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**Viruses: Impact on Science and Society**

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**Introduction**

When we began writing this article in April/May 2020, we were in the middle of the first 'lockdown' in the UK, a quarantine measure adopted in most countries in attempts to contain the exponentially spreading viral disease we call COVID-19. Caused by a novel strain of coronavirus, named SARS-CoV-2, the COVID-19 pandemic, which was first recognized in Wuhan, China in December 2019, had by May 2020 knocked trillions of dollars off international markets and drastically changed the way we lived, at least for the time being. Daily life and livelihoods have been paralyzed by the mandatory, but unfortunately necessary, quarantine measures, separating us from our families, friends and colleagues. Hospitals were overflowing while stores, theaters and restaurants have been closed, many already bankrupt.

Months later, as this article goes to print (November 2020), the death toll of COVID-19 has exceeded one million, and there are no signs that the pandemic is abating, let alone ending. Indeed, some medical historians contend that epidemic endings are a form of collective amnesia, transmuting the disease that remains into merely someone else’s problem. The current coronavirus pandemic is neither the first, nor likely the last, viral visitation that humans have experienced on a mass scale. The impact of viruses on our lives predates our knowledge of their existence, as manifested in the way societies have responded to viral epidemics regardless of whether the cause was known at the time.

Often described as entities hovering on the threshold of life, viruses are found in parasitic, commensal or symbiotic association with the entire range of living organisms from single celled Archaea and bacteria to plants, animals and humans. They play a dual role in the laboratory, both as objects of investigation and as experimental tools. They have greatly enhanced our understanding, not only of human disease, but also of the living world more broadly.

In this article we consider the tremendous impact, past and present (and undoubtedly future), of viruses on humans, in both science and society. Recognizing that every interaction is a two-way street, we also remark on the ways that human activities – both deliberate, e.g., in the way we use them in the laboratory, and unknowing, through lifestyle choices – have affected viruses. We also examine how the modern, interconnected world has little resilience in terms of socio-economic consequences of the emergence of a pandemic virus.

**Virus: Meanings and Metaphor**

Expressions such as "going viral" are so widely used today that it is easy to forget that viruses have a narrower, more precise meaning for scientists than for the public at large. In popular usage, the term is frequently elided with any invisible germ (much to the irritation of virologists), but this imprecision is not a serious matter unless it leads to inappropriate treatment of virus infections by antibiotics that target bacteria.

**Etymology and Evolution of the Meaning of Virus**

The notion of contagion by invisible agents specific for different diseases was expounded by Girolamo Fracastoro in 1546, and the word ‘virus’ appears to have been imported into the English language from Latin as a word for poison or venom sometime in the sixteenth century. One of the earliest documented references is in Edward Jenner's classic 1798 report on the prevention of smallpox. Jenner's use of the word virus was not precise, and it was not until the late nineteenth century in the wake of the germ theory that the word virus came to mean a type of disease agent. As the ability of bacteria to cause specific infectious diseases, e.g., tuberculosis, cholera and anthrax, was established, scientists found other infectious diseases from which they could not isolate bacteria. The two earliest examples were mosaic disease of tobacco plants by Dmitri Ivanowski (1892) and foot-and-mouth disease of cattle and swine by Friedrich Löffler and Paul Frosch (1898). They still considered the causative agents to be bacteria, only smaller than known ones. But in 1898, Martinus Beijerinck proposed that the tobacco mosaic agent (what we now call tobacco mosaic virus, TMV) is distinct from bacteria in being somehow dependent for its multiplication on the cells of its host. He described TMV as a *contagium vivum fluidum*, Latin for a 'living soluble contagion'. Without adequate techniques to test it, Beijerinck’s idea only gained traction 30 years later, when it helped establish virology as an independent discipline in its own right.

The next couple of decades witnessed many discoveries of viruses and viral diseases, as well as contentious debates over the nature of viruses as living versus non-living organisms. Virological concepts deepened with the development of new instruments and methods of visualizing and cultivating viruses, as well as the emergence of molecular biology, which gave scientists both new
techniques and a new language. In the 1950s, the French microbiologist, André Lwoff, formulated the modern definition of viruses as ‘obligate intracellular parasites’ composed of a single type of nucleic acid (either DNA or RNA) encased in a protein coat.

**Virus as Metaphor**

It seems a valid description to call self-propagating malware a “computer virus”, given that it can spread rapidly from one computer to another, reproducing itself and lead to malicious outbreaks. Similarly, descriptions of rumors on social media going “viral” are apt. They allow “pathogenic” entities such as fake news and conspiracy theories to germinate, propagate and become pandemic, such as SARS-CoV-2 escaping from a germ warfare laboratory – or the influence of G5 networks on its spread. Similar conspiracy theories were applied to the emergence of HIV and other viruses in the past.

