History of Epidemics and Plagues

Introduction

Every infection is a race between the microbes and the host. The germ, following the indelible rules of evolution, strives to survive and reproduce, while the host’s immune system mounts a warlike defense designed to find, destroy, and eliminate it. A microbe that kills its host quickly cannot be expected to survive long enough to reproduce. Thus excessive virulence is not necessarily an evolutionary advantage, rather germs that can reproduce and be passed from one host to another are usually favored.

Definitions

The **prevalence** of a disease is the proportion of diseased individuals at any one time (point prevalence) or over a given period (period prevalence). The **incidence** is the proportion of new cases of a disease that occur within a defined population over an established period of time. The Centers for Disease Control and Prevention (CDC) frequently reports prevalence and incidence of a disease as the numbers of cases in addition to the proportions of cases. Frequently either prevalence or incidence, or both, are given as a rate, meaning the number of cases in a fixed number of people, e.g., cases per 100,000 per year. Individual cases of disease in widely separated geographic areas or otherwise independent cases are said to be **sporadic**.

There is an **outbreak** of disease, if there are many related cases in a small geographic area. Any excessive (that means many cases, not just fifty or a hundred) and related incidence of a particular disease above what is normally expected in a human population is defined to be an **epidemic**. When an epidemic extends beyond the confines of a wide area, typically a continent, and becomes a more widespread problem, it is called a **pandemic**. AIDS today is a pandemic disease, insofar as cases have been diagnosed on every continent, save Antarctica. Any disease with a low to moderate normal base level incidence rate in the population, but not necessarily constant, is said to be **endemic**. The common cold is endemic in northern latitudes and sleeping sickness is endemic in tropical Africa.

Not all diseases can erupt into epidemics. The microbe needs to be transmitted to new hosts in order to continue reproducing. In small towns everyone could contract the disease in such a short time that the pathogen could die out as it killed all of the available hosts. There is a critical size for a group below which the disease cannot become an epidemic, but above which it can. Historical records seem to indicate that in human habitations this size is about 250,000. Thus major epidemics did not find their way into recorded history until cities evolved to this critical level of population.

Individuals who are infected and show either no or only mild symptoms are said to have a **subclinical infection**. Subclinically infected individuals, those with no evident symptoms, are identified as **carriers** of the disease because they are carrying and frequently shedding the disease agent.

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1 Just to complete the terminology, a sudden and large outbreak of a disease among animals is an **epizootic** and a sudden and large outbreak of disease among plants is an **epiphytotic**.
There are two major types of infectious diseases which can develop into epidemics: common source and host-to-host. **Common source** epidemics arise from a contaminated source, such as water or food, while **host-to-host** infections are transmitted from one infected individual to another via various, perhaps indirect, routes. The number of new cases as a function of time for each epidemic type are shown below.

![Graph showing common source and host-to-host epidemics](image)

Common source epidemics arise rapidly and, once the source is discovered and eliminated, the number of new cases drops off rapidly. On the other hand, host-to-host epidemics are slow to grow and harder to eliminate.

Anything causing disease is called a **pathogen**. A **vector** is an organism that serves as an intermediary in the transmission of a host-to-host disease. For instance, several infections are transmitted by mosquitoes, fleas, ticks, etc. to people.

**Coevolution**

The colonization of a susceptible host by a microbe may lead to exponential growth of the parasite. If there is active transmission to others, an epidemic may develop. If this continues over a long period of time, then it is possible that the host population will develop resistance and the spread of the microbe may be checked and some form of equilibrium may be reached. Genetic changes in the host could destroy the parasite or a change in the microbe could initiate another epidemic. The disease would continue until the host develops an appropriate response to check the microbes’ growth. As this process continues, each agent affects the evolution of the other; in this case, the two organisms are said to be **coevolving**. This coevolution is a process of continuous change as both organisms follow the rules of evolution and move toward some form of equilibrium.

A classic example of coevolution dates back to the 1950s. European settlers introduced rabbits to Australia in 1859. With few natural predators, the rabbits did what rabbits always do, and soon they covered most of the continent, wreaking environmental havoc.

Scientists studied the myxoma virus, spread by mosquitoes, which exists in equilibrium with South American rabbits, but is deadly to European rabbits. In 1950 the virus was introduced to Australia in an attempt to control the rabbit population. The first year saw 95% of the infected rabbits dead of the disease myxomatosis. As the weaker
hosts died off, the virus mutated to a less virulent strain. At the same time, the rabbit population consisted only of those remaining that, when challenged by the virus, survived. So what remained were more robust rabbits and a weaker strain of the virus. As the two organisms coevolved over about six years, both the virus and the rabbits survived, albeit at reduced levels. What remained were the less virulent virus and the immunologically stronger rabbits. The rabbit population stabilized at about 20% of the pre-epidemic levels.

Rabbits remain a problem in Australia and in 1995 another disease was introduced into the rabbit population with similar results.

The dread diseases faced by past societies, and largely (but not universally) absent today include, but are not limited to, the following.

**Plague**

Arguably the ultimate scourge of mankind (and over 100 species of animals) was the so-called Black Death. The generic “plague” (with a lower case p) has entered the language as a descriptor for any deadly epidemic disease. Plague (with an upper case P) is caused by *Yersinia pestis*, a rod-shaped, Gram-negative bacterium. As few as one bacterium is an infective dose! But a single flea bite will transfer between 25 and 100 thousand bacteria.

The bacteria’s *reservoir* consists of rats and the fleas live on them, like the Indian rat flea, of which only adult females feed on hosts. This flea is fairly hardy and can survive for 6 to 12 months off a host in dung, abandoned rodent’s nests, textile bales, and on rodents, such as prairie rats, squirrels, gerbils, field mice, etc.

*Y. pestis* is *enzootic*; meaning it is present in a low to moderate incidence rate among rodents and can even survive in their burrows after an *epizootic* (a high incidence outbreak among animals).

Black rats (*Rattus rattus*—which were common in ancient times, but have since been supplanted by the larger and more aggressive brown rats, *Rattus norvegicus*) rarely move more than 200 meters from their nest and are good climbers, hence their adaptability to the thatched roof homes of either the Middle Ages, present day rural Africa, or parts of the Asian subcontinent. Normally the fleas live on the rodents in a form of equilibrium, but sometimes that equilibrium is upset when the microorganism multiplies rapidly in the flea’s gut, eventually blocking the lumen (the space within its gut) so that the flea regurgitates infected material as it attempts to feed. This infects the rodent and it contracts a form of the fatal disease called *murine* or *silvatic Plague*. When infected, rats are asymptomatic until near death, whereupon they swell up (because the *Y. pestis* grow so rapidly and in such large numbers that they block the rat’s biliary duct) and stagger as if intoxicated. The fleas then leave their dying
hosts and seek residence in the nearest warm-blooded animals. Considering that fleas can jump several feet, “nearest” is a relative term.

One to six days after a human receives a flea-bite, the lymph nodes in the armpit (axilla) and groin become very tender and swollen (as large as an egg\(^2\)). These very painful swollen areas are called **buboes** (from the Greek *bubo*, meaning groin). The buboes may **suppurate**, i.e., break and discharge a particularly fetid pus. Each of the buboes shown below are on young children (to give you a perspective of size).

Sometimes the original bite site becomes infected and suppurates. It is not rare for the area of the bite to become gangrenous and necrotic, i.e., the tissue dies. Other symptoms include restlessness, staggering gait, mental confusion, prostration, delirium, rapid pulse, nausea, aching of the extremities and back, and a high fever (at least 40° C = 104° F). Then one of two avenues is followed. If the fever breaks, there is usually remission and the immune system has gained the upper hand over the pathogen, which it then proceeds to destroy and expel. If the fever doesn’t break, the infection spreads to the blood, causing “blood poisoning” and death. This is the course of **bubonic Plague**.

