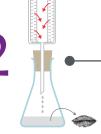
## SIGNIFICANT EVENTS IN THE HISTORY OF VIROLOGY



1796 Edward Jenner administers the first smallpox vaccine, which is heralded as the world's first vaccine. The vaccine consists of fluid from a cowpox blister, a virus similar to smallpox, which is scratched onto the skin of an 8-year old boy. When the boy is later inoculated with smallpox matter, no disease develops.

1892 Dmitri Ivanovsky shows that tobacco mosaic disease, a singlestranded RNA plant virus, can be transmitted by extracts passed through porcelain Pasteur-Chamberland filters, which exclude the smallest known bacteria.



1901 Walter Reed heads the U.S. Army Yellow Fever Commission, which discovers that yellow fever is transmitted by the bite of an Aedes aegypti mosquito rather than by direct contact.



1911 Peyton Rous discovers Rous sarcoma virus (RSV), the first oncogenic retrovirus to be described, which is found to cause sarcoma in chickens. Rous shares the Nobel Prize in Physiology or Medicine in 1966 for his discovery of tumor-inducing viruses

1935 Wendell Stanley produces the first crystals of tobacco mosaic virus and shows that the virus remains active after crystallization. Crystallization of the virus was the first step toward proving that the virus is particulate.

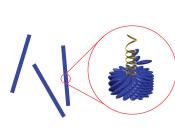


1937 Max Theiler grows the yellow fever virus in chicken eggs and produces a vaccine from an attenuated virus strain. In 1951, he receives the Nobel Prize in Physiology or Medicine for his discovery of an effective yellow ever vaccine, the only Nobel Prize ever awarded for the development of a virus vaccine.



1953 Jonas Salk announces on a national radio show and later reports in The Journal of the American Medical Association that he has successfully developed and tested an injectable, killed-virus vaccine against poliovirus, the virus responsible for poliomyelitis. Testing of the vaccine starts in 1954 and in 1955, it is announced that the vaccine is safe and effective. In 1962, an oral vaccine developed by Albert Sabin using a weakened form of the live virus becomes available

1951 Ludwik Gross identifies the first murine leukemia virus



1955 Rosalind Franklin proposes the full structure of tobacco mosaic virus, suggesting that the virus contains a single strand of RNA that spirals in a helical groove inside the center of the viral proteins. Solving the structure of the tobacco mosaic plant virus paved the way for solving the structure of animal viruses, which Franklin's lab subsequently pursued, leading to a publication following her death that described the crystal structure of poliovirus.

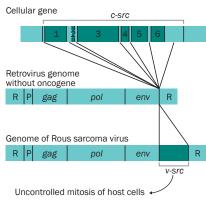
of causing tumors in experimentally-infected animals. This is the first known human virus reported to be capable of inducing

1962 John Trentin reports that human adenovirus is capable

1964 A paper describing the first virus directly associated with human cancer is published in The Lancet. The virus, known as Epstein-Barr virus, is a human herpesvirus discovered by Michael Epstein, Yvonne Barr, and Bert Achong through their

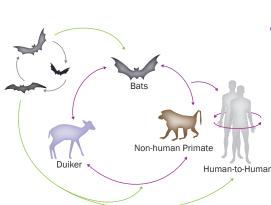


**1970** The first retroviral oncogene, *v-Src*, is discovered in Rous sarcoma virus. This gene encodes a tyrosine kinase involved in cell growth and differentiation.



1970 Reverse transcriptase is discovered by Howard Temin in RSV virions and independently isolated by David Baltimore from two RNA tumor viruses, R-MLV and RSV. The enzyme is used by retroviruses to generate complementary DNA from an RNA genome, which is then stably integrated into the chromosomal DNA of the host. Temin and Baltimore are jointly awarded the Nobel Prize in Physiology or Medicine in 1975, along with Renato Dulbecco, for their discoveries



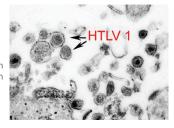


1976 The first known outbreaks of Ebola virus disease (EVD)

occur in South Sudan and in the Democratic Republic of the Congo, and are found to be caused by two distinct subtypes of Ebolavirus. While the natural host of Ebola remains unknown. bats are now believed to be the most likely reservoir.