In times of pestilence, myths of blame or denial often arise. Among the powerful, the blame game for viruses is evident today. As for denial, the former President of South Africa, Thabo Mbeki, became convinced by the notion propagated on the web that HIV did not cause AIDS, and he considered that anti-retroviral drugs were a ruse by Western pharmaceutical companies to profit at Africa’s expense. His ban on providing anti-retrovirals is estimated to have cost 350,000 lives.

**Viruses and Science**

The relationships between science, viruses and society are complex. Science is the study of the natural world, by which token viruses fall under its ambit. But whereas virology only became a scientific discipline in the twentieth century in the wake of scientific discoveries mentioned earlier (and reviewed by David Rowlands in this volume), viruses themselves have shaped general science for much longer, just as they have influenced society more broadly. Medical specialties such epidemiology and public health owe much of their
development to infectious diseases we now know to be caused by viruses, as do such medical technologies such as vaccination. The discovery of viruses stimulated a synergistic development between advances in virology and the broader development of science and technology.

**Impact of Science and Technology on Virology**

The expansion of virology owes a lot to the invention and development of novel instrumentation and laboratory techniques. Many of these tools came from disciplines outside the bounds of biology; from biophysical and engineering sciences and from analytical chemistry. Here too there was synergy, for the viruses spurred improvements of laboratory techniques as well as instrument design.

It was the development of improved bacteriological filters by Charles Chamberland in 1884, originally intended for purifying water, that enabled the discovery of TMV and foot mouth disease virus. The refinement of filtration – more accurately – ultrafiltration, also provided the means for determining the size of virus particles. For example, the British physical chemist, William Elford, developed a series of filters with graded pore sizes to determine the dimensions of a number of different viruses.

Elford also played a pioneering role in harnessing the ultracentrifuge, invented in 1925 by Theodor Svedberg in Sweden, which allowed the separation and concentration of virus particles of different densities. Ultracentrifugation became widely used as both an analytical and preparatory tool in virology, which in turn led to innovations in the design of future generations of the instrument. In 1936, the American physical chemist, Wendell Stanley, used ultracentrifugation to concentrate and purify TMV. He successfully crystallized the purified TMV and used X-ray crystallography to discern its structure thinking it contained only protein, but Frederick Bawden, Norman Pirie and colleagues soon revealed its all-important RNA core. As Bawden later remarked, “before 1936 it was tacitly assumed that all viruses were incompressible spheres”. The needle-like crystals of TMV showed otherwise.

The most dramatic change was wrought by the invention and development of the electron microscope, just as the optical microscope had done for bacteria in the seventeenth century which, in Robert Hooke’s words “opened up a whole new invisible World discovered to the Understanding”. The first electron microscope was designed in 1931 by Ernst Ruska, a German electrical engineer and it was his brother, Helmut Ruska, a medical student at that time, who grasped the potential for the new technology in biomedicine. He pursued the visualization of “sub-microscopic agents of disease” and produced the first electron-microscopic images of poxviruses in 1938. Electron microscopy proved a particularly synergistic development with virology; although it stood supreme in the visualization of viruses, it also gained in return, especially in areas of specimen preparation and staining technology (Fig. 1).

While crystallization and electron-microscopy gave scientists a handle on the physical and chemical properties of viruses, they yielded little information about their behavior and biology. The biggest hurdle in this arena was posed by the inability of scientists to isolate and propagate viruses in the laboratory as they could bacteria, because as we now know, viruses are obligate parasites that need a living host cell in order to multiply. With the technique for plating lawns of bacteria in petri dishes already in place, the first viruses to be successfully cultured in the laboratory were the bacteriophages, recognized by the ability to form discrete clear plaques of lysed bacteria. The serial dilution of the “phage” allowed accurate titration and biological cloning, as did titration of TMV on leaves. The cultivation of animal viruses proved more difficult until the propagation of viruses on the chorio-allantoic membrane of embryonated bird’s eggs by Ernest Goodpasture in the United States and Macfarlane Burnet in Australia. Virus propagation in cell cultures was first exploited for polio virus by John Enders, Thomas Weller and Frederick Robbins in 1949.

To illustrate the increasingly rapid pace of technology in virology, let us consider the emergence of novel pathogenic viruses over the past 40 years. Following the appearance of AIDS in 1981, it took two years to identify the virus, HIV-1, and a year more to persuade the world by independent studies that the correct culprit had indeed been found. A further 18 months led to the roll out diagnostic tests based on serology and to the cloning and sequencing of the HIV-1 genome. We had to await the development of the polymerase chain reaction (PCR) technique to monitor viral load in patients. Anti-viral therapy to HIV-1 only became effective in 1996 with the introduction of a combination of drugs targeting more than one step in the replication cycle.

