian disease. There is no evidence of efficient human-to-human transmission or of airborne transmission of HPAI A(H5N1) to humans. In almost all cases, those infected with H5N1 had extensive physical contact with infected birds. Still, around 60% of humans known to have been infected with the current Asian strain of HPAI A(H5N1) have died from it, and H5N1 may mutate or reassort into a strain capable of efficient human-to-human transmission.

In 2003, world-renowned virologist Robert G. Webster published an article titled "The world is teetering on the edge of a pandemic that could kill a large fraction of the human population" in *American Scientist*. He called for adequate resources to fight what he sees as a major world threat to possibly billions of lives. On 29 September 2005, David Nabarro, the newly-appointed Senior United Nations System Coordinator for Avian and Human Influenza, warned the world that an outbreak of avian influenza could kill anywhere between 5 million and 150 million people. Experts have identified key events (creating new clades, infecting new species, spreading to new areas) marking the progression of an avian flu virus towards becoming pandemic, and many of those key events have occurred more rapidly than expected.

Due to the high lethality and virulence of HPAI A(H5N1), its endemic presence, its increasingly large host reservoir, and its significant ongoing mutations, the H5N1 virus is the world's largest current pandemic threat, and billions of dollars are being spent researching H5N1 and preparing for a potential influenza pandemic. At least 12 companies and 17 governments are developing pre-pandemic influenza vaccines in 28 different clinical trials that, if successful, could turn a deadly pandemic infection into a nondeadly one. Full-scale production of a vaccine that could prevent any illness at all from the strain would require at least three months after the virus's emergence to begin, but it is hoped that vaccine production could increase until one billion doses were produced by one year after the initial identification of the virus.

H5N1 may cause more than one influenza pandemic as it is expected to continue mutating in birds regardless of whether humans develop herd immunity to a future pandemic strain. Influenza pandemics from its genetic offspring may include influenza A virus subtypes other than H5N1. While genetic analysis of the H5N1 virus shows that influenza pandemics from its genetic offspring can easily be far more lethal than the Spanish Flu pandemic, planning for a future influenza pandemic is based on what can be done and there is no higher Pandemic Severity Index level than a Category 5 pandemic which, roughly speaking, is any pandemic as bad the Spanish flu or worse; and for which *all* intervention measures are to be used.

H5N1 is just one of the many subtypes of the species Influenza A virus. Any one of them can combine with each other or with different variant genotypes within its own subtype creating new variants, any one of which could become a pandemic strain. We know enough about the genetics to know what strains to fear most (example: only H5 and H7 subtypes are "highly pathogenic") and we know what genetic factors make a flu virus a human virus (i.e. easily passed human to human); so we know H5N1 is the biggest pandemic threat of all the strains in circulation and we know it is only a few antigenic

shift mutations or antigenic drift mutations from being an avian influenza virus to being a human flu virus. If it does this it may or may not still be in the H5N1 subtype. Both the drift and the shift can happen in any infected animal and then be passed to a human and spread like wildfire. Possible shift scenarios include the shift occurring in humans, pigs, or cats. To acquire the needed mutation through drift, it simply has to continue being an epidemic in birds long enough for the mutations to occur and then be passed to a human.

Other pandemic threat subtypes

"Human influenza virus" usually refers to those subtypes that spread widely among humans. H1N1, H1N2, and H3N2 are the only known Influenza A virus subtypes currently circulating among humans.

Genetic factors in distinguishing between "human flu viruses" and "avian influenza viruses" include:

> **PB2**: (RNA polymerase): Amino acid (or residue) position 627 in the PB2 protein encoded by the PB2 RNA gene. Until H5N1, all known avian influenza viruses had a Glu at position 627, while all human influenza viruses had a lysine.
> **HA**: (hemagglutinin): Avian influenza HA bind alpha 2–3 sialic acid receptors while human influenza HA bind alpha 2–6 sialic acid receptors. Swine influenza viruses have the ability to bind both types of sialic acid receptors.

"About 52 key genetic changes distinguish avian influenza strains from those that spread easily among people, according to researchers in Taiwan, who analyzed the genes of more than 400 A type flu viruses." "How many mutations would make an avian virus capable of infecting humans efficiently, or how many mutations would render an influenza virus a pandemic strain, is difficult to predict. We have examined sequences from the 1918 strain, which is the only pandemic influenza virus that could be entirely derived from avian strains. Of the 52 species-associated positions, 16 have residues typical for human strains; the others remained as avian signatures. The result supports the hypothesis that the 1918 pandemic virus is more closely related to the avian influenza A virus than are other human influenza viruses."

Highly pathogenic H5N1 avian influenza kills 50% of humans that catch it. In one case, a boy with H5N1 experienced diarrhea followed rapidly by a coma without developing respiratory or flu-like symptoms.

The Influenza A virus subtypes that have been confirmed in humans, ordered by the number of known human pandemic deaths, are:

- H1N1 caused "Spanish Flu" and the 2009 swine flu outbreak (novel H1N1)
- H2N2 caused "Asian Flu"
- H3N2 caused "Hong Kong Flu"
- H5N1 is "bird flu", endemic in avians
- H7N7 has unusual zoonotic potential

- H1N2 is currently endemic in humans and pigs
- H9N2, H7N2, H7N3, H10N7

H1N1

H1N1 is currently endemic in both human and pig populations. A variant of H1N1 was responsible for the Spanish flu pandemic that killed some 50 million to 100 million people worldwide over about a year in 1918 and 1919. Controversy arose in October 2005, after the H1N1 genome was published in the journal, *Science*. Many fear that this information could be used for bioterrorism . "When he compared the 1918 virus with today's human flu viruses, Dr. Taubenberger noticed that it had alterations in just 25 to 30 of the virus's 4,400 amino acids. Those few changes turned a bird virus into a killer that could spread from person to person."

In mid-April 2009, an H1N1 variant appeared in Mexico, with its center in Mexico City. By 26 April the variant had spread widely; with cases reported in Canada, the US, New Zealand, the UK, France, Spain and Israel. On 29 April WHO raised the worldwide pandemic phase to 5. On 11 June 2009 the WHO raised the worldwide pandemic phase to 6, which means that the H1N1 swine flu has reached pandemic proportions, with nearly 30,000 confirmed cases worldwide. 8 November 2009 worldwide update by the UN's World Health Organization (WHO) states that "206 countries and overseas territories/communities have officially reported over 503,536 laboratory confirmed cases of the influenza pandemic H1N1 infection, including 6,250 deaths."

1. Microscopic image of the H1N1 virus

2. Microscopic image of the H1N1 virus

H2N2

The Asian Flu was a pandemic outbreak of H2N2 avian influenza that originated in China in 1957, spread worldwide that same year during which a influenza vaccine was developed, lasted until 1958 and caused between one and four million deaths.

H3N2

H3N2 is currently endemic in both human and pig populations. It evolved from H2N2 by antigenic shift and caused the Hong Kong Flu pandemic of 1968 and 1969 that killed up to 750,000. "An early-onset, severe form of influenza A H3N2 made headlines when it claimed the lives of several children in the United States in late 2003."

The dominant strain of annual flu in January 2006 is H3N2. Measured resistance to the standard antiviral drugs amantadine and rimantadine in H3N2 has increased from 1% in 1994 to 12% in 2003 to 91% in 2005.

"[C]ontemporary human H3N2 influenza viruses are now endemic in pigs in southern China and can reassort with avian H5N1 viruses in this intermediate host."

H7N7

H7N7 has unusual zoonotic potential. In 2003 in Netherlands 89 people were confirmed to have H7N7 influenza virus infection following an outbreak in poultry on several farms. One death was recorded.

H1N2

H1N2 is currently endemic in both human and pig populations. The new H1N2 strain appears to have resulted from the reassortment of the genes of the currently circulating influenza H1N1 and H3N2 subtypes. The hemagglutinin protein of the H1N2 virus is similar to that of the currently circulating H1N1 viruses and the neuraminidase protein is similar to that of the current H3N2 viruses.

Strategies to prevent a flu pandemic

Here we, explain strategies to prevent a flu pandemic by a Council on Foreign Relations panel.

If influenza remains an animal problem with limited human-to-human transmission it is not a pandemic, though it continues to pose a risk. To prevent the situation from progressing to a pandemic, the following short-term strategies have been put forward:

- Culling and vaccinating livestock
- Vaccinating poultry workers against common flu
- Limiting travel in areas where the virus is found

The rationale for vaccinating poultry workers against common flu is that it reduces the probability of common influenza virus recombining with avian H5N1 virus to form a pandemic strain. Longer term strategies proposed for regions where highly pathogenic H5N1 is endemic in wild birds have included:

- changing local farming practices to increase farm hygiene and reduce contact between livestock and wild birds.
- altering farming practices in regions where animals live in close, often unsanitary quarters with people, and changing the practices of open-air "wet markets" where birds are kept for live sale and slaughtered on-site. A challenge to implementing these measures is widespread poverty, frequently in rural areas, coupled with a reliance upon raising fowl for purposes of subsistence farming or income without measures to prevent propagation of the disease.
- changing local shopping practices from purchase of live fowl to purchase of slaughtered, pre-packaged fowl.
- improving veterinary vaccine availability and cost.