In some cases the microbe can proceed directly to the blood stream and this **septicemic Plague** can occur before the formation of buboes and results in death before a diagnosis can be made. Some scientists feel that this form of Plague can even be carried by either the common human flea or the body louse. In this infection of the blood, called septicemia, blood vessels break and leak under the skin causing a dark rash as the blood dries (hence the name **Black Death**, which was given in the 1500s). This blackening tends to begin at the extremities (as in the fingers of the hand shown below).

For both bubonic and septicemic Plague, there is hemorrhagic illness (internal bleeding), multiple system failure, and death. All of this occurs within three to seven days. The mortality rate for untreated bubonic Plague is about 50–75% and 100% for septicemic Plague. The observed mortality rate for treated bubonic Plague is 14% and 22% for septicemic Plague.

Neither bubonic nor septicemic Plague is known to be transmitted from person-to-person.

As it rages throughout the population, Plague can change to a more virulent form and enter the lungs, whereupon the victims initially cough up a blood-spotted mucus and then graduate to coughing bloody froth, all the while spreading the disease via aerosol droplets. This **pneumonic Plague** has a 100% mortality rate, if

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\(^2\) They range in diameter from 1 to 10 cm.
untreated\(^3\), and death can occur in a matter of hours. Small children having the Plague frequently went into convulsions, wherein their bodies jerked about uncontrollably prior to death—not a pleasant sight.

Streptomycin, gentamicin, and tetracycline are treatments of choice for all three varieties of Plague. Penicillin has no effect. Medication must be given within the first 18 hours of infection to be completely effective.

Quarantine (from the Italian \textit{quarentina}, meaning forty days\(^4\) for the time of isolation of ships entering harbor which were suspected of carrying some form of contagion) is only somewhat effective at the outset of an outbreak. In the 14\(^{th}\) century, Milan, Florence, and Venice employed quarantines with a vengeance. The homes of sufferers were sealed—well and sick left to die for lack of food and water. Of course, the human residents of such dwellings were constrained, while the rats could come and go as they pleased. Even rats aboard docked quarantined ships had easy egress, because they could climb down the mooring ropes and onto the docks.

Plague predated the Middle Ages by more than 1000 years. The first recorded epidemic erupted in Mongolia in 46 CE. Before it burned itself out, it had taken about two-thirds of the population with it. China was next to play host in 312. Its northern and western provinces were decimated; more than 90% of the population was lost to the disease. 468 bore witness to another major epidemic in China.

The next major Plague epidemics (pandemics?) occurred:

- in 540 CE at Pelusium, Egypt and reached Constantinople in 542 and spread into Europe and Asia (the Plague of Justinian\(^5\)) in the following decade;
- 14\(^{th}\) century Europe, following the caravan routes, it was in the lower Volga River basin in 1345, the Caucasus and Crimea by 1346, Constantinople by 1347, Alexandria in the autumn of 1347, Cyprus and Sicily in that year, Italy by winter 1347, Marseilles by January of 1348, Paris in spring 1348, followed by Germany and the Low Countries in that year, Norway in May 1349, eastern Europe by 1350, and finally Russia in 1351, but smaller outbreaks continued for about 200 more years;
  - London in 1664–1666;
  - Austria in 1711;
  - the Balkans from 1770–1772.
- The last major pandemic ran from 1855–1896 worldwide, but mostly in China and India, wherein more than 12 million died.
- Manchuria in 1910–1911 lost about 60,000 to pneumonic Plague with a repeat in 1920–1921;
- A minor outbreak occurred as recently as the summer of 1994 in Surat, India closely following an earthquake in September 1993.

\textbf{Plague in the Middle Ages}

When most people think of Plague, the Middle Ages come to mind. Let’s look at that particular event in more detail.

From 1150–1200 there had been a major warming trend throughout Europe. This, coupled with the rise of the mercantile class, led to improved diet and greater population growth. By 1340, Europe was significantly overpopulated. This was followed by the so-called Little Ice Age, which ended by 1351. The resulting climate was colder and wetter than normal. With the population larger than it had been in some time, and crop yields greatly reduced, per capita caloric intake fell precipitously, general health declined, and the pest population increased. Not a welcome combination of circumstances.

There are several theories to explain the onset of Plague, but they all agree that a major source was China, Mongolia, and Hunan province, in particular. The nomadic tribesmen that populated the region seemed to know instinctively that something was amiss. A series of customs arose designed to keep the microbe in check. Trapping marmots (a host for \textit{X. cheopsis}) was taboo; marmots could be shot at a distance only; slow-moving animals were to be avoided; furs of certain rodents could not be used.

\(^3\) Treated pneumonic Plague has an observed mortality rate of 57%.

\(^4\) Based on no scientific reason, but rather on the number of days the bible said Christ spent in the wilderness.

\(^5\) Historians only recently have developed an interest in this particular pandemic that ranged from 541 to 767. Research indicates that its victims may have numbered as many as 100 million. Population losses of 50–60% in North Africa, Europe, and central and southern Asia have been estimated. The historian Procopius claimed 10,000 deaths each day. Whole provinces were wiped out. “All the inhabitants, like beautiful grapes, were trampled and squeezed dry without mercy,” wrote Bishop John of Ephesus of the Plague’s destruction in Palestine.
Around 1330 Plague affected the local residents of the Orient and following the elaborate trade routes established in the previous two centuries, made its way west. By 1345, it was in the lower Volga; by 1346 Astrakhan, the Caucasus, and Azerbaijan; by 1346 Constantinople and the Byzantine Empire; late autumn 1347 Alexandria, Egypt and southward along the Nile; India and what is now the middle east were next to be depopulated by the, soon to be ubiquitous, flea and its internal traveling companions.

During 1343 Genoese merchants and their families were living in Caffa (now called Feyodosija in the Ukraine) on the Black Sea, in the Crimea, when the city was subjected to a siege by Tartars led by Janibeg. The city was heavily fortified within two stout concentric walls, with 6,000 houses within the inner wall and 11,000 within the outer wall. An attack by Italian reinforcements broke the siege in 1344. Throughout the siege, Caffa received food through its protected port.

Not one to be overcome by something as minor as the loss of 15,000 of his troops to the Italians, Janibeg renewed the siege the following year. As the effects of the renewed siege seemed to be wearing down the resistance of the residents, an outbreak of disease decimated the Tartar forces, killing thousands. In a fit of rage, the remains of the departing army are said to have catapulted thousands of corpses of the dead soldiers into the city; hoping that the stench of the putrefying flesh would cause disease. The residents promptly dumped as many of the new arrivals into the sea as they could, but still these airborne visitors came. The defenders of the city were likely affected by wounds of battle and could easily have contracted Plague through contact with any one of the abundance of corpses that darkened their skies. Besides, a week-old corpse traveling at the requisite speed to make the arcing journey did not likely land intact.

Upon the departure of the Tartars, the merchants hastily left the city in twelve vessels and set sail for Italy. By October 1347 the Genoese fleet was outside the port of Messina, Sicily and the crews, or what was left of them, were found to be dying of some unknown malady. Michael of Piazza described the arrival of the sailors as “sickness clinging to their very bones.” City officials sealed the vessels for two days—but, of course, this had little effect on the rats, and their accompanying fleas—and then dispatched them to their home port. Within two months nearly half of the population of Messina was dead. The disease soon spread throughout the ports of Italy and reached the inland cities by early spring, in most cases halving their populations.

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6 Historical texts describe their great machines of war as being capable of hurling a large stone (several hundred kilos!) some 300 meters.

7 This was another case, but not the first, of biological warfare. For more information go to the 2002 Emerging Infectious Disease article by Mark Wheelis at http://www.cdc.gov/ncidod/EID/vol8no9/01-0536.htm
Reports of another Genoese merchant ship carrying the disease to Marseilles came in January 1348. By that summer, the Plague reached Paris. It then spread east to Germany and north to England, reaching London in December 1348.