When SARS emerged in 2003, it took less than 2 months to characterize the virus as a member of the coronavirus family, whereas in January 2020, Chinese scientists obtained the full genetic sequence of SARS-CoV-2 from a COVID-19 patient within 2 days. They devised a reliable PCR test to detect infection within a week, although diagnostic tests for SARS-CoV-2 antigens and antibodies have taken a little longer, especially for large scale usage. Pseudotype viruses, based on retrovirus or rhabdovirus vectors incorporating reporter genes that bear the SARS-CoV-2 envelope “S” (spike) glycoprotein, are providing highly sensitive and specific virus neutralization assays without the need for high level containment facilities. These are being employed to study whether recovered patients have protective immunity and as a preliminary test of vaccines based on antibody responses.

DNA sequencing has become ever higher in throughput. In 1987, it was considered quite an achievement to gain the complete DNA sequence of the 150k kilobase genome of human cytomegalovirus. Compare that to today, when a cohort of 1000 COVID patients and healthy controls are each having their total host genome sequenced to identify possible genetic risk factors, and to see if more severely affected people are infected with more virulent variants of SARS-CoV-2.

Virology has benefited from advances in computational sciences, such as bioinformatics, sequence analysis, “big data” and mathematical modeling. The science of tracking and intervening in the course of epidemics using mathematical models began in earnest in 1760, when the Swiss mathematician, Daniel Bernoulli, showed how large-scale variolation against smallpox would
benefit not only the individual but also the population at large, which was the origin of the concept of herd immunity. Had the physicians attending his lecture to the Academie Française heeded his message, Louis XVth and many courtiers at Versailles might not have succumbed to smallpox during the epidemic in May 1774.

### Impact of Viruses on Science

Due to their unique characteristics, viruses have wielded a huge influence on advances in biology and medicine, exploited as tiny, precise tools to reveal the inner workings of the cells they infect. One rough measure of the impact of viruses on science can be garnered from the number of Nobel Prizes awarded in Medicine & Physiology and in Chemistry to discoveries made about and through viruses (Table 1).

Leading the way as a scientific tool were the bacteriophages, to which the physicist-turned-biologist, Max Delbrück turned his attention as a means to study genes at the individual and molecular level. Together with Salvador Luria and Alfred Chase, Delbrück created the famed “American Phage Group” which throughout the 1940s laid the foundations of modern molecular biology and set the scene for studies in DNA replication, recombination, and protein studies. Meanwhile André Lwoff and colleagues at the Institut Pasteur in Paris studied another group of bacterial viruses known as the lysogenic or temperate phages, which can persist in latent form within the host bacterium. Lytic and lysogenic phages played a crucial role in defining viruses as...
distinct from other replicating entities. Jacques Monod and François Jacob employed phages to study mechanisms of genetic regulation and established much of our basic knowledge of universal rules of replication, transcription and translation.

TMV was aptly dubbed by the virologist Heinz Fraenkel-Conrat as “almost always the first” in virology, being the first, as mentioned, to be crystallized, and a major player in the commercial development of the ultracentrifuge and electron microscope. Animal virology, too, led to important discoveries in other areas such as the inner workings of cells and of genes. Split genes with introns and RNA splicing was revealed in 1977 through studies by Phillip Sharp and by Richard Roberts of transcription of human adenovirus type 2. Enveloped viruses, such as the DNA virus, vaccinia, and RNA viruses, such as influenza virus and alphaviruses (Semliki Forest and Sindbis viruses) have been excellent tools exploited by the Finnish virologist, Ari Helenius, and others to probe endocytosis, membrane fusion, conformational changes, secretory pathways, and post-translational modification of proteins like glycosylation. Paramyxoviruses like Sendai virus, which enter cells at the cell surface rather than through receptor-mediated endocytosis, were used to effect cell-to-cell fusion by inactivating the RNA genome without affecting envelope glycoprotein function. Inactivated Sendai virus was exploited to fuse human cells with murine cells by John Watkins and Henry Harris in pioneering studies of human somatic cell genetics.

It was not until the 1950s that Renato Dulbecco and Marguerite Vogt developed plaque assays for lytic viruses on animal cell monolayers beneath an agar gel overlay. From the mid-1960s to the 1980s oncogenic viruses played the leading role in opening up the molecular biology of cancer, including the discovery of oncogenes, which promote malignancy, and of tumor suppressor genes, which keep it in check. Rous sarcoma virus (RSV), the prototype retrovirus, was discovered by Peyton Rous in 1911, but was largely ignored by cancer experts for many decades, who did not believe that the agent was a virus until, in 1958, Harry Rubin and Howard Temin developed an in vitro cell transformation assay for RSV. Thus, oncogenic viruses began to reveal their secrets, including reverse transcriptase in 1970, the integration of viral genomes into host DNA, and the identification of viral genes with oncogenic potential. Reverse transcription permitted the synthesis of complementary DNA from spliced messenger RNA and hence led to the manufacture in bacteria of eukaryotic proteins and biological pharmaceuticals.