Strategies to slow down a flu pandemic

Vaccines

A vaccine probably would not be available in the initial stages of population infection. A vaccine cannot be developed to protect against a virus which does not exist yet. The Avian Flu virus H5N1 has the potential to mutate into a pandemic strain, but so do other types of flu virus. Once a potential virus is identified and a vaccine is approved, it normally takes five to six months before the vaccine becomes available.

The capability to produce vaccines varies widely from country to country; in fact, only 19 countries are listed as "influenza vaccine manufacturers" according to the World Health Organization. It is estimated that, in a best scenario situation, 750 million doses could be produced each year, whereas it is likely that each individual would need two doses of the vaccine to become immuno-competent. Distribution to and inside countries would probably be problematic. Several countries, however, have well-developed plans for producing large quantities of vaccine. For example, Canadian health authorities say that they are developing the capacity to produce 32 million doses within four months, enough vaccine to inoculate every person in the country.

Another concern is whether countries which do not manufacture vaccines themselves, including those where a pandemic strain is likely to originate, will be able to purchase vaccine to protect their population. Cost considerations aside, they fear that the countries with vaccine-manufacturing capability will reserve production to protect their own populations and not release vaccines to other countries until their own population is protected. Indonesia has refused to share samples of H5N1 strains which have infected and killed its citizens until it receives assurances that it will have access to vaccines produced with those samples. So far, it has not received those assurances. However, in September 2009, The United States and France agreed to make 10 percent of their H1N1 vaccine supply available to other countries through the World Health Organization.

There are two serious technical problems associated with the development of a vaccine against H5N1. The first problem is this: seasonal influenza vaccines require a single injection of 15 μg haemagluttinin in order to give protection; H5 seems to evoke only a weak immune response and a large multicentre trial found that two injections of 90 μg H5 given 28 days apart provided protection in only 54% of people (Treanor 2006). Even if it is considered that 54% is an acceptable level of protection, the world is currently capable of producing only 900 million doses at a strength of 15 μg (assuming that all production were immediately converted to manufacturing H5 vaccine); if two injections of 90 μg are needed then this capacity drops to only 70 million (Poland 2006). Trials using adjuvants such as alum, AS03, AS04 or MF59 to try and lower the dose of vaccine are urgently needed. The second problem is this: there are two circulating clades of virus, clade 1 is the virus originally isolated in Vietnam, clade 2 is the virus isolated in Indonesia. Vaccine research has mostly been focused on clade 1 viruses, but the clade 2 virus is antigenically distinct and a clade 1 vaccine will probably not protect against a pandemic caused by clade 2 virus.

Since 2009, most vaccine development efforts have been focused on the current pandemic influenza virus H1N1. As of July 2009, more than 70 known clinical trials are have been completed or are ongoing for pandemic influenza vaccines. In September

2009, the US Food and Drug Administration approved four vaccines against the 2009 H1N1 influenza virus, and expect the initial vaccine lots to be avaialable within the following month.

Anti-viral drugs

Many nations, as well as the World Health Organization, are working to stockpile anti-viral drugs in preparation for a possible pandemic. Oseltamivir (trade name Tamiflu) is the most commonly sought drug, since it is available in pill form. Zanamivir (trade name Relenza) is also considered for use, but it must be inhaled. Other anti-viral drugs are less likely to be effective against pandemic influenza.

Both Tamiflu and Relenza are in short supply, and production capabilities are limited in the medium term. Some doctors say that co-administration of Tamiflu with probenecid could double supplies.

There also is the potential of viruses to evolve drug resistance. Some H5N1-infected persons treated with oseltamivir have developed resistant strains of that virus.

Tamiflu was originally discovered by Gilead Sciences and licensed to Roche for late-phase development and marketing.

Public Response Measures

- **Social distancing:** By traveling less, working from home or closing schools, there is less opportunity for the virus to spread. Reduce the time spent in crowded settings if possible. And keep your distance (preferably at least 1 metre) from people who show symptoms of influenza-like illness, such as coughing and sneezing.
- **Respiratory hygiene:** Advise people to cover their coughs and sneezes. If using a tissue, make sure you dispose of it carefully and then clean your hands immediately afterwards. If you do not have a tissue handy when you cough or sneeze, cover your mouth as much as possible with the crook of your elbow.
- **Handwashing Hygiene:** Frequent handwashing with soap and water (or with an alcohol-based hand sanitizer) is very important, especially after coughing or sneezing, and after contact with other people or with potentially contaminated surfaces (such as handrails, shared utensils, etc.)
- **Other hygiene:** Avoid touching your eyes, nose and mouth as much as possible.
- **Masks:** No mask can provide a perfect barrier but products that meet or exceed the NIOSH N95 standard recommended by the World Health Organization are thought to provide good protection. WHO recommends that health-care workers wear N95 masks and that patients wear surgical masks (which may prevent respiratory secretions from becoming airborne). Any mask may be useful to remind the wearer not to touch the face. This can reduce infection due to contact with contaminated surfaces, especially in crowded public places where coughing

or sneezing people have no way of washing their hands. The mask itself can become contaminated and must be handled as medical waste when removed.

- **Risk communication:** To encourage the public to comply with strategies to reduce the spread of disease, "communications regarding possible community interventions [such as requiring sick people to stay home from work, closing schools] for pandemic influenza that flow from the federal government to communities and from community leaders to the public not overstate the level of confidence or certainty in the effectiveness of these measures."

The Institute of Medicine has published a number of reports and summaries of workshops on public policy issues related to influenza pandemics. They are collected in Pandemic Influenza: A Guide to Recent Institute of Medicine Studies and Workshops and some strategies from these reports are included in the list above.

Phases

WHO Pandemic Influenza Phases (2009)	
Phase	**Description**
Phase 1	No animal influenza virus circulating among animals have been reported to cause infection in humans.
Phase 2	An animal influenza virus circulating in domesticated or wild animals is known to have caused infection in humans and is therefore considered a specific potential pandemic threat.
Phase 3	An animal or human-animal influenza reassortant virus has caused sporadic cases or small clusters of disease in people, but has not resulted in human-to-human transmission sufficient to sustain community-level outbreaks.
Phase 4	Human to human transmission of an animal or human-animal influenza reassortant virus able to sustain community-level outbreaks has been verified.
Phase 5	Human-to-human spread of the virus in two or more countries in one WHO region.

Phase 6	In addition to the criteria defined in Phase 5, the same virus spreads from human-to-human in at least one other country in another WHO region.
Post peak period	Levels of pandemic influenza in most countries with adequate surveillance have dropped below peak levels.
Post pandemic period	Levels of influenza activity have returned to the levels seen for seasonal influenza in most countries with adequate surveillance.

The World Health Organization (WHO) has developed a global influenza preparedness plan, which defines the stages of a pandemic, outlines WHO's role and makes recommendations for national measures before and during a pandemic.

In the 2009 revision of the phase descriptions, the WHO has retained the use of a six-phase approach for easy incorporation of new recommendations and approaches into existing national preparedness and response plans. The grouping and description of pandemic phases have been revised to make them easier to understand, more precise, and based upon observable phenomena. Phases 1–3 correlate with preparedness, including capacity development and response planning activities, while phases 4–6 clearly signal the need for response and mitigation efforts. Furthermore, periods after the first pandemic wave are elaborated to facilitate post pandemic recovery activities.

The phases are defined below.

In nature, influenza viruses circulate continuously among animals, especially birds. Even though such viruses might theoretically develop into pandemic viruses, in **Phase 1** no viruses circulating among animals have been reported to cause infections in humans.

In **Phase 2** an animal influenza virus circulating among domesticated or wild animals is known to have caused infection in humans, and is therefore considered a potential pandemic threat.

In **Phase 3**, an animal or human-animal influenza reassortant virus has caused sporadic cases or small clusters of disease in people, but has not resulted in human-to-human transmission sufficient to sustain community-level outbreaks. Limited human-to-human transmission may occur under some circumstances, for example, when there is close contact between an infected person and an unprotected caregiver. However, limited transmission under such restricted circumstances does not indicate that the virus has gained the level of transmissibility among humans necessary to cause a pandemic.

Phase 4 is characterized by verified human-to-human transmission of an animal or human-animal influenza reassortant virus able to cause "community-level outbreaks". The ability to cause sustained disease outbreaks in a community marks a significant upwards shift in the risk for a pandemic. Any country that suspects or has verified such an event should urgently consult with the WHO so that the situation can be jointly assessed and a decision made by the affected country if implementation of a rapid pandemic containment operation is warranted. Phase 4 indicates a significant increase in risk of a pandemic but does not necessarily mean that a pandemic is a foregone conclusion.