During this time it came to be known by the names (all linguistic variations on the theme): the Great Dying, *das Grosse Sterben*, and *Magna Mortalis*.

At this time, the population of England was estimated to be about four million, yet within a mere two and a half years about one third of them had died. Fully one third of the residents of Florence died in the first six months and 45%–75% in a single year. Venice lost 60% of its populace over the year and a half that the epidemic raged. Death was so rampant that the pope had to consecrate the Rhone River so corpses could be dumped into it. The death toll throughout Europe was at least 25 million out of a total population of 40 million. (In warmer months and in southern Europe, at this time, there was at least one family of black rats per household and an estimated average of three fleas per rat.)

Rats were not shunned by the populace as they are now. They were even used as food, as the following bit of doggerel suggests.

*Rats are not a dainty dish to set before a king,*
*But for a really hungry man, they're just the very thing;*
*Wrap each rat in bacon fat, roast slow before the fire,*
*Take him down and serve him brown, you've all you can desire.*

Clergy were especially hard hit; 50% of the English clergy died; in Montpellier, France of 140 Dominican friars at the outset, only seven survived; one third of the cardinals went to their eternal reward. Their numbers were slow to recover—taking several generations—and some orders remained depleted until well into the seventeenth century.

This outbreak and spread of Plague was accelerated by a total absence of sanitary procedures and lack of knowledge. For instance, the dead were heaped in piles like so much cordwood, whereupon rats and dogs fed on the corpses and the cycle was extended. Also, one of the first actions taken upon reports of the contagion was the hunting and killing of cats and dogs.

Homes of the poor were more like what we would call pig sties than what we would associate with buildings fit for human habitation. Roofs and walls were made of straw; floors were dirt; animals were regularly kept inside. The streets, if that’s what you could call them, of cities were barely wide enough for a single cart to pass, and they were perpetually covered with mud, garbage, and excrement. For lack of heated water, people rarely bathed and fleas were commonplace.

When St. Thomas à Becket was prepared for burial in England in 1170, he was found to be wearing (from the outside in):

(i) a large brown mantle (a loose sleeveless coat worn over outer garments),
(ii) a white surplice,
(iii) a coat of lambs’ wool,
(iv) a woolen pelisse (a long cloak),
(v) another woolen pelisse,
(vi) the black robe of the Benedictine order,
During preparation for burial, the cold English air stimulated so many of the critters occupying his multilayered hair suit that it “boiled over with them like water in a simmering cauldron, and the onlookers burst into alternate weeping and laughter …”

Simple children’s rhymes illustrate some profundities associated with the times,

\[
\begin{align*}
\text{Ring a ring of rosies}, \\
\text{A pocket full of posies}, \\
\text{Ashes, ashes!} \\
\text{We all fall down.}
\end{align*}
\]

It has been suggested that Rosies are rosary beads, presumably to gain divine intercession against this mysterious enemy. Most Plague victims emitted a rather strong and fairly objectionable odor, so flowers (posies) were carried to mask the smell. Ashes are all that was left of a burnt corpse. Of course, to fall down means to die. Sometimes the second last line is replaced with “A Tishoo, a tishoo,” sounding out the sneezes of the victims of pneumonic Plague. To be sneezed on by them was a sure death sentence for all but the hardiest souls.

Throughout Europe, many areas were abandoned. Agriculture came to a virtual standstill as farmers fled or died in their fields. Consequently, food shortages compounded the problems of society. Governments ground to a halt as bureaucrats died. No civil authority remained and crime was rampant. Station in life was not an indicator of immunity. Plague attacked merchants and peasants with equal voracity. Only the very rich could afford to move to protected environs far from the disease and even that was no guarantee of survival.

Everyone feared the spreading contagion and no efforts were spared to avoid its fatal embrace.

\[
\text{Kinsmen held aloof, brother was forsaken by brother, oftentimes husband by wife; nay, what is more, and scarcely to be believed, fathers and mothers were found to abandon their own children to their fate, untended, unvisited as if they had been strangers,}
\]

wrote Boccacio in his preface to the Decameron. The pope’s physician, Guy de Chauliac, characterized the period as one where “Charity is dead.” What more can be said?

Unaware of the cause of the disease (or even the rudiments of Germ Theory), people took to:

- burning incense,
- dipping handkerchiefs in aromatic oils,
- ringing church bells and firing cannons,
- wearing talismans,
- bathing in human urine,
- placing “stinks” (dead animals) in their dwellings,
- bleeding via leeches and bloodletting,
- drinking the pus extracted from a suppurated bubo,
- applying dried toads to relieve the pain of the buboes by absorbing the “poisons,”
- drinking liquid gold or powdered emeralds (only for the very rich, of course), and
- joining groups of flagellants.

One common remedy of the day called for an egg near hatching. The tip was carefully removed and the unhatched chick was withdrawn. What remained of the yolk was removed and mixed with saffron and this was reinserted, and the egg was sealed with the pieces of the removed shell. Some time later, the egg was fried until well-done, i.e., none of the original color remaining. This was mixed with an equal amount of white mustard, a dash of dill, a crane’s beak, and theriac (a purported blood tonic and cleanser that remains available to this day). The infected person was to swallow this whole and then fast for seven hours. Although this was part of the pharmacopoeia of the day, its effect was not recorded for us to read.

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8 There is some debate about the relevance of this to Plague because the first printed version of this rhyme appeared in 1822. The last major outbreak in the British Isles before 1822 was the Great Plague of London that extended from 1664–1666. Most children’s rhymes appeared in print shortly after their introduction and general use.

9 Catherine the Great, tsarina of Russia, was a proponent and practitioner of this treatment. Disgusting though it may be, in another, much less repugnant form, it has value.
The “doctor,” shown below, may look a little like Big Bird with a trench coat, but there was some method to this madness. It was believed that the heavy coat kept out the vapors that caused disease. The beak-like mask contained aromatic herbs and salts also thought to deter infection. The cane was used to probe the patient without direct contact with the doctor. All this was for naught since medicine had advanced little since the time of Galen, physician to Imperial Rome from 169 CE till his death.

A Plague “doctor” of the period.

The “order” of flagellants, also called the Brethren of the Cross, (initially active in the late 1200s) was re-formed in Germany in 1348 and initially blessed by the pope. It forbade its members from bathing, washing their heads, shaving, sleeping in a bed, having any contact with the opposite sex\(^\text{10}\), or even changing their clothes during a procession without permission of the “Master”. Washing of hands was allowed, but only once a day and that had to be done when kneeling. Each member had to donate funds to cover the cost of their food for the duration. As if to satisfy the ascetic needs of a squeamish populace, the groups went from town to town and whipped themselves with scourges, i.e., sticks with three or four leather tails with large knots containing sharpened iron spikes. They continued until the blood ran and even when the spikes stuck in the skin and had to be torn out. Many of them died of infections of these open wounds. They formed in bands of 50 to 300 and moved in pairs with men in the front and women in the rear of this serpentine procession. Each group’s “Master” heard confessions, imposed penances, and granted absolution—all to the total horror of the local clergy, who had enjoyed an absolute monopoly (and accompanying fees) over such practices for centuries. Each procession lasted 33\(\frac{1}{3}\) days, the number of years Christ was said to have spent on earth. During their travels through Germany and the Low Countries they preached anti-Semitism. Their asceticism had no effect on the state of the epidemic and their personal hygiene may have helped to carry Plague from village to village. Eventually, in October of 1349, the pope ordered the military arm of the church to force the groups to disband.

A procession of Flagellants.