The cellular origin of oncogenes – genes that induce tumors – was first revealed by Harold Varmus, Michael Bishop and colleagues with the transforming src gene of RSV, and its gene product became the first known tyrosine kinase. The host homologs of most of the 30 or more oncogenes discovered in various oncogenic animal retroviruses, eg., abl, myc, ras, have important roles in cancer signaling pathways. Several have become successful targets for anti-cancer therapy. Conversely, the discovery of endogenous proviruses in the germ line of chickens and mice led to the realization that a substantial proportion of vertebrate host genomes is represented by ‘fossil’ retroviruses; approximately 8% of human DNA comprises retroviral genomes, some of which have been repurposed by the host for essential functions such as placental development.

Another important milestone with oncogenic viruses was the discovery of the tumor suppressor protein (TSp53) in cells transformed by simian 40 virus (SV40). In 1979, David Lane and Lionel Crawford in London, reported that immunoprecipitation of the large T (tumor) antigen encoded by the SV40 transforming gene also brought down a 53kd host protein. Daniel Linzer and Arnold Levine reported similar data and it became clear that T antigen blocks the natural function of p53 to regulate cell division and to direct cells to an apoptotic pathway. TSp53 became the “canonical” tumor suppressor that Lane dubbed the “guardian of the genome”. Mutations of the p53 gene in human cancers have a similar effect to its sequestration by T-antigen. Many other types of oncogenic DNA viruses encode proteins that block Tsp53 function, such as E6 of HPV and the latent nuclear antigen of Kaposi’s sarcoma virus. Knocking out Tsp53 function triggers the “S” phase of the cell division cycle which the viruses need to synthesize their own DNA.

Harnessing of Viruses by Humans

In this section, we cite examples of how humans have harnessed or attempted to harness viruses, not only for economic and medical benefits, but also for darker ends.

Commerce and Tulip Mania

Compared to centuries-old industries of fermentation that rely on bacteria and yeasts – think of wine, beer and bread – the exploitation of viruses for commercial purposes is still in its infancy. One exception was the unwitting use in the seventeenth century of plant viruses to develop varieties of tulips with different variegations in their flowers. The tulip mania in The Netherlands led to the sale of single tulip bulbs at prices up to 10-fold higher than the average annual earnings of farmers. In February 1637, the market suddenly collapsed, ruining many businessmen who had invested in tulip “futures”. The most treasured tulips were difficult to breed consistently because the pattern of the color “breaks” in the petals was erratic. We now know that the streaked appearance of the prized tulips is caused by the Potyvirus, Tulip Breaking Virus – discovered in 1928 by Dorothy Caley.

Vaccines

The development of vaccines as a means to prevent viral diseases is one of the best known and oldest examples of humans harnessing viruses. As in the cases of fermentation and horticulture mentioned above, the practice predates actual knowledge about the existence of the effector. The English physician Edward Jenner developed the first safe vaccine against smallpox, which was based on the fact that cowpox causes a mild lesion when introduced into the skin of uninfected persons, but cross-protects them against smallpox itself. It represented a major advance to the previous use of immunization with low doses of variola virus.
(the smallpox agent) itself, which had a 2% risk of causing smallpox. Live, attenuated viruses such as Sabin polio vaccine, tend to be efficacious because, while the virus propagates to a lower level than wild-type virus, it is sufficient to elicit immunity without causing disease. Other virulent viruses can elicit protective immune responses after they have been chemically inactivated, e.g., the Salk polio vaccine. Influenza virus vaccines are typically made up of immunogenic components of disassembled viral antigens. Several of the current attempts to design a vaccine against SARS-CoV-2 are targeting the "S" spike glycoprotein.

Despite vaccination having led to immense advances in public health to protect against many infectious diseases, there has been a rise in recent years of antagonism to childhood immunizations such as the combined measles, mumps and rubella vaccine. The fear of parents has been fueled by fake news of vaccine dangers and false associations of vaccines with other diseases. Sadly, this situation has resulted in unnecessary outbreaks of measles and mumps in developed countries.

