PROJECT REPORT

ON

"PREDICTING EVOLUTION OF INFLUNZA VIRUS"

SUBMITTED TO

RTM UNIVERSITY NAGPUR, FOR FULFILLMENT OF THE DEGREE OF MASTER OF SCIENCE IN ZOOLOGY

SUBMITTED BY

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2020-2021

POST GRADUATE DEPARTMENT OF ZOOLOGY & DR. ARUN MOTGHARE MAHAVIDYALAYA, KONDHA-KOSRA

CERTIFICATE

This is to certify that investigation described in this project entitled**, "PREDICTING EVOLUTION OF INFLUNZA VIRUS"**was carried out by **Miss. Bhagyashri B. Bawankar**in Post Graduate department of zoology & Dr. ArunMothgareCollege Kondha-

Kosra, Under My supervision and guidance in partial fulfillment of the requirememt for the degree

Of Master of Science in Zoology of RTM University, Nagpur.

This work is the won work of the candidate, complete in all respects and is of sufficiently high

standard to warrant its submission to the said degree.

The assistance and resources used for this work are duly acknowledged.

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DECLARATION

I hereby declare that this project titled **"Predicting Evolution OfInflunza Virus"** is bonafide and authentic record of work done by me under supervision of Miss. Sangita S. Talmale during academic session 2020-2021.

The work presented here is not duplicated from any other source & also not submitted Earlier for any other degree to any university. I understand that any such duplication is liable to be Punished in accordance with the university rules.

The source material, data used in this research study have been duly acknowledged.

Date: **Miss. Bhagyashri B. Bawankar**

Place: PAUNI

ACKNOWLEDGEMENT

These is my privilege to express deepest sense of gratitude and in debt sense to my supervisor Miss. Sangita S. Talmale for his invaluable supervision, unending and constructive criticism. All this provided us the needed moral and confidence to carry out this project.

I am honorable thankful to Dr. Arun L. Motghare Principal, Dr. ArunMotghare College, Kondha-Kosra for making us all facilities available.

I am also thank full to all other faculty members of Dr. ArunMotghare College, Kondha-Kosra for their help during my project work.

I take pleasure in expressing heartiest thanks to my parents, colleagues and Classmates for their moral support and helpfulness through my project work. I am also Thankful to my other friends excluding Dr. ArunMotghare College, for giving me full support in my project work.

Date: **Miss. Bhagyashri B. Bawankar**

Place: Pauni

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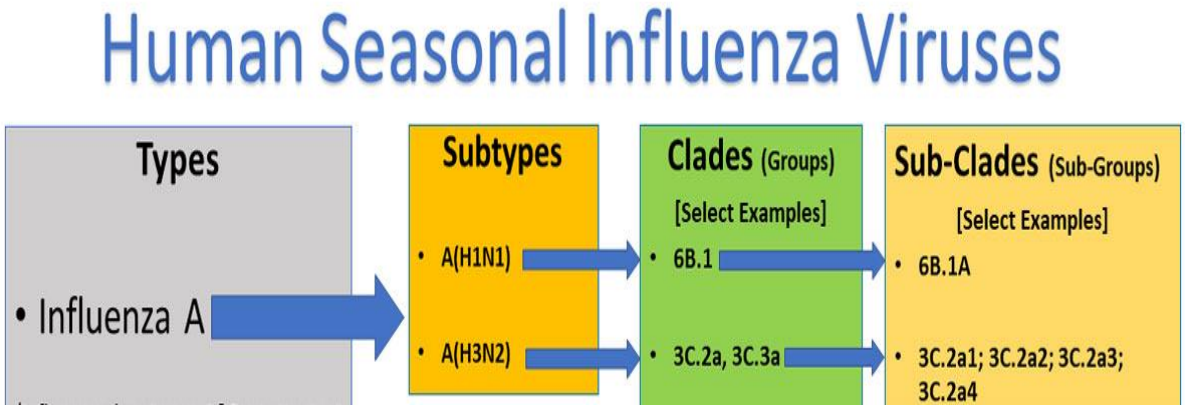
Chapter 1

INTRODUCTION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Introduction

Influenza viruses and the disease that bears the same name have fascinated researchers for decades. While some researchers are interested in the clinical illness, disease severity and its complications, others focus on virus biology, specific viral proteins, and virus-host interactions whereas some immunologists have used influenza viruses and proteins as model antigens in basic research. Technical advances in the last decade, many within the last few years, have made it possible to investigate influenza virus infection from the cellular and subcellular level to intact animals and humans. As a result, we have gained a new understanding of the virus and disease; some dogma has been questioned or even overturned and, in some instances, investigators have re-discovered what was previously known. I will present my own perspective on advances that have occurred during my career, with the caveat that this is not a comprehensive or thorough assessment of progress in the field as a whole.