Phase 5 is characterized by human-to-human spread of the virus into at least two countries in one WHO region. While most countries will not be affected at this stage, the declaration of Phase 5 is a strong signal that a pandemic is imminent and that the time to finalize the organization, communication, and implementation of the planned mitigation measures is short.

Phase 6, the pandemic phase, is characterized by community level outbreaks in at least one other country in a different WHO region in addition to the criteria defined in Phase 5. Designation of this phase will indicate that a global pandemic is under way.

During the **post-peak period**, pandemic disease levels in most countries with adequate surveillance will have dropped below peak observed levels. The post-peak period signifies that pandemic activity appears to be decreasing; however, it is uncertain if additional waves will occur and countries will need to be prepared for a second wave.

Previous pandemics have been characterized by waves of activity spread over months. Once the level of disease activity drops, a critical communications task will be to balance this information with the possibility of another wave. Pandemic waves can be separated by months and an immediate "at-ease" signal may be premature.

In the **post-pandemic period**, influenza disease activity will have returned to levels normally seen for seasonal influenza. It is expected that the pandemic virus will behave as a seasonal influenza A virus. At this stage, it is important to maintain surveillance and update pandemic preparedness and response plans accordingly. An intensive phase of recovery and evaluation may be required.

Government preparations for a potential H5N1 pandemic (2003–2009)

According to *The New York Times* as of March 2006, "governments worldwide have spent billions planning for a potential influenza pandemic: buying medicines, running disaster drills, [and] developing strategies for tighter border controls" due to the H5N1 threat.

[T]he United States is collaborating closely with eight international organizations, including the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO), the World Organization for Animal Health (OIE), and 88 foreign governments to address the situation through planning, greater monitoring, and full transparency in reporting and investigating avian influenza occurrences. The United States and these international partners have led global efforts to encourage countries to heighten surveillance for outbreaks in poultry and significant numbers of deaths in migratory birds and to rapidly introduce containment measures. The U.S. Agency for International Development (USAID) and the U.S. Departments of State, Health and Human Services (HHS), and Agriculture (USDA) are coordinating future international response measures on behalf of the White House with departments and agencies across the federal government.

Together steps are being taken to "minimize the risk of further spread in animal populations", "reduce the risk of human infections", and "further support pandemic planning and preparedness".

Ongoing detailed mutually coordinated onsite surveillance and analysis of human and animal H5N1 avian flu outbreaks are being conducted and reported by the USGS National Wildlife Health Center, the Centers for Disease Control and Prevention, the World Health Organization, the European Commission, the National Influenza Centers, and others.

United Nations

In September 2005, David Nabarro, a lead UN health official warned that a bird flu outbreak could happen anytime and had the potential to kill 5–150 million people.

World Health Organization

The World Health Organization (WHO), believing that the world was closer to another influenza pandemic than it has been any time since 1968, when the last of the 20th century's three pandemics swept the globe, has developed guidelines on pandemic influenza preparedness and response. The March 2005 plan includes guidance on roles and responsibilities in preparedness and response; information on pandemic phases; and recommended actions for before, during, and after a pandemic.

United States

"[E]fforts by the federal government to prepare for pandemic influenza at the national level include a $100 million DHHS initiative in 2003 to build U.S. vaccine production. Several agencies within Department of Health and Human Services (DHHS) – including the Office of the Secretary, the Food and Drug Administration (FDA), CDC, and the National Institute of Allergy and Infectious Diseases (NIAID) – are in the process of working with vaccine manufacturers to facilitate production of pilot vaccine lots for both H5N1 and H9N2 strains as well as contracting for the manufacturing of 2 million doses

of an H5N1 vaccine. This H5N1 vaccine production will provide a critical pilot test of the pandemic vaccine system; it will also be used for clinical trials to evaluate dose and immunogenicity and can provide initial vaccine for early use in the event of an emerging pandemic."

Each State and Territory of the United States has a specific Pandemic Flu Plan which covers Avian Flu, Swine Flu (H1N1) and other potential influenza epidemics. The State Plans together with a professionally vetted search engine of flu related research, policies, and plans, is available at the current portal: Pandemic Flu Search.

On 26 August 2004, Secretary of Health and Human Services, Tommy Thompson released a draft Pandemic Influenza Response and Preparedness Plan, which outlined a coordinated national strategy to prepare for and respond to an influenza pandemic. Public comments were accepted for 60 days.

In a speech before the United Nations General Assembly on 14 September 2005, President George W. Bush announced the creation of the International Partnership on Avian and Pandemic Influenza. The Partnership brings together nations and international organizations to improve global readiness by:

- elevating the issue on national agendas;
- coordinating efforts among donor and affected nations;
- mobilizing and leveraging resources;
- increasing transparency in disease reporting and surveillance; and
- building capacity to identify, contain and respond to a pandemic influenza.

On 5 October 2005, Democratic Senators Harry Reid, Evan Bayh, Dick Durbin, Ted Kennedy, Barack Obama, and Tom Harkin introduced the Pandemic Preparedness and Response Act as a proposal to deal with a possible outbreak.

On 27 October 2005, the Department of Health and Human Services awarded a $62.5 million contract to Chiron Corporation to manufacture an avian influenza vaccine designed to protect against the H5N1 influenza virus strain. This followed a previous awarded $100 million contract to sanofi pasteur, the vaccines business of the sanofi-aventis Group, for avian flu vaccine.

In October 2005, President Bush urged bird flu vaccine manufacturers to increase their production.

On 1 November 2005 President Bush unveiled the National Strategy To Safeguard Against The Danger of Pandemic Influenza. He also submitted a request to Congress for $7.1 billion to begin implementing the plan. The request includes $251 million to detect and contain outbreaks before they spread around the world; $2.8 billion to accelerate development of cell-culture technology; $800 million for development of new treatments and vaccines; $1.519 billion for the Departments of Health and Human Services (HHS) and Defense to purchase influenza vaccines; $1.029 billion to stockpile antiviral

medications; and $644 million to ensure that all levels of government are prepared to respond to a pandemic outbreak.

On 6 March 2006, Mike Leavitt, Secretary of Health and Human Services, said U.S. health agencies are continuing to develop vaccine alternatives that will protect against the evolving avian influenza virus.

The U.S. government, bracing for the possibility that migrating birds could carry a deadly strain of bird flu to North America, plans to test nearly eight times as many wild birds starting in April 2006 as have been tested in the past decade.

On 8 March 2006, Dr. David Nabarro, senior UN coordinator for avian and human influenza, said that given the flight patterns of wild birds that have been spreading avian influenza (bird flu) from Asia to Europe and Africa, birds infected with the H5N1 virus could reach the Americas within the next six to 12 months.

"5 Jul 2006 (CIDRAP News) – In an update on pandemic influenza preparedness efforts, the federal government said last week it had stockpiled enough vaccine against H5N1 avian influenza virus to inoculate about 4 million people and enough antiviral medication to treat about 6.3 million."

Canada

The Public Health Agency of Canada follows the WHO's categories, but has expanded them. The Avian Flu scare of 2006 prompted The Canadian Public Health Agency to release an updated Pandemic Influenza Plan for Health Officials. This document was created to address the growing concern over the hazards faced by public health officials when exposed to sick or dying patients.