Phage therapy
When d’Herelle first observed the lytic effect of bacteriophages on bacteria in 1916, he immediately envisaged their use in controlling bacterial diseases, describing his finding as the ‘true microbe of immunity.’ He believed that phages were responsible for natural resistance of populations to diseases such as dysentery and cholera in regions of the world where the diseases were endemic, maintaining an interest throughout his career. Phage therapy attracted wide attention at first, even spurring the imagination of the American novelist Sinclair Lewis who included phages in his Pulitzer Prize-winning novel, Arrowsmith. Phage therapy all but disappeared from the West after WW II, owing to the greater efficacy and reliability of antibiotics, but in the pre-antibiotic world in 1930s and early 1940s, various bacteriophage products were commercially available in many countries. It was promoted in the Soviet Union, and continues at the Eliava Institute of Bacteriophage, Microbiology & Virology which d’Herelle helped to found in Tbilisi, Georgia. Recently, the emergence of antibiotic-resistant bacterial pathogens has stimulated a revival of interest in phage therapy, although bacteria can become resistant to phage as well as to antibiotics.

Gene therapy and cancer therapy
Ever since the advent of recombinant DNA technology, medical researchers have been using viruses as vectors or vehicles for delivering specific genes to target host cells as a possible means of therapy for single gene inherited disorders, such as cystic fibrosis, as well as for treating cancer. Vectors such as vaccinia virus and retroviruses may also be designed to carry genes encoding antigens of different viruses or other pathogens for immunization. Recombinant viruses, such as aden-associated virus, can express high levels of antibody as a means of delivering passive immunotherapy. Lytic viruses can be modified to replicate only in proliferating cells in order to treat cancer. All these approaches are recent developments and are likely to have greater impact on human health in the future.

Bioweapons
The use of viruses for biological warfare is poorly documented. Smallpox may have been spread deliberately by Francisco Pizzaro during the conquest of the Inca empire because its inadvertent effect on the Aztecs 11 years earlier had been noted. One record of the use of viruses in conflict occurred during the Franco-British war for control of North America. Different Native American communities sided with the French or the English. The Redcoat Colonel Henry Bouquet sent his commander, General Lord Jeffrey Amherst, a request “to inoculate the Indians” by sending smallpox-impregnated blankets to them who, under the leadership of Chief Pontiac, were besieging Fort Pitt (Pittsburgh). In a postscript to his reply on 16 July 1763, Amherst approved this request and added that Bouquet should 'try every method that can serve to extirpate this execrable race'.

We look upon multi-ethnic USA differently 250 years later! In 2016, student activists at Amherst College demanded the deletion of Jeffrey Amherst’s name. The Trustees of Amherst College dismissed the issue of the College’s name by stating that the College is named after the town and not the general. They did, however, remove the College’s “Lord Jeff” mascot and change the name of the “Lord Jeff Inn” on campus.

In the twentieth century, most of the potential germ warfare agents were bacterial such as anthrax and tularemia, but it appears that the Nazi regime also tested highly pathogenic viruses on concentration camp victims. The Friedrich Löfler Institute on Riems island in the Baltic Sea, founded in 1910 by the discoverer of foot and mouth disease virus, became a testing ground for bioweapons during World War II, but is now devoted to vaccine research and development. In the Soviet Union, there was a bioweapons establishment near Novosibirsk in Siberia. Vozrozhdeniya Island, in what used to be the Aral Sea, was a testing ground for bioweapons until the collapse of the Soviet Union and it remains contaminated.

Following the eradication of smallpox as a naturally occurring infection, there was debate whether to destroy the remaining stocks of the virus, officially stored in Russia (at Novosibirsk) and in the USA (at the Centers for Disease Control and Prevention – CDC – in Atlanta). In 1996, on the 200th anniversary of Jenner’s first vaccination of young James Phipps, the World Health Organization voted to destroy all official laboratory stocks of the smallpox virus, but this deliberate extinction of a species has yet to be carried out. The issue remains controversial among virologists, some of whom say that preservation is advisable for future work on vaccines or on any novel pox viruses that might emerge, while others argue that, with full genome sequence data of variola in the open domain, there is no need to preserve the virus itself.

It is not clear whether any terrorist organizations or ‘rogue’ nations possess dangerous viruses such as smallpox or Crimean-Congo Hemorrhagic Fever virus (a frequently fatal orthonairovirus), which is naturally transmitted by animal ticks but can also spread among humans via bodily fluids and aerosols. Unofficial stocks of smallpox virus might still exist, either hidden by those
with malicious intent, or which have simply been overlooked. An example of the latter was the discovery in 2016 of vials of variola virus in a freezer at the US National Institutes of Health in Bethesda, Maryland, which were subsequently shipped to the CDC.

**Impact of Viruses on Society**

It might be appropriate to call this section “the impact of viruses on other aspects of society”, because science is, after all, very much a human activity and thus part of society. Here, we address the impact of viruses beyond the laboratory. Undoubtedly the most recognizable impact of viruses is their ability to cause epidemic disease. While our primary focus here will be on human disease, we also touch on viral pathogens of livestock and crops, before ending with a brief look at the influence of viruses on other spheres of human activity, notably the arts and literature.