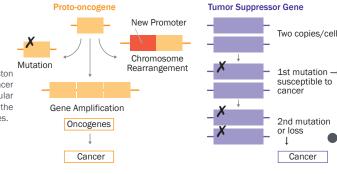
1980 Robert Gallo discovers the first human retrovirus, Human T-Lymphotrophic Virus (HTLV-1), by visualizing viral particles in cultured human T cell lymphoma cells.



1983-1984 Harald zur Hausen shows that two strains of the human papillomavirus (HPV) cause most cases of cervical cancer, a discovery for which he was awarded jointly the Nobel Prize in Physiology or Medicine in 2008, along with Luc Montagnier and Francoise Barré-Sinoussi, who



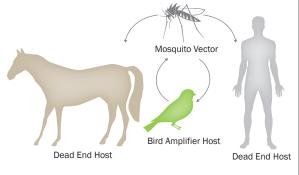
Ed Harlow and David Livingston demonstrate that viruses can promote cancer either by activating the products of cellular proto-oncogenes or by inactivating the products of cellular tumor suppressor genes.





1989 Michael Houghton and his colleagues at Chiron Corporation along with Dan Bradley at the CDC discover the hepatitis C virus (HCV). Chronic HCV infection is found to be associated with hepatocellular carcinoma (HCC).

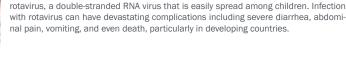
1999 The first documented cases of West Nile Virus (WNV) infection in the Western Hemisphere are recorded in New York City in August of this year, following reports of a number of severe cases of encephalitis and avian deaths. During August and September, 59 patients are hospitalized with WNV infection. This initial outbreak is followed by years of progressive spread of the virus throughout the U.S., with the largest annual epidemic of WNV in North America occuring in 2003.



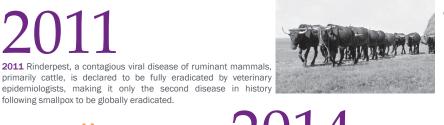


2006 A vaccine protecting against the two cancer-causing strains of human papilloma

virus (HPV) is approved by the U.S. Food and Drug Administration. While more than 100 HPV types have been identified. HPV 16 and HPV 18 are the two strains that have been found to cause 70% of cervical cancers. The HPV vaccine approved in this year targets both of these strains and two other low-risk HPV types, HPV 6 and HPV 11. 2006 The U.S. Food and Drug Administration approves a vaccine for preventing



primarily cattle, is declared to be fully eradicated by veterinary epidemiologists, making it only the second disease in history following smallpox to be globally eradicated.





2014 The largest Ebola outbreak in history occurs in West Africa, resulting in the death of more than 11,300 people in Guinea, Liberia, and Sierra Leone. In September of this year, the CDC confirms the first laboratory-confirmed case of Ebola to be diagnosed in the U.S., which was found in a man who had traveled from Liberia to Texas.

2018 The world's second largest Ebola outbreak on record begins in August of this year with four cases being confirmed in North Kivu Province in the Democratic Republic of the Congo (DRC). On July 17, 2019, the outbreak is declared a Public Health Emergency of International Concern by the World Health Organization as there are more than 2,500 cases and more than 1,600 deaths reported by the DRC Ministry of Health. By March 16, 2020, more than 3,400 cases of Ebola virus disease are confirmed, and more than 2,260 people have died since the outbreak was first declared.