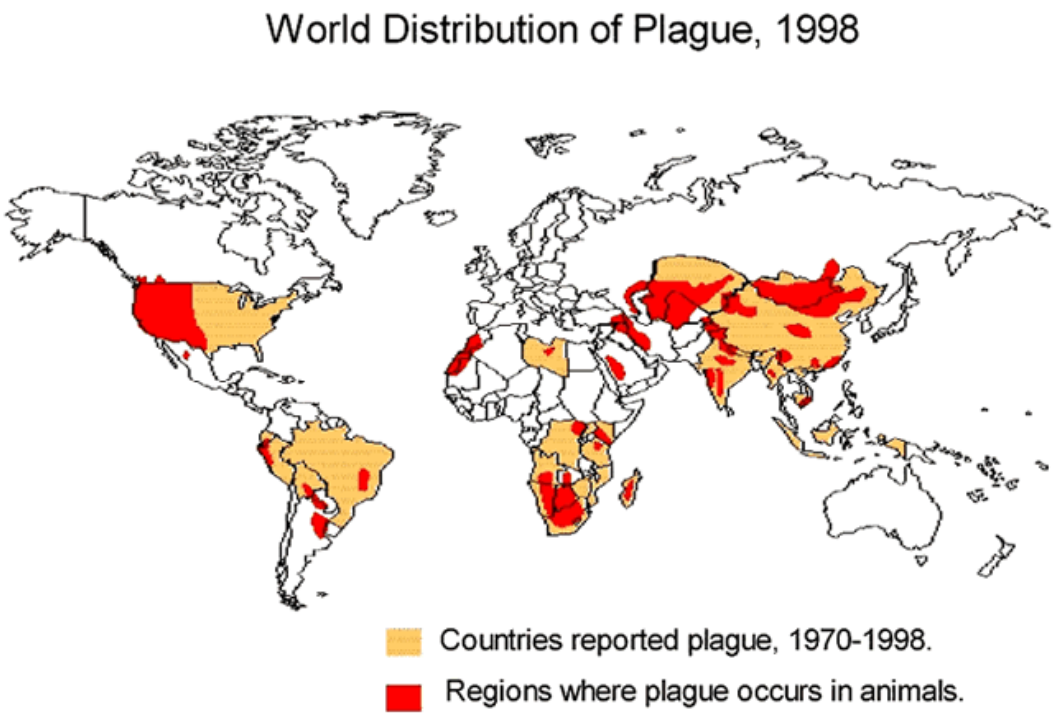
Malaysia

Since the Nipah virus outbreak in 1999, the Malaysian Health Ministry have put in place processes to be better prepared to protect the Malaysian population from the threat of infectious diseases. Malaysia was fully prepared during the Severe Acute Respiratory Syndrome (SARS) situation (Malaysia was not a SARS affected country) and the episode of the H5N1 (bird flu) outbreak in 2004.

The Malaysian government has developed a National Influenza Pandemic Preparedness Plan (NIPPP) which serves as a time bound guide for preparedness and response plan for influenza pandemic. It provides a policy and strategic framework for a multisectoral response and contains specific advice and actions to be undertaken by the Ministry of Health at the different levels, other governmental departments and agencies and non governmental organizations to ensure that resources are mobilized and used most efficiently before, during and after a pandemic episode.

Chapter- 6

Third Pandemic



Worldwide distribution of plague infected animals 1998

Third Pandemic is the designation of a major plague pandemic that began in the Yunnan province in China in 1855. This episode of bubonic plague spread to all inhabited continents, and ultimately killed more than 12 million people in India and China alone. According to the World Health Organization, the pandemic was considered active until 1959, when worldwide casualties dropped to 200 per year.

Bubonic plague is an infectious disease that is widely thought to have caused several epidemics or pandemics throughout history, including two previous pandemics commonly designated as the Plague of Justinian and the Black Death. New research suggests Black Death is lying dormant.

Casualty patterns indicate that waves of this late 19th century/early 20th century pandemic may have been from two different sources. The first was primarily bubonic and was carried around the world through ocean-going trade, through transporting infected persons, rats and cargoes harboring fleas. The second, more virulent strain, was primarily pneumonic in character with a strong person-to-person contagion. This strain was largely confined to Asia, particularly Manchuria and Mongolia.

Pattern of the pandemic

The bubonic plague was endemic in populations of infected ground rodents in central Asia, and was a known cause of death among migrant and established human populations in that region for centuries; however, an influx of new people due to political conflicts and global trade led to the distribution of this disease throughout the world.

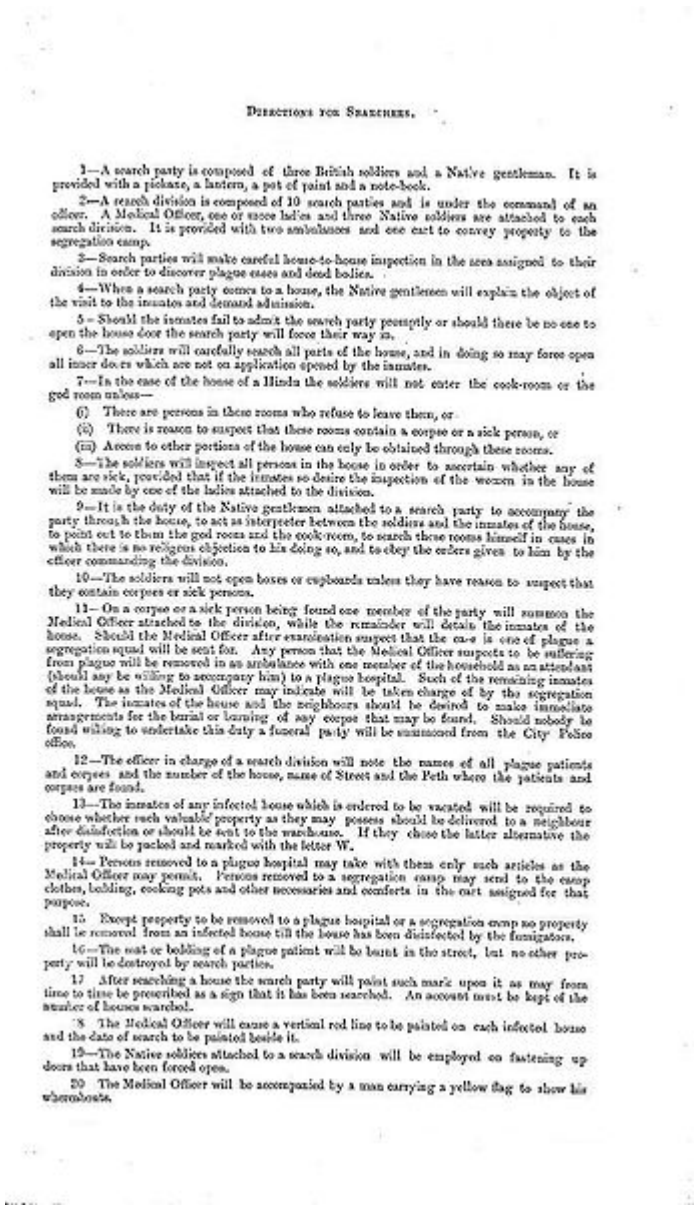
Outbreak in China

Picture of Manchurian Plague victims in 1910-1911

The initial outbreak was in China's Yunnan Province in the 1850s. The disease was stable within the province, but was spread due to a Muslim rebellion. The rebellion displaced local tribes, and also changed animal harvesting practices, leading to greater contact with infected animals. In addition, the rebellion meant that refugees from the conflict moved south, into regions of China with larger populations. The plague went with them, producing an increasing number of casualties. In the city of Canton, beginning in March 1894, the disease killed 60,000 people in just a few weeks. Daily water traffic with the nearby city of Hong Kong rapidly spread the plague. Within two months, after

100,000 deaths, the death rates dropped below epidemic rates, although the disease continued to be endemic in Hong Kong until 1929.

Political impact in colonial India



DIRECTIONS FOR SEARCHERS.

1—A search party is composed of three British soldiers and a Native gentleman. It is provided with a pickaxe, a lantern, a pot of paint and a note-book.

2—A search division is composed of 10 search parties and is under the command of an officer. A Medical Officer, one or more ladies and three Native soldiers are attached to each search division. It is provided with two ambulances and one cart to convey property to the segregation camp.

3—Search parties will make careful house-to-house inspection in the area assigned to their division in order to discover plague cases and dead bodies.

4—When a search party comes to a house, the Native gentleman will explain the object of the visit to the inmates and demand admission.

5—Should the inmates fail to admit the search party promptly or should there be no one to open the house door the search party will force their way in.

6—The soldiers will carefully search all parts of the house, and in doing so may force open all inner doors which are not on application opened by the inmates.

7—In the case of the house of a Hindu the soldiers will not enter the cook-room or the god room unless—

(i) There are persons in these rooms who refuse to leave them, or

(ii) There is reason to suspect that these rooms contain a corpse or a sick person, or

(iii) Access to other portions of the house can only be obtained through these rooms.

8—The soldiers will inspect all persons in the house in order to ascertain whether any of them are sick, provided that if the inmates so desire the inspection of the women in the house will be made by one of the ladies attached to the division.

9—It is the duty of the Native gentleman attached to a search party to accompany the party through the house, to act as interpreter between the soldiers and the inmates of the house, to point out to them the god rooms and the cook-room, to search these rooms himself in cases in which there is no religious objection to his doing so, and to obey the orders given to him by the officer commanding the division.

10—The soldiers will not open boxes or cupboards unless they have reason to suspect that they contain corpses or sick persons.

11—On a corpse or a sick person being found one member of the party will summon the Medical Officer attached to the division, while the remainder will detain the inmates of the house. Should the Medical Officer after examination suspect that the case is one of plague a segregation squad will be sent for. Any person that the Medical Officer suspects to be suffering from plague will be removed in an ambulance with one member of the household as an attendant (should any be willing to accompany him) to a plague hospital. Such of the remaining inmates of the house as the Medical Officer may indicate will be taken charge of by the segregation squad. The inmates of the house and the neighbours should be desired to make immediate arrangements for the burial or burning of any corpse that may be found. Should nobody be found willing to undertake this duty a funeral party will be summoned from the City Police office.