**Impact on Human Disease**

We know little of the precise times and origins of the plagues of old, but they seem to have appeared when dense populations developed on irrigated land. This seems evident from the cultural myths of those regions: the Nile delta, the Fertile Crescent, the Indus Valley and the area between the Yellow and Yangtze rivers. Yet based on both historical records and archeological evidence one can say that the humans have been subject to viral diseases for as long as we have existed.

The success of vaccines and antibiotics in the mid-twentieth century led to hopes that infectious diseases in general may become largely a phenomenon of the past, like smallpox. In their fine book *Natural History of Infectious Disease* (1972), McFarlane Burnet and David White commented: “The most likely forecast about the future of infectious disease is that it will be very dull. There may be some wholly unexpected emergence of a new and dangerous infectious disease, but nothing of the sort has marked the past fifty years”. A half century later, however, we can see that infections have been anything but dull. Ebola broke out in the Congo in 1976, AIDS began to take lives in the early 1980s and at the time of writing we are in the throes of the COVID-19 crisis which began in December 2019.

**The origins and historical demographics of viral infections in humans**

Some human viruses have always been with us whereas others have transferred from animal hosts. From the “germ’s eye view” it appears that it was the massive changes to human society in the wake of the prehistoric agricultural revolution some 10,000 years ago that provided the opportunity for so many new types of viruses to take up residence in humans. The successful colonization by viruses of foreign origin was a consequence, first of human dispersion out of Africa, second of domestication of livestock and most importantly, the development of large, densely populated communities.

There are many zoonotic viruses, e.g. rabies and H5N1 influenza, that have never become epidemic in humans. An estimated 60% of the 1400 species of infectious microbes known to be pathogenic in humans are transmitted by animals, for which the human usually represents a dead-end host. Viruses that do adapt to human-to-human spread, however, can become self-sustaining providing there is a human population of 250,000 or greater of naïve hosts to infect. Measles, according to recent phylogenetic molecular clock studies, is believed to have diverged from rinderpest of cattle approximately 2400 years ago, and the smallpox strain that was present until eradication, most likely arose in the early Christian era from the Bactrian camel, though burrowing rodents were the ultimate source. These viruses have diverged from their progenitors and only circulate in the human population.

Influenza viruses emerge and re-emerge from reservoirs in waterfowl. Having segmented genomes, they can re-assort with genes of existing strains circulating in humans and other mammals to form new epidemic variants. The “Spanish Flu” pandemic of 1918/1919 was an H1N1 strain that may have arisen in horses of the trenches in World War I. Many modern sources of zoonoses indicate a shift from an origin in livestock or in “companion animals” like dogs and rats, to viruses from exotic species. Deforestation, a taste for bushmeat and other environmental or behavioral factors have increased the opportunities for viruses to reach humans from bats, like Ebola, SARS and Nipah, often via a short-term intermediate host, and from simians, like Zika and other mosquito-borne viruses.

For populations in which epidemic viruses are already resident and widespread, most surviving adults have acquired what is called herd immunity and new infections typically occur in children. However, when the virus reaches a host population that has not previously had experience of that virus, it can infect children and adults alike. The globalization of maritime travel following the explorations of Christopher Columbus and Vasco da Gama at the end of the fifteenth century allowed smallpox, measles and other “Old World” viruses reach new human populations.

The impact on the societies previously unexposed to these viruses proved to be devastating. No other viral disease has affected as many people throughout history as smallpox. Its accumulated mortality was huge, and it has repeatedly ravaged different populations. The introduction of smallpox to the New World during the 1521 conquest of the Aztec empire by Hernán Cortes and his band of Conquistadors, is recounted in vivid detail by Bernal Díaz in his diary, *The Conquest of New Spain*. In the ensuing 100 years, the populous regions of North America from Guatemala to the Mississippi basin lost around 90% of its indigenous peoples from smallpox and measles. This population decline was significantly greater than that in Europe following the Black Death. While it took 200 years for Western Europe to regain its pre-1348 population level, the lot of the survivors improved. For peasants, it became a bull labor market and they fought for and won freedom from serfdom (heredity indentured labor). The decimation of indigenous peoples in America by smallpox had a greater and more sinister consequence: the need for manpower in the New World plantations engendered the trans-Atlantic slave trade.
This pattern of devastation by viruses was repeated globally as further new worlds were contacted in South America, Australia and Oceania. It continues today when isolated Amazonian tribes are contacted by “civilization”. As observed by Charles Darwin in his Notes of the Voyage of the Beagle in 1838: ‘Wherever the European has trod, death seems to pursue the aboriginal … Most of the diseases have been introduced by ships and what renders this fact remarkable is that there might be no appearance of the disease among the crew which conveyed this destructive importation.’