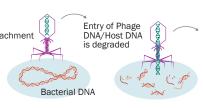
1885 French scientists, Louis Pasteur and Emile Roux, develop the first effective rabies vaccine. The virus is grown in rabbits and a vaccine is made from dried rabbit nervous system tissue, which is successfully administered to a boy that was bitten by a rabid dog.

experiments performed by Dmitri Ivanovsky and calls the infectious agent that causes tobacco mosaic disease a "virus", which he describes as a "contagium vivum fluidum" or "contagious living fluid". Beijerinck along with Ivanovsky are considered to be the founders of virology

1898 The first animal virus, known as foot and mouth disease virus, is discovered by German scientists, Friedrich Loeffler and Paul Frosch. They show that cows and sheep can be vaccinated against the virus using a heat-inactivated, filtered vesicle extract.



1936 John Bittner reports that an infectious, filterable agent present in the milk of certain cancer-prone mouse strains can be transmitted to newborn, cancer-resistant mice by suckling and it can lead to the development of mammary tumors. This infectious agent later came to be known as mouse mammary tumor virus.



Phage DNA Replication/

1933 Cottontail rabbit papillomavirus (CRPV) is discovered and is shown

to be the first oncogenic DNA virus in 1935. CRPV causes skin tumors and

warts that are typically located on the heads of infected rabbits.

1939 Emory Ellis and Max Delbruck establish the concept of the one-step virus growth cycle, which serves as the basis for understanding viral replication and the virus life cycle. They demonstrate that virus particles do not grow, but rather are assembled from preformed components.

T2 virus with radioactively labeled DNA

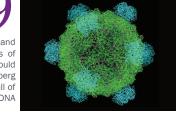
1952 Hershey and Chase demonstrate that DNA alone, not protein, enters a bacterial cell upon infection with enterobacteria phage T2, which is a virus that infects and kills E. coli.

1954 John Franklin Enders, known as "The Father of Modern Vaccines", along with Thomas Huckle Weller and Frederick Chapman Robbins share the Nobel Prize in Physiology or Medicine for their discovery that poliovirus could be grown in cultures using various types of tissues without needing an intact organism. This finding allowed both inactivated and live polio vaccines to be produced for the first time

and was critical to being able to create large quantities of different kinds of viruses

1959 The Nobel Prize in Physiology or Medicine is jointly awarded to Severo Ochoa and Arthur Kornberg for their discovery of the mechanisms in the biological synthesis of ribonucleic acid and deoxyribonucleic acid. Ochoa discovered an enzyme that could

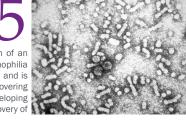
synthesize RNA, while Kornberg discovered an enzyme that could synthesize DNA. Kornberg later showed that DNA synthesized in a test tube by purified enzymes could produce all of the features of a natural virus using the bacteriophage Phi X 174, a single-stranded DNA



T2 virus with radioactively labeled protein

School in Massachusetts to develop a vaccine. This vaccine, based on the attenuated Edmonston strain, is licensed by the U.S. in 1963.

1965 Baruch Blumberg and his colleagues discover a new antigen in the serum of an Australian aborigine that reacts with an antibody in the sera from patients with hemophilia who had received blood transfusions. This antigen is called the Australian antigen, and is later found to be a surface antigen on the hepatitis B virus (HBV). In addition to discovering HBV, Blumberg later develops a screening test for the virus and an approach for developing a vaccine. In 1976, he shares the Nobel Prize in Physiology or Medicine for his discovery of the new mechanisms for the origin and dissemination of infectious diseases.



1963 John Franklin Enders uses cultivated measles virus that was isolated from blood samples collected from David Edmonston during a measles outbreak at the Fay



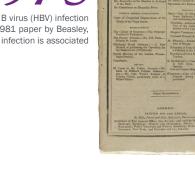
Merck Pharmaceutical Co. The vaccine is a mixture of the three attenuated viruses. Over his lifetime, Hilleman is credited with developing over 40 vaccines and saving millions of lives

THE LANCET.