Upon commission of the pope in 1348, a group of learned men (and at that time only men were deemed capable of being educated and hence, learned) of the medical faculty at Paris concluded that the disaster caused by

\(^{10}\) This seems to have been more honored in the breach than the observance. There are contemporary chronicles of nighttime orgies between the “chaste” brethren and camp followers.
Plague was a result of a conjunction of Saturn, Jupiter, and Mars in the 40th degree of Aquarius at 1:00 p.m. on March 20, 1345. This caused hot, moist conditions, which forced the earth to exhale a virulent sulfurous miasma. So much for the Age of Aquarius!

The horror and fear faced by medieval people confronted with the bizarre and almost totally unknown symptoms of Plague is inconceivable to us today. To those who believed in spirits and devils (that was most of the people of the time), this infestation was a scene from their worst nightmares; one in which they were completely unable to effect relief, no less a cure. It was as if all the monsters of their psyches were being unleashed for reasons they could not comprehend. When your worldview is limited, your options in the face of calamity are even more limited. Any explanation is believable. The pope declared that it was not divine punishment for the sins of the world, but local clergy gave that as the only reason for such horrors.

As a referent, you may want to look at a partial copy of the rightmost part of the triptych of Heironymous Bosch’s the Garden of Earthly Delights, which was completed about one hundred years after the Great Dying.
As with most mysterious, unknowable, and uncontrollable tragedies, the thin veneer of human rationality is peeled back to expose a dark undersurface capable of incomprehensible horrors and unimaginable evil. People sought to blame others; scapegoating was in season; **xenophobia**\(^{11}\) was the norm—all strangers were suspected of spreading disease. As had happened before and since, Jews were the targets of choice (even though they died of Plague at the same rate as others). Rumors of them having poisoned wells ran rampant. There were pogroms and massacres. The rabble was loose and beyond control.

\(^{11}\) Xenophobia is fear of strangers.
Zurich expelled all its Jews and closed its gates to them. On a single day in 1349, 2000 Jews were burned to death by a mob in Strausborg. Even officialdom entered the fray. The canton of Basel gathered all 4500 of its Jews in a specially-built structure on an island in the Rhine and burned them to death, after which the town fathers passed a law forbidding Jewish residence in the canton for 200 years. The largest Jewish community in Europe was in Mainz, Germany where at least 6000 Jews were incinerated after they fought and killed 200 of an attacking mob. Pogroms also occurred in Baden, Brussels, Burren, Dresden, Eisenach, Erfurt, Freiburg, Gotha, Landsberg, Lindau, Memmingen, Solothurn, Speyer, Stuttgart, Ulm, Worms, and Zofingen. There were over 350 separate recorded massacres of Jews during the years of the medieval Plague.

The approach of a group of flagellants frequently incited townsfolk to embark on pogroms and when they didn’t, the Brethren proceeded posthaste to the Jewish quarter where they murdered and looted with viciousness, ferocity, and completeness. Western Europe killed or expelled the Jews even as Pope Clement VI issued papal bulls forbidding plundering and killing them. As if on cue, local clergy either instigated anti-Semitic actions or failed to stop them—likely because properties of the Jews reverted to the Catholic Church upon the deaths of the Jewish families. What the Church lost in clergy and followers, it gained in tangible assets.

Eastern Europe, relatively unscathed by the Plague, tolerated the Jews. King Casimir of Poland offered to protect them. Some say it was because he had a Jewish mistress, but it is more likely that his country needed the skills they possessed. A return of the Jews to their former lands in western Europe was slow.

Once it ebbed, by the end of 1351, the Plague left Europe with a sizable shortage of workers and helped to destroy the feudal system when labor found itself in a seller’s market. Abandoned homes were taken over by complete strangers, as there was a default redistribution of wealth.

The most generally agreed upon mortality figure was that one in three people were killed by the Plague—a total loss of well over 20 million in Europe and perhaps as many as 40 million worldwide. Advanced geographical modeling work presented in 2005 indicates that these mortality figures may be low. These newer estimates point to at least a 60% mortality rate with as many as 80 million dead.

The major cities kept some records of mortality. The following table lists (with varying and unquantified accuracy) some of the historical numbers and the year of the outbreak.

<table>
<thead>
<tr>
<th>City</th>
<th>Year</th>
<th>Mortality</th>
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<tr>
<td>Dantzig</td>
<td>1427</td>
<td>80,000</td>
</tr>
<tr>
<td>Paris</td>
<td>1466</td>
<td>40,000</td>
</tr>
<tr>
<td>Moscow</td>
<td>1570</td>
<td>200,000</td>
</tr>
<tr>
<td>Lyon</td>
<td>1572</td>
<td>50,000</td>
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<td>Venice</td>
<td>1576</td>
<td>70,000</td>
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<td>1,000,000</td>
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<td>London</td>
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<td>68,596</td>
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</table>

Although the Plague no longer killed millions there, it remained present on the European continent for more than three hundred years, erupting in seemingly random locations until its final gasp in Marseilles in 1720.

The world’s last major infestation of Plague bacilli arose in China and India in 1855 and reached Hong Kong in 1894. Estimates are that 12–15 million died over this period. It was through study of this epidemic that Alexandre Yersin and Shibasaburo Kitasato independently described the causative agent in 1895. Strangely enough, it wasn’t until 1897 that P.L. Simond identified the mode of transmission.

Today, Plague is endemic in various parts of the globe: Madagascar, Tanzania, Brazil, Peru, Burma, and Vietnam have experienced cases almost every year since the start of the last pandemic in 1880. Rodents in the southwestern United States carry fleas infected with these bacteria to this very day! In fact, more than 40% of the U.S land area is infested by Plague-carrying animals, mostly prairie dogs, rats, mice, voles, and other rodents! Some national parks have signs saying not to feed the squirrels because they have Plague. As I write this (7/27/2008), there is an outbreak of Plague among endangered black-footed ferrets in South Dakota. This will be

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12 As with all things ancient and historical, there remains room for controversy. Scott & Duncan wrote *Biology of Plagues: Evidence from Historic Populations* wherein they claim that the medieval plague was not due to Plague at all, but rather to some form of hemorrhagic viral disease. S. Cohn disagrees with those authors only insofar as the cause of the disease. Nevertheless, French researchers found *Y. pestis* in the dental pulp of bodies buried in Montpellier during the 14th century. Adding to this is an October 2001 paper of Parkhill, et al. in *Nature* 413:523-527. They announced the complete mapping of the bacterium’s genome, all 4,653,728 base pairs (more of this in a later chapter). They found 149 deactivated genes that once enabled the bacterium to thrive in the human gut, but are no longer needed.
the first use of an vaccine for an epizootic. Previous surveys, the last of which was taken in the fall of 2007, indicate there may be as many as 290 ferrets in the Conata Basin, some of whom occupy the lairs of their favorite prey, prairie dogs.

Since 1947, there have been 390 cases of Plague in the U.S. resulting in 60 deaths. From 1980–1994 this country has had 229 cases with 33 deaths. Two Americans succumbed to Plague in August 1996, both due to transmission by way of prairie dogs. In 2006 a total of 13 cases of Plague were reported from the states of New Mexico (7), Colorado (3), California (2), and Texas (1). Two of these cases were fatal.

In Madagascar in 1997, one person with bubonic Plague and secondary pneumonic infection transmitted the pneumonic Plague to eighteen people, eight of whom died. A thirteen year-old Kazakhstani boy died of bubonic Plague on August 9, 1999—the first such death in that country in 25 years. Many other nonfatal cases have been reported every year. During the summer of 2002, two New York residents, recently having moved from New Mexico, contracted bubonic Plague and were cured.

Today east Africa and Hunan province in China are permanent reservoirs, called inveterate foci, for the disease. During 1965–1971, Vietnam (in addition to fighting a war against the United States) reported 25,000 cases of Plague.

The World Health Organization received reports of 18,739 cases in the period from 1980–1994, of which there were 1853 deaths (that’s a tad less than a 10% death rate) and between 2000 and 3000 infections every year. What is disconcerting is that more cases were reported from 1990–1994 than in the entire previous decade (an average of 2025 cases/year versus 861 cases/year).