12—The officer in charge of a search division will note the names of all plague patients and corpses and the number of the house, name of Street and the Peth where the patients and corpses are found.

13—The inmates of any infected house which is ordered to be vacated will be required to choose whether such valuable property as they may possess should be delivered to a neighbour after disinfection or should be sent to the warehouse. If they chose the latter alternative the property will be packed and marked with the letter W.

14—Persons removed to a plague hospital may take with them only such articles as the Medical Officer may permit. Persons removed to a segregation camp may send to the camp clothes, bedding, cooking pots and other necessaries and comforts in the cart assigned for that purpose.

15 Except property to be removed to a plague hospital or a segregation camp no property shall be removed from an infected house till the house has been disinfected by the fumigators.

16—The mat or bedding of a plague patient will be burnt in the street, but no other property will be destroyed by search parties.

17 After searching a house the search party will paint such mark upon it as may from time to time be prescribed as a sign that it has been searched. An account must be kept of the number of houses searched.

18 The Medical Officer will cause a vertical red line to be painted on each infected house and the date of search to be painted beside it.

19—The Native soldiers attached to a search division will be employed on fastening up doors that have been forced open.

20 The Medical Officer will be accompanied by a man carrying a yellow flag to show his whereabouts.

Directions for searchers, Pune plague of 1897

Plague came to India in 1896, most likely from Hong Kong where the epidemic had been festering since 1894. Over the next thirty years, the country would lose 12.5 million people to the disease. Almost all cases were bubonic, with only a very small percentage changing to pneumonic plague.(Orent, p. 185) The disease was initially seen in port cities, beginning with Bombay (now Mumbai), but later emerged in Pune, Kolkata and Karachi (now in Pakistan). By 1899, the outbreak spread to smaller communities and

rural areas in many regions of India. Overall, the impact of plague epidemics was greatest in western and northern India – in the provinces then designated as Bombay, Punjab and the United Provinces - while eastern and southern India were not as badly affected.

The colonial government's measures to control the disease included quarantine, isolation camps, travel restrictions and the exclusion of India's traditional medical practices. Restrictions on the populations of the coastal cities were established by Special Plague Committees with overreaching powers, and enforced by the British military. Indians found these measures culturally intrusive and generally repressive and tyrannical. Government strategies of plague control underwent significant changes during 1898-1899. By that time it was apparent that the use of force in enforcing plague regulations was proving counter-productive and, now that the plague had spread to rural areas, enforcement in larger geographic areas would be impossible. At this time, British health officials began to press for widespread vaccination using Waldemar Haffkine's plague vaccine, although the government stressed that inoculation was not compulsory. British authorities also authorized the inclusion of practitioners of indigenous systems of medicine into plague prevention programs.

Repressive government actions to control the plague gave the Pune nationalists an opportunity to berate the government publicly. On 22 June 1897, the Chapekar brothers, young Pune brahmins, shot and killed W. C. Rand, an Indian Civil Services officer acting as Pune Special Plague Committee chairman, and his military escort, Lt. Ayerst. The action of the Chapekars has been considered the worst violence against political authority seen anywhere in the world during the third plague pandemic. The government also found the nationalist press guilty of incitement. Independence activist Bal Gangadhar Tilak was charged with sedition for his writings as editor of the Kesari newspaper. He was sentenced to eighteen months rigorous imprisonment. This punishment made him a living martyr to the struggle for Indian independence.

Public reaction to the exceptionally intrusive health measures enacted by the British Indian state ultimately revealed the political constraints of medical intervention in the country. These experiences were formative in the development of India's modern public health services.

Global Distribution

The network of global shipping ensured the widespread distribution of the disease over the next few decades. Recorded outbreaks include:

- Pakhoi, China 1882.
- Canton, China 1894.
- Hong Kong 1894.
- Formosa, Japan 1896.
- Bombay Presidency, India 1896-1898.
- Calcutta, India 1898.
- Madagascar, 1898.

- Egypt, 1899.
- Manchuria, China 1899.
- Paraguay, 1899.
- South Africa, 1899-1902.
- Republic of Hawaii, 1899.
- San Francisco, United States, 1900.
- Australia, 1900-1905.
- Russia/Soviet Union, 1900-1927.
- Fukien Province, China 1901.
- Thailand, 1904.
- Burma, 1905.
- Tunisia, 1907.
- Trinidad, Venezuela, Peru and Ecuador, 1908.
- Bolivia and Brazil, 1908.
- Cuba and Puerto Rico, 1912.

Each of these areas, as well as Great Britain, France and other areas of Europe, continued to experience plague outbreaks and casualties until the 1950s. The last significant outbreak of plague associated with the pandemic occurred in Peru and Argentina in 1945.

Disease research

Researchers working in Asia during the "Third Pandemic" identified plague vectors and the plague bacillus. In 1894, in Hong Kong, Swiss-born French bacteriologist Alexandre Yersin isolated the responsible bacterium (*Yersinia pestis*) and determined the common mode of transmission. Japanese physician and researcher Kitasato Shibasaburō initially mis-identified the bacterium. In 1898, French researcher Paul-Louis Simond demonstrated the role of fleas as a vector.

The disease is caused by a bacterium usually transmitted by the bite of fleas from an infected host, often a black rat. The bacteria are transferred from the blood of infected rats to the rat flea (*Xenopsylla cheopsis*). The bacillus multiplies in the stomach of the flea, blocking it. When the flea next bites a mammal, the consumed blood is regurgitated along with the bacillus into the bloodstream of the bitten animal. Any serious outbreak of plague in humans is preceded by an outbreak in the rodent population. During the outbreak, infected fleas that have lost their normal rodent hosts seek other sources of blood. The bacterium which causes this disease, *Yersinia pestis*, was named for Yersin. His discoveries led in time to modern treatment methods, including insecticides, the use of antibiotics and eventually plague vaccines.

The British colonial government in India pressed medical researcher Waldemar Haffkine to develop a plague vaccine. After three months of persistent work with a limited staff, a form for human trials was ready. On January 10, 1897 Haffkine tested it on himself. After the initial test was reported to the authorities, volunteers at the Byculla jail were used in a control test, all inoculated prisoners survived the epidemics, while seven inmates of the control group died. By the turn of the century, the number of inoculees in India alone

reached four million. Haffkine was appointed the Director of the Plague Laboratory (now called Haffkine Institute) in Bombay.

Chapter- 7

Viral Hemorrhagic Fever & Antibiotic Resistance

Viral hemorrhagic fever

The **viral hemorrhagic fevers** (**VHFs**) are a diverse group of animal and human illnesses that are caused by four distinct families of RNA viruses: the Arenaviridae, Filoviridae, Bunyaviridae, and Flaviviridae. All types of VHF are characterized by fever and bleeding disorders and all can progress to high fever, shock and death in extreme cases. Some of the VHF agents cause relatively mild illnesses, such as the Scandinavian *nephropathia epidemica*, while others, such as the African Ebola virus, can cause severe, life-threatening disease.

Etiologic agents

- The Arenaviridae include the viruses responsible for Lassa fever and Argentine, Bolivian, Brazilian and Venezuelan hemorrhagic fevers.
- The Bunyaviridae include the members of the *Hantavirus* genus that cause hemorrhagic fever with renal syndrome (HFRS), the Crimean-Congo hemorrhagic fever (CCHF) virus from the *Nairovirus* genus, and the Rift Valley fever (RVF) virus from the *Phlebovirus* genus.
- The Filoviridae include Ebola and Marburg viruses.
- Finally, the Flaviviridae include dengue, yellow fever, and two viruses in the tick-borne encephalitis group that cause VHF: Omsk hemorrhagic fever virus and Kyasanur Forest disease virus.

The most recently recognized virus capable of causing hemorrhagic fever is Lujo virus, a new member of the arenaviruses described in 2009 and found in South Africa.

Clinical and treatment aspects

Signs and symptoms of VHFs include (by definition) fever and bleeding diathesis. Manifestations of VHF often also include flushing of the face and chest, petechiae, frank bleeding, edema, hypotension, and shock. Malaise, myalgias, headache, vomiting, and diarrhea occur frequently. Definitive diagnosis is usually made at a reference laboratory with advanced biocontainment capabilities.

The findings of laboratory investigation vary somewhat between the viruses but in general there is a decrease in the total white cell count particularly the lymphocytes, a decrease in the platelet count, an increase in the serum liver enzymes and an increase in both the prothrombin (PT) and activated partial thromboplastin times (PTT). The hematocrit may be elevated. The serum urea and creatine may be raised but this is dependent on the hydration status of the patient. The bleeding time tends to be prolonged.