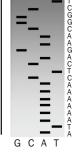
1971 The measles, mumps, rubella (MMR) vaccine is developed by Maurice Hilleman at

1975 Baruch Blumberg discovers a link between chronic hepatitis B virus (HBV) infection

and hepatocellular carcinoma (HCC). This link is confirmed in a 1981 paper by Beasley, R.P. et al. published in The Lancet, which reports that chronic HBV infection is associated with a 100-fold increase in the risk of developing HCC.



1977 Frederick Sanger completes the first full genome sequencing project for an organism using DNA from the bacteriophage Phi X 174, a single-stranded DNA



1979 The global eradication of smallpox is certified in December of this year, with the last known natural case occurring in Somalia in 1977. This certification is later endorsed by the World Health Assembly in 1980.



cervical cancer.

1981 The U.S. Food and Drug Administration (FDA) licenses Maurice Hilleman's hepatitis B virus (HBV) vaccine, known as Heptavax-B, which was developed at Merck Pharmaceutical Co. Hilleman made the vaccine by purifying a HBV surface protein called the Australian antigen from blood collected from HBV-infected donors that had been heat- and formaldehyde-treated to inactivate the virus. In 1986, a recombinant HBV surface antigen vaccine is produced due to safety and cost concerns associated with the first vaccine. This vaccine is the first to be produced based on recombinant DNA technology

jointly the Nobel Prize in Physiology or Medicine in 2008 for their discovery, along with Harald zur Hausen, who identified the link between human papillomaviruses



**·**1994

which is later confirmed to be the causative agent of SARS.

time in the Americas in late 2013 on islands in the Caribbean.

1994 Yuan Chang and Patrick Moore discover Kaposi's sarcoma herpesvirus (KSHV) in Kaposi's sarcoma tissue from AIDS patients. In addition to being the causative agent of Kaposi's sarcoma, KSHV is also associated with Castleman's disease, primary effusion lymphoma, and KSHV inflammatory cytokine syndrome.

2003 The Centers for Disease Control and Prevention and Canada's National Microbiology Laboratory identify the severe acute respiratory syndrome (SARS) coronavirus genome,



2005-2006 A severe Chikungunya outbreak occurs on the islands of Mauritius and Réunion in the Indian Ocean with more than 272,000 cases being reported. This outbreak is followed by an outbreak in India in 2006 and 2007 during which more than 1,500,000 cases of Chikungunya or dengue



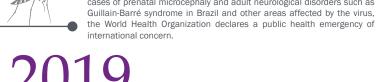


outbreak that occurs in this year to be a global pandemic. The H1N1 virus responsible for the outbreak is found to have a unique combination of swine, avian, and human genes that had not been seen before. Although the 2009 pandemic was caused by human-to-human transmission, it was called "swine flu" because genetic analysis of the virus showed that it was most similar to H1N1 viruses with swine origins. President Obama declared the swine flu outbreak in the U.S. to be a national emergency in October of this year. 2012 The first case of Middle East Respirato-

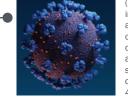
2009 The World Health Organization declares the H1N1/Influenza A, or swine flu,

ry Syndrome (MERS) is reported in Saudi Arabia. It is found to be caused by Middle East Respiratory Syndrome coronavirus (MERS-CoV), which is thought to have come from an animal source, possibly camels, in the Arabian Peninsula.





international concern. 2019 In late December of this year, a novel coronavirus called severe acute respiratory syndrome



(SARS)-CoV-2, is found to be responsible for an outbreak of respiratory illness that was first reported in the city of Wuhan in the Hubei Province of China. The disease caused by SARS-CoV-2 is designated as coronavirus disease 19 (COVID-19), which in severe cases, can lead to potentially life-threatening complications including pneumonia and respiratory failure. On January 30, 2020, the outbreak is declared a global health emergency by the World Health Organization (WHO) as nearly 8,000 cases are reported worldwide and there is evidence that the virus can be transmitted from person-to-person, Six weeks later on March 11, 2020, the WHO declares COVID-19 to be a pandemic as there are over 118,000 cases reported in more than 114 countries and territories around the world, and 4,291 people are reported to have died from the disease.