The last known U.S. case of human-to-human transmission occurred in Los Angeles in 1924. The latest large, but not major, outbreak occurred on September 20, 1994 in the Indian city of Surat in the state of Gujarat. Initially the government of India did not recognize the presence of the disease until several hundred thousand people had fled the region. By October 2, there had been 2500 cases reported and an official figure of 58 deaths. Considering that this strain was the highly contagious pneumonic variety, thus spread by aerosol droplets upon respiration, such a low mortality figure may or may not be comforting.

A vaccine was available for those who expected to come in contact with animals that may have been infected, but it was not completely effective. The manufacturer discontinued production in 1999 and it is no longer available. It worked moderately well on bubonic but not at all on pneumonic Plague.

Rather ominously, the September 4, 1997 issue of the New England Journal of Medicine carried a brief report from Galimand et al. describing a case of multiple antibiotic resistant bubonic Plague. The thought of another pandemic of Plague that is resistant to modern medical treatment boggles the mind.

On August 26, 1999 the wire services carried a story announcing the development of another vaccine for bubonic Plague. Human trials were to begin shortly. Eight years later, we await the results.

Despite the havoc wreaked by previous Plague epidemics, at this time, it seems unlikely that a natural resurgence of Y. pestis will kill untold millions. Testing and treatment for the disease and medications that destroy the bacteria are well-known and readily available.

An entirely separate issue is the use of Y. pestis for bio-warfare.

Syphilis

Syphilis, or the Great Pox and later known as lues (named after the French kings Louis and pronounced the same), is caused by the spirochete Treponema pallidum, a form of bacterium. Notice the corkscrew structure.

This organism is closely related to those treponemes that cause the nonfatal and nonsexually transmitted diseases yaws, pinta, and bejel. Although some medical historians claim the disease originated in the Western
hemisphere and was brought back to Europe by Columbus’s crew, others believe that it evolved (or more accurately, coevolved) from yaws by mutation. You may consider the question as unresolved to this day.

Its original form was more virulent than what we see today and its symptoms were more florid. Despite all efforts, *T. pallidum* has not been cultivated in the laboratory in any artificial media and it is difficult to cultivate in the presence of human cells.

The disease is spread by close personal contact: either by contact with the exudate from open sores through breaks in the skin, sexual transmission, or vertical transmission from mother to developing fetus (resulting in congenital syphilis). The symptoms are highly variable. The spirochete multiplies at the initial site of entry and a characteristic primary lesion, called a chancre, forms within two to ten weeks.

![Characteristic chancres associated with syphilis, the great pox.](image)

The exudate from the chancre is teeming with treponemes and therefore highly infectious. Despite its rather gruesome appearance, it usually heals and leaves no scar. Since syphilis attacks nerve cells, there is usually no pain associated with these sores.

**Primary syphilis:** from one to three months after exposure the host experiences enlarged inguinal lymph nodes as the immune system mounts a defense. **Secondary syphilis:** a flu-like illness develops and sometimes the immune system succeeds in its efforts and there is spontaneous resolution. If the immune system does not destroy the microbes, a generalized skin rash develops and the patient will be highly infectious, but within time, the organism disappears from the secondary lesions and the skin rash. Notice the circular marks with a light halo and dark interior.

![A similar sore on the tongue should be compared to the much smaller typical cold sore.](image)

**Tertiary Syphilis:** Some of the treponemes spread to other parts of the body, in particular, the mucous membranes, liver, eyes, joints, bones, muscles, or the central nervous system (CNS), where they again either multiply or remain dormant. Subsequently, the course of the disease is highly variable. About 25% of the victims undergo a spontaneous cure, another 25% exhibit no further symptoms, and the remaining 50% proceed to the tertiary stage. At this stage, the symptoms depend on what organs have active pathogen replication; they range from a mild skin rash to significant central nervous system involvement resulting in paralysis and death.
Third stage syphilitic ulcers that will not heal to their original state.

None of these third stage gummas or ulcers will heal to their original state. When the spirochete enters the central nervous system it can affect the spinal column and the resulting tissue puts pressure on the cord, resulting in a condition that can cause postural instability with a staggering wide base gait that can damage the joints of the leg. The condition, shown to the right, is called Charcot’s knee. Surprisingly, there is usually no pain in the knee (Yes, that is a knee).

The ultimate effect is on the brain. In the tertiary stage, neuro-syphilis only a short step from death. The following picture shows severe cerebral atrophy (tissue death) on the left side.

Penicillin G is effective in curing the disease, although the dosage and length of treatment are functions of the extent of infection. Usually, an injection of 1–3 million units for one, three, or eight days—depending on the form used—is sufficient during the primary stage.\(^\text{13}\)

Syphilis spread throughout Europe in the 1490s and was particularly lethal in its original manifestation. The disease symptoms were quick to develop and the skin eruptions were especially gruesome. It caused genital sores, advanced to a general rash, and then developed into particularly ugly abscesses and scabs over the entire body. The sores changed to open ulcers that could erode bone and destroy tissue, especially eyes, lips, nose, throat, and genitals. As with most epidemics, the victims were blamed for the disease (debauchery, lechery, etc.) and frequently ostracized.

The bellicose nature of the regimes of the time, with their many standing armies, extensive use of mercenaries, and frequent battles, was conducive to rapid and efficient spread of disease via the usual “camp followers” of the warring parties. The disease reached Germany and Switzerland in 1495, England and Holland in 1496. Vasco da Gama’s crew carried it around the Cape in 1497 causing an outbreak in India in 1498, which in turn spread eastward. China and Japan were affected in 1505, a full fifteen years before the arrival of Portuguese sailors in Canton.

As if to repeat both history and human frailty,

- the English called the disease the French Pox,
- the French called it the Neapolitan or Italian disease,
- the Italians and the Dutch called it the Spanish disease,
- Portuguese called it the Castilian disease,
- Russians called it the Polish disease,
- Polish called it the Russian disease,
- Turks called it the Christian disease,
- Persians called it the Turkish disease, and
- Japanese called it either the Portuguese or Chinese disease.

Between 1497 and 1501, a number of medical tracts on the disease appeared. The writings of Leonicenus were especially good, insofar as the general symptoms were enumerated, their relation to sexual transmission was

\(^{13}\) In an advanced tertiary stage of syphilis administration of antibiotics can lead to Herxheimer’s reaction, whereby symptoms increase following treatment.
recognized, and the external use of mercurial salts (an older Arabian practice) was advocated for treating the associated skin eruptions. Two famous Renaissance medical leaders, Paracelsus and Fracastorius\textsuperscript{14}, made major contributions to the study of this disease.

In the United States the incidence rate of all syphilis has varied from a high of 447.0 in 1943 to a low of 26.5 in 1995. Unfortunately, the rate is no longer decreasing and the rate of congenital syphilis is now substantially higher than it was in the 1980s. Worldwide there are an estimated twelve million new cases per year.

The graph shows the U.S. incidence numbers by gender per year for the years 1956 through 1995.

**Cholera**

Cholera is caused by infection by *Vibrio cholerae*, comma-shaped Gram-negative bacteria. Notice the “tail,” called a *flagellum* and used for locomotion, on each of the Vibrios.

\textsuperscript{14} Paracelsus was the first medical teacher to challenge the long-held theories of Galenic medicine. Fracastorius was a true Renaissance man; he wrote on the temperature of wines, the rise of the Nile, poetries, the mind, and the soul. He was an astronomer, geographer, botanist, mathematician, philosopher, and physician. He understood the true nature of sedimentary rocks, anticipated the principle of the Mercator projection, and described a primitive telescope. In 1530 he published the poem *Syphilis Sive Morbus Gallicus* (Syphilis or the French Disease), from which the name of the disease was derived.
An infective dose varies from $10^3$ to $10^6$ bacteria, with the higher number applying when the stomach’s acidity is high (i.e., low pH), but it can go as low as 100 when ingested together with an antacid or food. The standard pH of an empty stomach is between 0.9 and 3.0, generally around 1.0, and *Vibrios* are killed when the pH is below 2.4, so some people will not succumb to the disease except possibly when the causative agent is masked by the intake of food.