Medical management of VHF patients may require intensive supportive care. Antiviral therapy with intravenous ribavirin may be useful in Bunyaviridae and Arenaviridae infections (specifically Lassa fever, RVF, CCHF, and HFRS due to Old World Hantavirus infection) and can be used only under an experimental protocol as investigational new drug (IND) approved by the U.S. Food and Drug Administration (FDA). Interferon may be effective in Argentine or Bolivian hemorrhagic fevers (also available only as IND). Experimental vaccines for other VHFs are not readily available.

Prophylactic (preventive) ribavirin may be effective for some Bunyaviridae and Arenaviridae infections (again, available only as IND).

VHF isolation guidelines dictate that all VHF patients (with the exception of dengue patients) should be cared for using strict contact precautions, including hand hygiene, double gloves, gowns, shoe and leg coverings, and faceshield or goggles. Lassa, CCHF, Ebola, and Marburg viruses may be particularly prone to nosocomial (hospital-based) spread. Airborne precautions should be utilized including, at a minimum, a fit-tested, HEPA filter-equipped respirator (such as an N-95 mask), a battery-powered, air-purifying respirator, or a positive pressure supplied air respirator to be worn by personnel coming within six feet of a VHF patient. Multiple patients should be cohorted (sequestered) to a separate building or a ward with an isolated air-handling system. Environmental decontamination is typically accomplished with hypochlorite or phenolic disinfectants.

Pathophysiology

The diversity of clinical features seen among the VHF infections probably originates from varying mechanisms of pathogenesis. An immunopathogenic mechanism, for example, has been identified for dengue hemorrhagic fever, which usually occurs among patients previously infected with a heterologous dengue serotype. An influential theory explaining this phenomenon is called “antibody-dependent enhancement.” In contrast, disseminated intravascular coagulation (DIC) is thought to underlie the hemorrhagic features of Rift Valley, Marburg and Ebola fevers. In most VHFs, however, the etiology of the coagulopathy is most likely multifactorial (e.g., hepatic damage, consumptive coagulopathy, primary marrow dysfunction, etc).

The reasons for variation among patients infected with the same virus are unknown but stem from a complex system of virus-host interactions. Moreover, why some infected persons develop full-blown VHF while others do not also remains an unresolved issue. Virulence of the infecting agent clearly plays an important role. The “VHF syndrome” (capillary leak, bleeding diathesis and hemodynamic compromise leading to shock)

occurs in a majority of patients manifesting disease from filoviruses, CCHF and the South American hemorrhagic fever viruses, while it occurs in a small minority of patients with dengue, RVF and Lassa fever. This can also cause severe bleeding through openings in your body.

Notable VHF outbreaks

- Cocoliztli in New Mexico 1545.
- Mékambo in Gabon is the site of several outbreaks of Ebola hemorrhagic fever.
- Orientale, Congo villages of Durba and Watsa were the epicenter of the 1998–2000 outbreak of Marburg hemorrhagic fever.
- Uige Province in Angola is the site of world's worst hemorrhagic fever epidemic, which occurred in 2005.
- The ongoing VHF outbreak in the village of Mweka, Democratic Republic of the Congo (DRC) that started in August, 2007, and that has killed 103 people (100 adults and three children), has been shown to be caused (at least partially) by the Ebola virus.
- Some experts believe that the Black Death of the Middle Ages may have been caused by a VHF and not by the bubonic plague.

Antibiotic resistance

Antibiotic resistance is a type of drug resistance where a microorganism is able to survive exposure to an antibiotic. Genes can be transferred between bacteria in a horizontal fashion by conjugation, transduction, or transformation. Thus a gene for antibiotic resistance which had evolved via natural selection may be shared. Evolutionary stress such as exposure to antibiotics then selects for the antibiotic resistant trait. Many antibiotic resistance genes reside on plasmids, facilitating their transfer. If a bacterium carries several resistance genes, it is called multiresistant or, informally, a **superbug** or **super bacterium**.

The primary cause of antibiotic resistance is genetic mutation in bacteria. The prevalence of antibiotic resistant bacteria is a result of antibiotic use both within medicine and veterinary medicine. The greater the duration of exposure the greater the risk of the development of resistance irrespective of the severity of the need for antibiotics. As resistance becomes more common there becomes a greater need for alternative treatments. However despite a push for new antibiotic therapies there has been a continued decline in the number of newly approved drugs. Antibiotic resistance therefore poses a significant problem.

Causes

The widespread use of antibiotics both inside and outside of medicine is playing a significant role in the emergence of resistant bacteria. Antibiotics are often used in rearing animals for food and this use among others leads to the creation of resistant strains of bacteria. In some countries antibiotics are sold over the counter without a prescription which also leads to the creation of resistant strains. In supposedly well-regulated human medicine the major problem of the emergence of resistant bacteria is due to misuse and overuse of antibiotics by doctors as well as patients. Other practices contributing towards resistance include the addition of antibiotics to the feed of livestock. Household use of antibacterials in soaps and other products, although not clearly contributing to resistance, is also discouraged (as not being effective at infection control). Also unsound practices in the pharmaceutical manufacturing industry can contribute towards the likelihood of creating antibiotic resistant strains.

Certain antibiotic classes are highly associated with colonisation with superbugs compared to other antibiotic classes. The risk for colonisation increases if there is a lack of sensitivity (resistance) of the superbugs to the antibiotic used and high tissue penetration as well as broad spectrum activity against "good bacteria". In the case of MRSA, increased rates of MRSA infections are seen with glycopeptides, cephalosporins and especially quinolones. In the case of colonisation with C difficile the high risk antibiotics include cephalosporins and in particular quinolones and clindamycin.

In medicine

The volume of antibiotic prescribed is the major factor in increasing rates of bacterial resistance rather than compliance with antibiotics. A single dose of antibiotics leads to a greater risk of resistant organisms to that antibiotic in the person for up to a year.

Inappropriate prescribing of antibiotics has been attributed to a number of causes including: people who insist on antibiotics, physicians simply prescribe them as they feel they do not have time to explain why they are not necessary, physicians who do not know when to prescribe antibiotics or else are overly cautious for medical legal reasons. A third of people for example believe that antibiotics are effective for the common cold and 22% of people do not finish a course of antibiotics primarily due to that fact that they feel better (varying from 10% to 44% depending on the country). Compliance with once daily antibiotics is better than with twice daily antibiotics. Sub optimum antibiotic concentrations in critically ill people increase the frequency of antibiotic resistance organisms. While taking antibiotics doses less than those recommended may increase rates of resistance, shortening the course of antibiotics may actually decrease rates of resistance.

Poor hand hygiene by hospital staff has been associated with the spread of resistant organisms and an increase in hand washing compliance results in decreased rates of these organisms.

Role of other animals

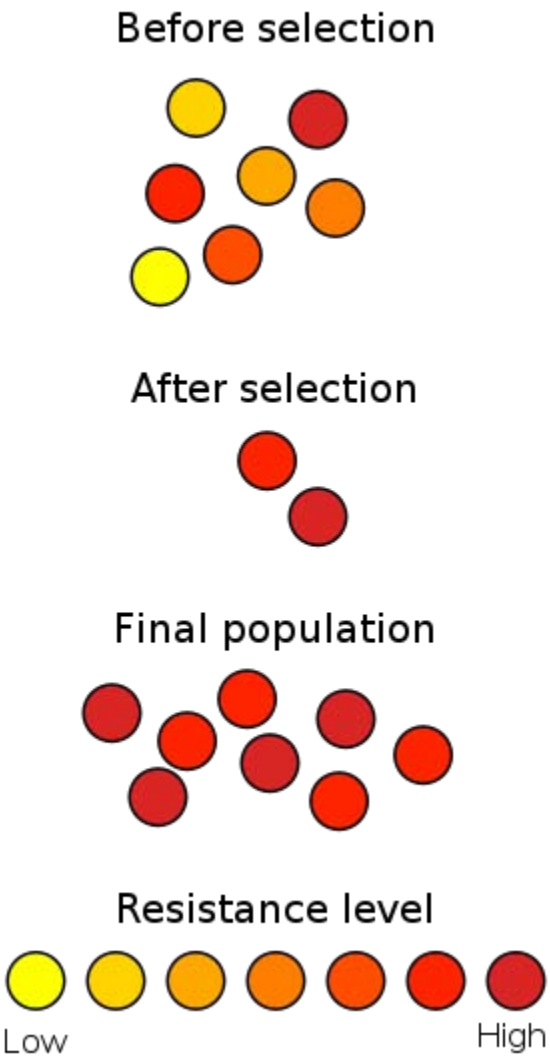
Drugs are used in animals that are used as human food, such as cows, pigs, chickens, fish, etc., and these drugs can affect the safety of the meat, milk, and eggs produced from those animals and can be the source of superbugs. For example, farm animals, particularly pigs, are believed to be able to infect people with MRSA. The resistant bacteria in animals due to antibiotic exposure can be transmitted to humans via three pathways, those being through the consumption of meat, from close or direct contact with animals, or through the environment.