**Viral epidemics in the past century**

Perhaps our best weapon against viral infections in the past century and a half has been vaccination; it has effectuated the eradication of smallpox, and the control of many other viral diseases including rabies, influenza, yellow fever, polio myelitis, measles, mumps and rubella, and most recently the human papilloma viruses associated with cervical cancer.

But we haven’t conquered all viruses by any means. Despite the development of vaccines against it, influenza virus continues to wreak havoc, killing an estimated extra 280,000 people as recently as the H1N1 pandemic in 2009. Since it first appeared four decades ago, HIV has accounted for some 39 million AIDS deaths, 66% of them in Africa. In addition, AIDS has had an enormous socio-political impact.

In the early phases of the epidemic in North America, HIV targeted marginalized social groups, notably male homosexuals and intravenous drug-users. On the one hand, this apparent predilection exacerbated the discrimination against homosexuals by fundamentalist religious groups and by political conservatives who opposed certain types of demographic surveys about sexual behavior, which was detrimental for learning about disease epidemiology. On the other hand, the AIDS epidemic mobilized the gay community, especially in the US, to social activism, resulting in widespread appeals and funding for research and public awareness about the disease. Meanwhile, the demographics of AIDS incidence in low income nations, especially Africa, also mobilized efforts to roll out anti-retroviral therapy across Africa, and by public health communities for better sex education and safer sexual practices.

**Impact on human capital in the era of COVID-19**

Plunged in the COVID-19 pandemic as we are, it is not yet possible to accurately estimate its mortality rate. SARS-CoV-2 has a high mortality rate in hospitalized cases of infection, whereas the mortality in the general population is likely to be much lower, once the prevalence of infection has been ascertained by serological studies. The SARS and MERS coronaviruses are more highly pathogenic than SARS-CoV-2, but fortunately could be contained. That makes them easier to hunt down and box in via contact tracing because, like smallpox virus, there is little onward transmission before symptoms appear.

Four other strains of human coronavirus are highly transmissible and represent around 20% of ‘common colds’. One can speculate whether they caused similar mortality to SARS-CoV-2 when first introduced to humankind. With COVID-19, elderly people are at most risk of severe disease and death, which contrasts with the 1918/19 ‘flu pandemic, when many old people got off ‘lightly’. The reason why the elderly were relatively protected in 1918/19 was possibly due to an immune memory of a previous outbreak of a related ‘flu virus sometime in the late nineteenth century.

A better social indicator of disease impact than mortality is the disability-adjusted life year (DALY) expressed as the number of years lost due to ill-health, disability or early death. Given that COVID-19 tends to be most severe in older people, if we were to measure DALYs, the cost to society of COVID-19 affecting human capital, the workforce and those still in formative years of education ought to be relatively slight compared to the Spanish ‘flu and HIV. These two 20th century pandemics took out mainly young adults, the very cohorts in whom society had invested maximum social capital.

SARS-CoV-19 infection, nonetheless, appears set to exceed the mortality of any other novel virus since HIV (~39 million over a “flattened” 40 years), and the Spanish ‘flu a century ago (over 50 million deaths within a mere 18 months). The main driver of the profound effects that we are currently witnessing on the global economy and our livelihoods lies in our attempts to ameliorate the spread COVID-19, for which most nations were ill-prepared. It appears that complex, inter-connected modern societies and economies are more fragile in the face of a novel pandemic than 100 year ago.

While we may marvel at the speed of the identification of the new coronavirus and the use of rapid early diagnostic tests by genome amplification, we are humbled by the fact that we still rely on centuries old means of trying to contain the pandemic. We are using quarantine methods (self-isolation) dating from Venice’s approach to the Black Death 670 years ago, and the social distancing imposed on lepers. The advice “wash your hands” is a legacy from Ignaz Semmelweis whose medical colleagues ignored him as they made their way from the morgue to the delivery room. We hope that a COVID-19 vaccine will soon be developed given the number of candidates under preclinical and clinical trial, but an efficacious and long-lasting one may take a little longer to achieve.

**Impact of Viruses on Livestock and Crops**

Textbooks of veterinary virology and plant virology are as weighty as those about human viruses, owing to the great variety of viruses that threaten animal and plant health. Our 120-year knowledge that foot and mouth disease is caused by a virus has not entirely prevented it, as evidenced by the 2001 outbreak in the UK that resulted in serious economic loss to farmers through obligatory culling of livestock. The epidemic was probably triggered by the illegal addition of kitchen food waste containing imported ham to pig swill, and it then spread rapidly by transport of cattle and sheep traded in markets. Probably the best recognized viral pathogens of animals are strains of influenza, with reservoirs in wild waterfowl but initiating epidemics in domestic birds, horses and pigs. Tick-borne African Swine Fever Virus, endemic in wart hogs and bush pigs, has spread in recent
decades far beyond East Africa and is currently a serious problem in China. The orbivirus causing bluetongue disease in ruminants is broadening its geographic range northwards from Africa to Europe with the spread of its midge vector due to global warming, as well as colonization of new midge species. Tilapia lake virus first emerged in 2014 and is affecting Tilapia pisciculture in South America, Africa and south-east Asia where the fish is an important source of protein in the human diet.