Cholera is transmitted through fecally contaminated water and manifests itself as an acute infection of the gastrointestinal tract. Although *Vibrios* are free-living in water (in fact, they can survive on algae for quite some time), they cause infection only in humans. Upon exposure to the human digestive tract *V. cholerae* transforms itself to a much more virulent form—as much as seven hundred times more virulent. The bacteria bind to the walls of the small intestine where they secrete a potent toxin. This toxin alters the membrane transport mechanism; instead of causing the water to leave the lumen of the gut and enter the tissues, large quantities of water, chloride, and sodium are drawn into the gut.

The disease precedes in possibly three stages (a) *Invasion*: at the end of the incubation period the symptoms are malaise, headache, severe (as much as 20 liters per day) diarrhea resulting in the so-called “rice water stool,” (which derives its characteristic whitish color from intestinal tissue which is shed and excreted along with large numbers of vibrios), anorexia, and a slight fever. This severe diarrhea can be as high as one liter per hour. The resulting loss of fluid and the accompanying electrolyte imbalance can lead to hypovolemic shock, renal failure, and cardiac failure. (b) *Collapse*: circulation is almost completely arrested, accelerated respiration, weak pulse, decreased systolic blood pressure, diminished or no urine output. This stage lasts from a few hours to one or two days. The mind remains clear until just before death, when coma occurs. Death follows shortly thereafter. Death can follow the onset of symptoms in as little as six hours. (c) *Reaction*: sometimes, even when the grim reaper is about to claim victory, vomiting ceases, diarrhea becomes less frequent and less watery, and convalescence follows. Talk about your near-death experiences!

Immediate oral or intravenous rehydration is essential to survival. Of course, victims may be in no mood to substantially increase their oral intake of liquids, even when sweeteners and essential minerals are added. Untreated, the mortality rate is 40–60%, whereas immediate treatment can lower this to less than 1%, even with only oral rehydration therapy. As few as 30% and as many as 80% of those infected can be asymptomatic, and hence carriers who shed the vibrios in their fecal matter, thus furthering infection of the populace. Once infected, further infection with the same subtype of *Vibrio* usually leads to at worst a subclinical infection, with no appearance of classic symptoms. Although there is a vaccine, it is of modest value, because it is effective at most 50% of the time and lasts only for 3–6 months for vibrios of the same subtype. The dominant biotype was *O1 classical*, but that has now been superseded by the *El Tor* biotype, which is less virulent, but more long-lasting and has more carriers. Clinical trials of newer vaccines are ongoing.

This disease has swept the world in seven major pandemics, including a major outbreak in South America, particularly Peru, as recently as 1991. Cases have also been reported along the Gulf coast of the U.S., usually the result of eating raw, infected shellfish. Cholera is endemic in India, Pakistan, Bangladesh, and the Americas.


The second and third pandemics were enhanced by the concomitant Industrial Revolution, subsequent migration to the cities in search of jobs, and the unregulated growth of tenements and slums. Thoughts of supplying fresh water and removing wastes from new construction was furthest from developers’ minds as they cut corners in order to maximize profits (Adam Smith’s invisible hand?). If there were cesspools for buildings, they were only accessible from the ground floor. Chamber pots filled with human waste were emptied from windows in the upper stories, much to the displeasure of pedestrians who served as potential and usually rapidly moving targets. A sewer was no more than an extended cesspool with some provision for overflow, usually on one end. The excess ran into the streets or adjoining property. These so-called sewers had to be mucked out by hand, any dangers of methane poisoning or explosion notwithstanding.

Upon discovering cholera cases, most countries took immediate, if not altogether effective, action. England’s first case was William Sproat of Sunderland who shuffled off his mortal coil on October 26, 1831. Officials were loath to quarantine ports or even incoming ships lest the emerging textile industry be harmed. The administration’s spin was that there was no cholera in England. This remained in effect for almost twenty years. When in doubt, deny everything—a policy that has found its way into this century. Needless to say, this did little to ameliorate the extent of the epidemic.
When the sixth pandemic erupted in the Middle East, Russia, and other parts of Europe during the summer of 1892, American newspapers warned of the potential spread westward. This came at a time when immigration into New York was at an all-time high. The strength of the Russian cholera epidemic and an earlier outbreak of 200 cases of typhus amongst Russian Jews who had arrived on January 30 aboard the *S.S. Massilia* from Marseilles only compounded the problem. Jewish passengers and their American contacts were forcibly separated from relatives and sent to North Brother Island, downwind of the garbage dump on Riker’s Island, in the East River near 140th Street. Neither cabin-class passengers nor the 470 Italian immigrants who shared steerage with the Russian Jews were detained. Of the 1200 detained Jews, fully 1150 never showed any symptoms of typhus. Nevertheless, because of a lack of space, most were forced to live in tents. Soap was scarce and when available, bathing required a dip in the frigid river. Medical care was totally inadequate, resulting in at least six unnecessary deaths. Not only was there no contact with the mainland, but the Jews were deprived of kosher food. Those who died were either cremated or interred in tightly sealed metal canisters, thus violating Jewish burial laws. Only after major protests from the well-established German Jewish community were regular burials and kosher food allowed.

Many political figures argued against unrestricted immigration, especially by groups with uncommon customs and costumes. A strict quarantine had proven effective in combating the typhus epidemic, so when the *S.S. Moravia* arrived from Hamburg with 22 cholera deaths, of which 20 were Russian children under age 10, a strict 20 day quarantine was imposed on all steerage passengers—but not for cabin-class passengers. Other ships brought more cholera and cases were found in New York City. Without any supporting scientific evidence, kosher butcher shops were closed for the most trivial health code violations; many immigrants were evicted from their tenements and left to fend for themselves in the streets. Measures unrelated to the germ theory of disease (long after it was well known) were taken against Jewish immigrants, mostly at the instigation of the Surgeon General, Walter Wyman. Then president Benjamin Harrison was an ardent proponent of restricting Russian Jewish immigration, urging Congress “to keep out the vicious, the ignorant, the civil disturber, the pauper, and the contract laborer…” It was not a happy time for the Jewish community of New York.

**Smallpox**

Smallpox (variola) is caused by an orthopoxvirus\(^\text{15}\) (shown below with the characteristic dog bone shape of its interior) and is spread from person to person by contact with skin lesions or via the respiratory tract. It is currently extinct in the wild.

\[\text{![Smallpox virus](image)}\]

Its name was derived from the small indentations, or pockmarks, on the skin that it caused and also to differentiate it from the great pox, syphilis. The following picture shows the progression of the disease from Day 3 to Day 7 after infection. The rash tends to be *centrifugal*, meaning that it is more pronounced on the extremities than the central regions of the body.

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\(^\text{15}\) Diseases in this family also include buffalopox, camelpox, cowpox, monkeypox, rabbitpox, and raccoonpox.
The mortality rate ranged from 20% to as high as 40% depending on the age and health of the host. The disease usually came in two forms, *variola major* and *variola minor*, with the latter being less virulent and causing only a sparse rash and a low-grade fever\(^{16}\). The virus is extremely stable and has not changed in, what may very well be, hundreds or even thousands of years. The infective dose is 1000 virus particles per milliliter\(^{17}\) and maybe as low as five.

Experts claim that smallpox killed more than one billion people in the past thousand years\(^{18}\). As recently as 1967 it sickened upwards of 10 million and killed about 2 million.