The World Health Organization concluded that antibiotics as growth promoters in animal feeds should be prohibited (in the absence of risk assessments). In 1998, European Union health ministers voted to ban four antibiotics widely used to promote animal growth (despite their scientific panel's recommendations). Regulation banning the use of antibiotics in European feed, with the exception of two antibiotics in poultry feeds, became effective in 2006. In Scandinavia, there is evidence that the ban has led to a lower prevalence of antimicrobial resistance in (non-hazardous) animal bacterial populations. In the USA federal agencies do not collect data on antibiotic use in animals but animal to human spread of drug resistant organisms has been demonstrated in research studies. Antibiotics are still used in U.S. animal feed—along with other ingredients which have safety concerns.

Growing U.S. consumer concern about using antibiotics in animal feed has led to a niche market of "antibiotic-free" animal products, but this small market is unlikely to change entrenched industry-wide practices.

In 2001, the Union of Concerned Scientists estimated that greater than 70% of the antibiotics used in the US are given to food animals (e.g. chickens, pigs and cattle) in the absence of disease. In 2000 the US Food and Drug Administration (FDA) announced their intention to revoke approval of fluoroquinolone use in poultry production because of substantial evidence linking it to the emergence of fluoroquinolone resistant campylobacter infections in humans. The final decision to ban fluoroquinolones from use in poultry production was not made until five years later because of challenges from the food animal and pharmaceutical industries. Today, there are two federal bills (S. 549 and H.R. 962) aimed at phasing out "non-therapeutic" antibiotics in US food animal production.

Mechanisms



Schematic representation of how antibiotic resistance evolves via natural selection. The top section represents a population of bacteria before exposure to an antibiotic. The middle section shows the population directly after exposure, the phase in which selection took place. The last section shows the distribution of resistance in a new generation of bacteria. The legend indicates the resistance levels of individuals.

Antibiotic resistance can be a result of horizontal gene transfer, and also of unlinked point mutations in the pathogen genome and a rate of about 1 in 10^8 per chromosomal replication. The antibiotic action against the pathogen can be seen as an environmental pressure; those bacteria which have a mutation allowing them to survive will live on to reproduce. They will then pass this trait to their offspring, which will result in a fully resistant colony.

The four main mechanisms by which microorganisms exhibit resistance to antimicrobials are:

1. Drug inactivation or modification: e.g. enzymatic deactivation of *Penicillin* G in some penicillin-resistant bacteria through the production of β-lactamases.
2. Alteration of target site: e.g. alteration of PBP—the binding target site of penicillins—in MRSA and other penicillin-resistant bacteria.
3. Alteration of metabolic pathway: e.g. some sulfonamide-resistant bacteria do not require para-aminobenzoic acid (PABA), an important precursor for the synthesis of folic acid and nucleic acids in bacteria inhibited by sulfonamides. Instead, like mammalian cells, they turn to utilizing preformed folic acid.
4. Reduced drug accumulation: by decreasing drug permeability and/or increasing active efflux (pumping out) of the drugs across the cell surface.

There are three known mechanisms of fluoroquinolone resistance. Some types of efflux pumps can act to decrease intracellular quinolone concentration. In gram-negative bacteria, plasmid-mediated resistance genes produce proteins that can bind to DNA gyrase, protecting it from the action of quinolones. Finally, mutations at key sites in DNA gyrase or Topoisomerase IV can decrease their binding affinity to quinolones, decreasing the drug's effectiveness. Research has shown that the bacterial protein LexA may play a key role in the acquisition of bacterial mutations giving resistance to quinolones and rifampicin.

Antibiotic resistance can also be introduced artificially into a microorganism through laboratory protocols, sometimes used as a selectable marker to examine the mechanisms of gene transfer or to identify individuals that absorbed a piece of DNA that included the resistance gene and another gene of interest.

Resistant pathogens

Staphylococcus aureus

Staphylococcus aureus (colloquially known as "Staph aureus" or a *Staph infection*) is one of the major resistant pathogens. Found on the mucous membranes and the human skin of around a third of the population, it is extremely adaptable to antibiotic pressure. It was one of the earlier bacteria in which penicillin resistance was found—in 1947, just four years after the drug started being mass-produced. Methicillin was then the antibiotic of choice, but has since been replaced by oxacillin due to significant kidney toxicity. MRSA (methicillin-resistant *Staphylococcus aureus*) was first detected in Britain in 1961 and is now "quite common" in hospitals. MRSA was responsible for 37% of fatal cases of sepsis in the UK in 1999, up from 4% in 1991. Half of all *S. aureus* infections in the US are resistant to penicillin, methicillin, tetracycline and erythromycin.

This left vancomycin as the only effective agent available at the time. However, strains with intermediate (4-8 μg/ml) levels of resistance, termed GISA (glycopeptide intermediate *Staphylococcus aureus*) or VISA (vancomycin intermediate *Staphylococcus aureus*), began appearing in the late 1990s. The first identified case was in Japan in 1996, and strains have since been found in hospitals in England, France and the US. The first

documented strain with complete (>16 μg/ml) resistance to vancomycin, termed VRSA (Vancomycin-resistant *Staphylococcus aureus*) appeared in the United States in 2002.

A *new* class of antibiotics, oxazolidinones, became available in the 1990s, and the first commercially available oxazolidinone, linezolid, is comparable to vancomycin in effectiveness against MRSA. Linezolid-resistance in *Staphylococcus aureus* was reported in 2003.

CA-MRSA (Community-acquired MRSA) has now emerged as an epidemic that is responsible for rapidly progressive, fatal diseases including necrotizing pneumonia, severe sepsis and necrotizing fasciitis. Methicillin-resistant *Staphylococcus aureus* (MRSA) is the most frequently identified antimicrobial drug-resistant pathogen in US hospitals. The epidemiology of infections caused by MRSA is rapidly changing. In the past 10 years, infections caused by this organism have emerged in the community. The 2 MRSA clones in the United States most closely associated with community outbreaks, USA400 (MW2 strain, ST1 lineage) and USA300, often contain Panton-Valentine leukocidin (PVL) genes and, more frequently, have been associated with skin and soft tissue infections. Outbreaks of community-associated (CA)-MRSA infections have been reported in correctional facilities, among athletic teams, among military recruits, in newborn nurseries, and among men who have sex with men. CA-MRSA infections now appear to be endemic in many urban regions and cause most CA-S. aureus infections.

Streptococcus and *Enterococcus*

Streptococcus pyogenes (Group A Streptococcus: GAS) infections can usually be treated with many different antibiotics. Early treatment may reduce the risk of death from invasive group A streptococcal disease. However, even the best medical care does not prevent death in every case. For those with very severe illness, supportive care in an intensive care unit may be needed. For persons with necrotizing fasciitis, surgery often is needed to remove damaged tissue. Strains of *S. pyogenes* resistant to macrolide antibiotics have emerged, however all strains remain uniformly sensitive to penicillin.

Resistance of *Streptococcus pneumoniae* to penicillin and other beta-lactams is increasing worldwide. The major mechanism of resistance involves the introduction of mutations in genes encoding penicillin-binding proteins. Selective pressure is thought to play an important role, and use of beta-lactam antibiotics has been implicated as a risk factor for infection and colonization. Streptococcus pneumoniae is responsible for pneumonia, bacteremia, otitis media, meningitis, sinusitis, peritonitis and arthritis.

Penicillin-resistant pneumonia caused by *Streptococcus pneumoniae* (commonly known as *pneumococcus*), was first detected in 1967, as was penicillin-resistant gonorrhea. Resistance to penicillin substitutes is also known as beyond *S. aureus*. By 1993 *Escherichia coli* was resistant to five fluoroquinolone variants. *Mycobacterium tuberculosis* is commonly resistant to isoniazid and rifampin and sometimes universally resistant to the common treatments. Other pathogens showing some resistance include *Salmonella*, *Campylobacter*, and *Streptococci*.

Enterococcus faecium is another superbug found in hospitals. Penicillin-Resistant Enterococcus was seen in 1983, vancomycin-resistant enterococcus (VRE) in 1987, and Linezolid-Resistant Enterococcus (LRE) in the late 1990s.

Pseudomonas aeruginosa

Pseudomonas aeruginosa is a highly prevalent opportunistic pathogen. One of the most worrisome characteristics of *P. aeruginosa* consists in its low antibiotic susceptibility. This low susceptibility is attributable to a concerted action of multidrug efflux pumps with chromosomally-encoded antibiotic resistance genes (e.g. *mexAB-oprM*, *mexXY* etc.) and the low permeability of the bacterial cellular envelopes. Besides intrinsic resistance, *P. aeruginosa* easily develop acquired resistance either by mutation in chromosomally-encoded genes, or by the horizontal gene transfer of antibiotic resistance determinants. Development of multidrug resistance by *P. aeruginosa* isolates requires several different genetic events that include acquisition of different mutations and/or horizontal transfer of antibiotic resistance genes. Hypermutation favours the selection of mutation-driven antibiotic resistance in *P. aeruginosa* strains producing chronic infections, whereas the clustering of several different antibiotic resistance genes in integrons favours the concerted acquisition of antibiotic resistance determinants. Some recent studies have shown that phenotypic resistance associated to biofilm formation or to the emergence of small-colony-variants may be important in the response of *P. aeruginosa* populations to antibiotics treatment.