The greatest success story in veterinary virology was the eradication of rinderpest, a disease of cattle caused by a morbillivirus. Regular outbreaks of rinderpest previously had a profound impact on herding communities in East Africa. This disease, together with the trypanosome parasite causing sleeping sickness, rendered large swathes of Africa inhospitable for imported domestic cattle. After a $5 billion campaign that began in 1995, the United Nations Food and Agricultural Organization declared the global disappearance of rinderpest in June 2011, the second virus after smallpox to be eradicated. In June 2019, the Pirbright Institute in the UK destroyed its repository of different rinderpest virus strains, having documented their genetic sequences.

The best studied viral pathogen of crops is undoubtedly TMV which played such an important role in virology discussed earlier. With hindsight, we know that tobacco itself is a scourge upon humankind, but through its introduction to the Old World in the sixteenth century Columbian Exchange, it became an important commodity. Cauliflower mosaic virus (no relation to TMV) is notable both as a pathogen of cruciferous plants and because it replicates via reverse transcriptase like retroviruses. One of the most important plant viruses that is currently affecting food security is African cassava mosaic virus, a member of the Geminivirus family.

Viruses in Art and Literature
As with almost anything that we humans have encountered, viruses have stirred our imaginations in different ways and have made their way into our creative pursuits. The functional beauty of virus particles has caught the attention of artists, designers and architects. Conversely, buildings have inspired virologists to deduce virus structures more precisely. In 1962, Donald Caspar and Aaron Klug proposed a model of icosahedral (20-sided) particles drawn from the architect-designer Buckminster Fuller’s geodesic domes who himself became enchanted with this analogy. He had solved a means to erect stable ‘spherical’ buildings composed of triangulated, pentagonal and hexagonal sided domes and it became apparent that viruses had solved the problem before humans did. Viruses with small genomes require many copies of one or two proteins to form the capsid surrounding the RNA or DNA genome. Bacteriophage MS2 has this type of structure and so do human adenoviruses. The recombinant human papilloma virus vaccine is self-assembled from one viral protein, L1, to form empty (genome free) “virus like particles” that possess this structural integrity. Moreover, the particulate nature of the vaccine renders it highly immunogenic.

Epidemic disease in particular has been the inspiration and subject of many works of literature. One of the most enduring examples is in Thucydides’ History of the Peloponnesian War, where he provided a first-hand account of the 430 BCE “Plague of Athens”, which may have been a typhus or viral outbreak.

No other disease in the twentieth century has generated as much as the AIDS pandemic in so many different spheres of the literary, performing and visual arts: The plays A Normal Heart by Larry Kramer (1985) and Angels in America by Tony Kushner (1992), were both explicit in their criticism of the social and medical response to the plight of the gay community in the early years of the AIDS outbreak; Randy Shilts’s And the Band Played On (1987) provided a chronicle of the new disease and the unfolding of scientific breakthroughs; Thom Gunn produced an anthology of poetry The Man With the Night Sweats (1992) while AIDS ravaged San Francisco; and Abraham Verghese provided a doctor’s perspective of treating the disease in the deeply conservative rural Tennessee in his moving My Own Country (1994). AIDS also gave a new guise to Giacomo Puccini’s La Boheme – itself based on tuberculosis – when Jonathan Larson’s award-winning rock opera Rent hit Broadway in the mid-1990s. Last but not least, there is one of the largest and possibly longest-running piece of community folk art in the world: the NAMES Project Memorial Quilt, better known as the AIDS Quilt. Conceived in 1985 by the activist Cleve Jones to celebrate the lives of those lost due to AIDS, it is currently estimated to weigh about 54 tons, and from 2020 will be on permanent display in San Francisco where it originated.

We end with an allusion to two modern classics: Chinua Achebe’s novel Things fall apart (1958) which describes the strain and collapse when a traditional West African society becomes ‘infected’ by a foreign culture of missionaries and colonial officers. Although not itself about viral epidemics, the title alludes to the famous lines in WB Yeats’ poem The Second Coming, written in 1919 at the height of the Spanish ‘flu pandemic:

- Things fall apart; the center cannot hold;
- Mere anarchy is loosed upon the world,
- The blood-dimmed tide is loosed, and everywhere
- The ceremony of innocence is drowned.
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