Some early physicians believed in the process of *variolation*, whereby the pus or infected scabs of pox victims were ground up and inserted under the skin\(^{19}\). Recipients of this treatment developed a mild form of the disease and attained a permanent resistance. Also, farmers and milkmaids deliberately infected themselves with cowpox because experience had taught them that this prevented the smallpox. Cotton Mather notified Thomas Jefferson of the merits of variolation and Jefferson had everyone in his household, freemen and slaves alike, variolated.

In the late eighteenth century England, Edward Jenner noticed that milkmaids rarely came down with smallpox, but did show mild symptoms of the related disease cowpox. He reasoned that cowpox infection resulted in immunity to the more serious disease. He concocted a mixture of extracts from the cowpox-infected milkmaid Sarah Nelmes and, contrary to the spirit of modern experimental medicine and the principle of informed consent of subjects, inserted\(^{20}\) it into an unknowing eight year-old boy, John (James) Phipps, on May 4, 1796.

He found that subsequently, despite all his attempts, the boy could *not* be infected with variola. Almost two years later, he took an extract from the hand of Thomas Virgoe, who had been infected through contact with the

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\(^{16}\) There are also two rare forms of smallpox: hemorrhagic and malignant. The first is characterized by significant subcutaneous bleeding. Both are usually 100% fatal if untreated.

\(^{17}\) Essentially several drops of material sneezed or breathed in your direction. *Bless you!*

\(^{18}\) The rich and famous have both succumbed to and survived this disease. Survivors include: George Washington (notice the pock marks on his face in the Gilbert Stuart portrait), Abraham Lincoln, Beethoven, Elizabeth I of England, Mozart, and Mary Shelley—the creator of Frankenstein.

\(^{19}\) This practice harkens back to India in 1000 BCE, from which it was transferred to Tibet, and then to China.

\(^{20}\) Current US technology for vaccinating against smallpox uses a bifurcated needle, which must puncture the skin about five to fifteen times.
heel of one of his mares. This was injected into one John Baker, who also became impervious to variola. Thus was born the smallpox vaccine\textsuperscript{21}.

As with all new discoveries, vaccination was very slow to take hold. Jenner had to publish the results himself, since no medical journals would accept it.

The disease has been “completely eradicated” after instigation from the Soviet Union before the World Health Assembly in 1958. At that time, the disease claimed two million lives each year with cases in thirty-three different countries. Smallpox was “eradicated” because:

1. There were no subclinical infections, so that there were \textit{no carriers};
2. Victims were \textit{infectious for at most five days} and the disease’s effects severely limited its victim’s mobility and the probability of further spread;
3. The virus was completely eliminated from the body upon recovery and resulted in \textit{total immunity to all future infection};
4. There were \textit{no animal reservoirs} for the infection, hence, no vectors of transmission; humans were the only hosts;
5. The symptoms were \textit{clearly recognizable} and infected cases could be readily identified;
6. An \textit{inexpensive, effective, and easily transported vaccine} was available.

The eradication program began in 1967 under the direction of the American Donald Henderson working for the United Nations. Each subsequent outbreak was attended by a cadre of experts who immunized everyone (whether they wanted it or not—although that frequently took quite a bit of diplomatic cajoling) in the area. Teams operated in times of natural disasters, wars, and insurrections, from Bangladesh to Sudan to Yugoslavia (it was a single country back then) to Ethiopia to India, and elsewhere. All-in-all, this effort involved 150,000 workers.

Finally, during November of 1975, a three-year-old Bangladeshi girl Rahima Banu was cured in the last \textit{natural case} of variola major. On October 26, 1977, Ali Maow Maalin\textsuperscript{22} (Merka, Somalia) was the last (cured) case of variola minor.

Unfortunately, in 1978 in Birmingham, England there was a major security breach in the ventilation system of a (supposed) BSL-2\textsuperscript{23} laboratory and a photographer, Janet Parker, working upstairs of the lab was infected and died of smallpox. Her mother, with whom she lived, came down with a mild form of the disease but survived.

On May 8, 1980, the World Health Assembly formally certified the earth free of smallpox. No other cases have been reported since.

There are supposedly only two stores of smallpox virus in the world today, the CDC BSL-4 lab in Atlanta and the Russian State Research Center of Virology and Biotechnology in Koltsovo, Novosibirsk. The stores had been scheduled to be destroyed on December 31, 1996, but Russia and the US have decided against destruction because of the possibility of the virus’ use in biological warfare.

In 1969, the US and the Soviet Union signed a treaty banning biological weapons. The US had more or less adhered to the treaty while it has been reported that Russia did not. Russia is alleged to currently have several metric tons genetically engineered hemorrhagic smallpox virus\textsuperscript{24}.

The conquest of smallpox had another, unpredictable outcome. Smallpox immunizations were no longer the rule in the 1970s. With that form of pox immunity no longer shared by the populace, the incidence of monkeypox has increased every year since 1980. Following hard on the heels of SARS was an outbreak of monkeypox infections in humans: 37 confirmed cases, 12 possible cases, 22 suspected cases, and 87 “persons of special interest.” These cases were spread over 10 states. The source was traced quickly to pet prairie dogs that had shared a cage with an African rodent. There was no person-to-person transmission and no one died. What many have viewed as an unusual result may come to be the norm in the not too distant future.

\textsuperscript{21} By the way, the word vaccine was first used in 1803 and it comes from the Latin word \textit{vacca}, meaning cow (as in cowpox) and the French word \textit{vaccinus}, meaning of or from cows.

\textsuperscript{22} Then 21 year-old Ali avoided getting vaccinated during an outbreak, because of his fear of needles. He was ill for a full 55 days. He now works for the World Health Organization and the U.N. Children’s Fund assisting with the administration of polio vaccine in Somalia.

\textsuperscript{23} BSL stands for Biological Safety Level. Level 1 applies to agents that do not ordinarily cause human disease. Level 2 is appropriate for agents that can cause human disease, but whose potential for transmission is limited. Level 3 applies to agents that may be transmitted by the respiratory route which can cause serious infection. Level 4: is used for the diagnosis of exotic agents that pose a high risk of life-threatening disease, which may be transmitted by the aerosol route and for which there is no vaccine or therapy.

\textsuperscript{24} For more details, read \textit{Germs: Biological Weapons and America’s Secret War} by Miller, Engelberg, and Broad: New York: Simon & Schuster, 2001, but be a little skeptical because Judith Miller has a reputation for transmitting "information" from government sources without additional validation.
Influenza

Influenza is caused by an orthomyxovirus that is readily spread by aerosol droplets. Notice the spikes sticking out of the viral surface.

The outside of the virion is covered with two kinds of spikes: about 500 H-spikes (hemagglutinin), which work to initiate infection, and about 100 N-spikes (neuraminidase), which allow the release of the virus from the cell surface so that it can infect other cells.

The characteristics of the spikes change from year to year due to antigenic shift (an abrupt and large genetic change of the surface antigens that occurs every twenty years or so) and antigenic drift (minor genetic change that can occur annually). Thus, those who suffer from one form of the flu virus need not gain immunity to any other form. The reservoir for influenza is thought to be pigs, ducks, and birds in general, especially in China and Southeast Asia.

There are three fundamental types of flu virus, type A, B and C. Type A infection results in a moderate to severe illness affecting humans and animals of all age groups and the virus is particularly susceptible to antigenic shift. Type B is a milder disease that affects primarily children. Type C is so mild that it is rarely reported as a disease amongst humans. Hence, it has not been associated with any epidemics. All types of influenza viruses can experience antigenic drift.

Each subtype of Type A flu is further characterized by an enumeration scheme for H and N. The 1998 avian flu in Hong Kong was listed as a Type A H5N1 and varieties up to H16 and N9 are known.