Clostridium difficile

Clostridium difficile is a nosocomial pathogen that causes diarrheal disease in hospitals world wide. Clindamycin-resistant *C. difficile* was reported as the causative agent of large outbreaks of diarrheal disease in hospitals in New York, Arizona, Florida and Massachusetts between 1989 and 1992. Geographically dispersed outbreaks of *C. difficile* strains resistant to fluoroquinolone antibiotics, such as Cipro (ciprofloxacin) and Levaquin (levofloxacin), were also reported in North America in 2005.

Salmonella and *E. coli*

Escherichia coli and *Salmonella* come directly from contaminated food. Of the meat that is contaminated with *E. coli*, eighty percent of the bacteria are resistant to one or more drugs made; it causes bladder infections that are resistant to antibiotics ("HSUS Fact Sheet"). *Salmonella* was first found in humans in the 1970s and in some cases is resistant to as many as nine different antibiotics ("HSUS Fact Sheet"). When both bacterium are spread, serious health conditions arise. Many people are hospitalized each year after becoming infected, and some die as a result.

Acinetobacter baumannii

On November 5, 2004, the Centers for Disease Control and Prevention (CDC) reported an increasing number of *Acinetobacter baumannii* bloodstream infections in patients at

military medical facilities in which service members injured in the Iraq/Kuwait region during Operation Iraqi Freedom and in Afghanistan during Operation Enduring Freedom were treated. Most of these showed multidrug resistance (MRAB), with a few isolates resistant to all drugs tested.

Alternatives

Prevention

Rational use of antibiotics may reduce the chances of development of opportunistic infection by antibiotic-resistant bacteria due to dysbacteriosis. In one study the use of fluoroquinolones are clearly associated with *Clostridium difficile* infection, which is a leading cause of nosocomial diarrhea in the United States, and a major cause of death, worldwide.

There is clinical evidence that topical dermatological preparations such as those containing tea tree oil and thyme oil may be effective in preventing transmittal of CA-MRSA. In addition, other phytotherapeutic medicines too can reduce the use of antibiotics or eliminate their use entirely.

Vaccines do not suffer the problem of resistance because a vaccine enhances the body's natural defenses, while an antibiotic operates separately from the body's normal defenses. Nevertheless, new strains may evolve that escape immunity induced by vaccines; for example an update Influenza vaccine is needed each year.

While theoretically promising, anti-staphylococcal vaccines have shown limited efficacy, because of immunological variation between *Staphylococcus* species, and the limited duration of effectiveness of the antibodies produced. Development and testing of more effective vaccines is under way.

The Australian Commonwealth Scientific and Industrial Research Organization (CSIRO), realizing the need for the reduction of antibiotic use, has been working on two alternatives. One alternative is to prevent diseases by adding cytokines instead of antibiotics to animal feed. These proteins are made in the animal body "naturally" after a disease and are not antibiotics so they do not contribute to the antibiotic resistance problem. Furthermore, studies on using cytokines have shown that they also enhance the growth of animals like the antibiotics now used, but without the drawbacks of non-therapeutic antibiotic use. Cytokines have the potential to achieve the animal growth rates traditionally sought by the use of antibiotics without the contribution of antibiotic resistance associated with the widespread non-therapeutic uses of antibiotics currently utilized in the food animal production industries. Additionally, CSIRO is working on vaccines for diseases.

Phage therapy

Phage therapy, an approach that has been extensively researched and utilized as a therapeutic agent for over 60 years, especially in the Soviet Union, is an alternative that might help with the problem of resistance. Phage therapy was widely used in the United States until the discovery of antibiotics, in the early 1940s. Bacteriophages or "phages" are viruses that invade bacterial cells and, in the case of lytic phages, disrupt bacterial metabolism and cause the bacterium to lyse. Phage therapy is the therapeutic use of lytic bacteriophages to treat pathogenic bacterial infections.

Bacteriophage therapy is an important alternative to antibiotics in the current era of multidrug resistant pathogens. A review of studies that dealt with the therapeutic use of phages from 1966–1996 and few latest ongoing phage therapy projects via internet showed: phages were used topically, orally or systemically in Polish and Soviet studies. The success rate found in these studies was 80–95% with few gastrointestinal or allergic side effects. British studies also demonstrated significant efficacy of phages against *Escherichia coli*, *Acinetobacter* spp., *Pseudomonas* spp and *Staphylococcus aureus*. US studies dealt with improving the bioavailability of phage. Phage therapy may prove as an important alternative to antibiotics for treating multidrug resistant pathogens.

Research

New medications

Until recently, research and development (R&D) efforts have provided new drugs in time to treat bacteria that became resistant to older antibiotics. That is no longer the case. The potential crisis at hand is the result of a marked decrease in industry R&D, and the increasing prevalence of resistant bacteria. Infectious disease physicians are alarmed by the prospect that effective antibiotics may not be available to treat seriously ill patients in the near future.

The pipeline of new antibiotics is drying up. Major pharmaceutical companies are losing interest in the antibiotics market because these drugs may not be as profitable as drugs that treat chronic (long-term) conditions and lifestyle issues.

The resistance problem demands that a renewed effort be made to seek antibacterial agents effective against pathogenic bacteria resistant to current antibiotics. One of the possible strategies towards this objective is the rational localization of bioactive phytochemicals. Plants have an almost limitless ability to synthesize aromatic substances, most of which are phenols or their oxygen-substituted derivatives such as tannins. Most are secondary metabolites, of which at least 12,000 have been isolated, a number estimated to be less than 10% of the total . In many cases, these substances serve as plant defense mechanisms against predation by microorganisms, insects, and herbivores. Many of the herbs and spices used by humans to season food yield useful medicinal compounds including those having antibacterial activity.

Traditional healers have long used plants to prevent or cure infectious conditions. Many of these plants have been investigated scientifically for antimicrobial activity and a large

number of plant products have been shown to inhibit growth of pathogenic bacteria. A number of these agents appear to have structures and modes of action that are distinct from those of the antibiotics in current use, suggesting that cross-resistance with agents already in use may be minimal. For example the combination of 5'-methoxyhydnocarpine and berberine in herbs like Hydrastis canadensis and Berberis vulgaris can block the MDR-pumps that cause multidrug resistance. This has been shown for Staphylococcus aureus.

Archaeocins is the name given to a new class of potentially useful antibiotics that are derived from the Archaea group of organisms. Eight archaeocins have been partially or fully characterized, but hundreds of archaeocins are believed to exist, especially within the haloarchaea. The prevalence of archaeocins is unknown simply because no one has looked for them. The discovery of new archaeocins hinges on recovery and cultivation of archaeal organisms from the environment. For example, samples from a novel hypersaline field site, Wilson Hot Springs, recovered 350 halophilic organisms; preliminary analysis of 75 isolates showed that 48 were archaeal and 27 were bacterial.

In research published on October 17, 2008 in *Cell*, a team of scientists pinpointed the place on bacteria where the antibiotic myxopyronin launches its attack, and why that attack is successful. The myxopyronin binds to and inhibits the crucial bacterial enzyme, RNA polymerase. The myxopyronin changes the structure of the switch-2 segment of the enzyme, inhibiting its function of reading and transmitting DNA code. This prevents RNA polymerase from delivering genetic information to the ribosomes, causing the bacteria to die.

One of the major causes of antibiotic resistance is the decrease of effective drug concentrations at their target place, due to the increased action of ABC transporters. Since ABC transporter blockers can be used in combination with current drugs to increase their effective intracellular concentration, the possible impact of ABC transporter inhibitors is of great clinical interest. ABC transporter blockers that may be useful to increase the efficacy of current drugs have entered clinical trials and are available to be used in therapeutic regimes.

Applications

Antibiotic resistance is an important tool for genetic engineering. By constructing a plasmid which contains an antibiotic resistance gene as well as the gene being engineered or expressed, a researcher can ensure that when bacteria replicate, only the copies which carry along the plasmid survive. This ensures that the gene being manipulated passes along when the bacteria replicates.

The most commonly used antibiotics in genetic engineering are generally "older" antibiotics which have largely fallen out of use in clinical practice. These include:

- ampicillin
- kanamycin

- tetracycline
- chloramphenicol

Industrially the use of antibiotic resistance is disfavored since maintaining bacterial cultures would require feeding them large quantities of antibiotics. Instead, the use of auxotrophic bacterial strains (and function-replacement plasmids) is preferred.