The disease is characterized by a sudden onset of fever, chills, headache, muscle aches in the neck and back, and sometimes prostration. Cough and sore throat are also common. Convalescence is slow and marked by fatigue and weakness. It is spread by discharges from the mouth and noses of infected persons. Young healthy adults appear to be particularly susceptible. As a rule, there are many more carriers than infected persons. The mortality rate is usually only as high as 0.1%, but because the number infected is so high, there is a significant excess mortality, usually due to pneumonia or other pulmonary complications. In a typical year in the 1970s in the US 20,000 people died of flu, more specifically bacterial pneumonia secondary to flu. But, as the American population has aged, the annual mortality due to flu has risen to 36,000 with an average of 114,000 people hospitalized. During the last decade 90% of all influenza deaths occurred among people older than 65. During heavy epidemic years the mortality figures can double to 70,000. In the US, and most temperate climates in the northern hemisphere, the disease usually peaks between December and March.

Hippocrates is credited as the first observer to record an influenza pandemic in the year 412 B.C. Since 1580, there have been thirty-one additional flu pandemics recorded.

As bad as all the previous pestilences had been, the twentieth century bore witness to what is arguably the most virulent epidemic in recorded memory. As the US entered the conflict, World War I had already claimed nine million lives in its four-year duration. But a far greater and more lethal killer was lurking in Camp Funston (now Fort Riley) in Kansas.

After one of the harshest winter’s on record, on the morning of March 11, 1918, Albert Mitchell, a company cook, reported to the infirmary complaining of a low-grade fever, sore throat, headache, and muscle aches—typical flu symptoms. He was sent to bed. By noon of that day, 107 soldiers exhibited similar symptoms and within two days, a total of 522 people were sick. Some were close to death with severe pneumonia, usually bacterial. (Remember, there were no antibiotics in general use until the 1950s.) Camp Funston was the tip of the
iceberg as other military bases reported similar figures almost immediately. Even shipboard sailors docked off the East Coast were affected. Within a week even isolated locales were hit; the island of Alcatraz reported cases. No state escaped infection. Neither was the disease held in check by the vast expanse of ocean; by April, French soldiers and civilians were infected. Within two weeks, it had spread to China and Japan. During May it was found in Africa and South America. By this time, it had eased its burden of illness and death on the Americas, but continued its onslaught elsewhere. This first wave, somewhat more than a minor annoyance, was more deadly than the typical flu, but far from what was to come.

During August and September 1918, very likely after experiencing antigenic shift, the flu reappeared in the Americas, starting in Boston, then traveling to Fort Devens, from which it was transported worldwide by the shipment of troops to the European front. This time it was much more virulent and lethal and continued its attack people in the 19–34 age group along with the usual population segments of children and the elderly. Fully 20% of the population was affected. Deaths from an especially deadly form of pneumonia were unusually high. At military camps, bodies could not be autopsied fast enough that the dead were piled like so much cordwood in storerooms. The civilian population was also decimated. Medical personnel were unable to offer more than palliative care. Some medical authorities claimed the cause was a bacterium previously discovered by the famous microbiologist Pfeiffer and recommended wearing gauze masks to prevent its spread. Schools and public places were closed25. Many cities mandated the wearing of masks and levied fines of $5 on those who failed to comply26.

The disease’s effect on military age men was so great that the American draft was suspended in October of 1918 due to the epidemic. As the Allies engaged Germany in a series of “final” offensives, the flu was a major player in the overall mortality rate and swung the outcome of some battles. Even General Pershing, the commander of the American Expeditionary Force (AEF, impolitely referred to as ass-end-first by the common foot soldier) was affected. So many soldiers died of it, that the flu had a significant influence on the cessation of hostilities. The AEF suffered 35,000 battle-related casualties and 9,000 deaths from flu. Of course, this means that many, many more soldiers had been unable to fight because of the disabling disease. Even the peace conference at Versailles was affected as all three major participants, President Woodrow Wilson of the United States, Prime Minister David Lloyd George of Great Britain, and Premier Georges Clemenceau of France, contracted the disease. This likely altered the outcome of the negotiations.

25 The effect of the closure of schools and theaters had little effect compared to the mammoth victory bond rallies at which many tens (and even hundreds) of thousands congregated to support our troops “over there.”

26 That was a princely sum in those days.
The disease was generally called the Spanish flu, although Germans called it the French flu and the French called it the German flu, etc.

About eighteen months after its first appearance, the disease abated, but reappeared at a much reduced level each year for many years thereafter.

At its height, mortality rates were 15.8% in Philadelphia, 14.8% in Baltimore, and 10.9% in Washington D.C. Sixty percent of the Inuit population in Nome, Alaska fell victim to the flu. Although overall death rates were relatively low, the incidence rate was abnormally high at around 20% of the population. Almost everyone in this country knew of someone who had succumbed to influenza. Between 80% and 90% of the Western Samoan population (under the governance of New Zealand) was infected. The total U.S. death toll was 650,000—out of a population of about 110 million; Russia lost 450,000; Italy 375,000; Britain 228,000; 500,000 in Mexico; 44,000 in Canada; unnumbered millions died in the Asian subcontinent. Estimates of the worldwide mortality for this epidemic range from 25 million to 50 million.

The unusual feature of this epidemic was the age-mortality curve: flu usually kills young children and the elderly, but this version also took a large proportion of males between 19 and 34. Compared to the Plague of the Middle Ages with its eight to thirteen million dead globally per year, this may have been the most lethal recorded epidemic in human history, especially when you consider that the lion’s share of the deaths occurred over a mere three month period in the fall of 1918.

In December of 1997 there was a minor eruption of an avian flu in Hong Kong. In the manner of Falstaff’s suggestion for curing the ills of society, public health officials ordered the killing of all the chickens, 1.2 million of them; a similar outbreak occurred in Europe in 2003, resulting in the destruction of 30 million birds. As of January 1, 2002, it has not been incontrovertibly established that that variant of the disease can be spread from human-to-human, although there may have been one or two such cases. The current flu strain of concern is an H5N1 avian flu, which if transferred from birds to humans could cause a major epidemic. In the first three months of 2004, 34 cases of this flu, with 23 deaths, had been discovered in Thailand and Vietnam. After a two month hiatus, it re-emerged in those two countries and in China and Indonesia with three added deaths in Vietnam. Over 100 million birds in these countries have either died of the infection or been culled to prevent transmission to pigs—the ultimate chemical mixing bowl for sharing genes and leading to significant antigenic shift. During 2006, there was a case of human-to-human transmission in Vietnam. To date, there have been 238 cases and 139 deaths due to this avian flu, mostly in Asia.

Back in September of 2001 it was announced that the full genome of the 1918 flu had been decoded and the protein that caused its virulence had been discovered. It was an H1N1 flu.

As a footnote to this pandemic, in 1918 the global population was about 1.8 billion people; it took four months to circle the globe using standard means of transportation; and this form of influenza killed at least 20 million people. The current population is well over 6 billion and it takes a mere four days to circle the globe using commercially available travel. If scaling were meaningful (which we hope it isn’t), we could expect 60 million or more to die in a similar pandemic.

Diseases of Childhood

Developed countries, with extensive required immunizations, see many diseases as mere annoyances. In fact, the causative agents remain quite virulent and potentially deadly to naïve hosts, especially naïve adult hosts. Measles, mumps, rubella, chickenpox, etc. exact a huge toll in developing countries. Even in the developed world, adults with no prior exposure to this pathogen have a fairly high mortality rate. What we take for granted need not be so elsewhere.

Infectious diseases must be closely watched and appropriately feared; as the past has taught us, humility is a far greater virtue than either arrogance or hubris when it comes to dealing with Nature.

References


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27 For no good reason other than announcements of its effect first came from the relatively open and neutral country of Spain.

28 In a typical year in the US, 114,000 are hospitalized and 36,000 people die.

29 Unless some of the newer estimates (100 million) for the Plague of Justinian are correct.
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