Influenza, commonly called "the flu", is an infectious disease caused by influenza viruses. Symptoms range from mild to severe and often include fever, runny nose, sore throat, muscle pain, headache, coughing, and fatigue. These symptoms typically begin 1–4 days after exposure to the virus and last for about 2–8 days. Diarrhea and vomiting can occur, particularly in children. Influenza may progress to pneumonia, which can be caused by the primary viral infection or by a secondary bacterial infection.

There are four types of influenza virus, termed influenza viruses A, B, C, and D. Aquatic birds are the primary reservoir of *Influenza A virus* (IAV), which is also widespread in various mammals, including humans and pigs. *Influenza B virus* (IBV) and *Influenza C virus* (ICV) primarily infect humans, and *Influenza D virus* (IDV) is found in cattle and pigs. IAV and IBV circulate in humans and cause seasonal epidemics, and ICV causes a mild infection, primarily in children. IDV can

infect humans but is not known to cause illness. In humans, influenza viruses are primarily transmitted through respiratory droplets produced from coughing and sneezing. Transmission through aerosols and intermediate objects and surfaces contaminated by the virus also occur. Frequent hand washing and covering one's mouth and nose when coughing and sneezing reduce transmission. Annual vaccination can help to provide protection against influenza.

Influenza viruses, particularly IAV, evolve quickly, so flu vaccines are updated regularly to match which influenza strains are in circulation. Vaccines currently in use provide protection against IAV subtypes H1N1 and H3N2 and one or two IBV subtypes. Influenza infection is diagnosed with laboratory methods such as antibody or antigen tests and a polymerase chain reaction (PCR) to identify viral nucleic acid. The disease can be treated with supportive measures and, in severe cases, with antiviral drugs such as oseltamivir. In healthy individuals, influenza is typically self-limiting and rarely fatal, but it can be deadly in high risk groups.

In a typical year, 5–15% of the population contracts influenza. There are 3–5 million severe cases annually, with up to 650,000 respiratory-related deaths globally each year. Deaths most commonly occur in high risk groups, including young children, the elderly, and people with chronic health conditions. In temperate regions of the world, the number of influenza cases peaks during winter, whereas in the tropics influenza can occur year-round. Since the late 1800s, large outbreaks of novel influenza strains that spread globally, called pandemics, have occurred every 10–50 years. Five flu pandemics have occurred since 1900: the Spanish flu in 1918–1920, which was the most severe flu pandemic, the Asian flu in 1957, the Hong Kong flu in 1968, the Russian flu in 1977, and the swine flu pandemic in 2009.

Chapter 2

REVIEW OF LITERATURE

Review of Literature

Influenza viruses are the most prominent members of the family *Orthomyxoviridae*. Their genome consists of eight (influenza A and B) or seven (influenza C) negative-sense RNA segments, each encoding one or more viral proteins. Owing to the segmented nature of the influenza virus genome, reassortment of RNA segments can occur upon co-infection of one cell with two or more viruses, resulting in viruses with new genetic constellations. Reassortment has been used to investigate functions of viral proteins and to generate candidate vaccine viruses for the production of influenza vaccines for decades. However, reassortment does not allow the targeted engineering of viral genes, limiting the scope of investigations. In contrast, reverse genetics (RG) in the context of viruses describes 'the ability to engineer deliberate genetic change into a viral genome'.

Isolated influenza virus RNA, when introduced into cells, is non-infectious. The minimal transcriptionally active unit of the influenza virus is the viral ribonucleoprotein complex (RNP), containing in addition to viral genomic RNA a set of at least four viral proteins, namely nucleoprotein (NP) and the trimeric viral RNA-dependent RNA polymerase (RdRp) consisting of one subunit each of polymerase basic protein 1 (PB1), polymerase basic protein 2 (PB2) and polymerase acidic protein (PA). Influenza virus RG methods, that is, the generation of influenza viruses from cloned DNA, therefore have to provide both viral genomic RNA and the set of essential proteins to a susceptible cell. RG has been crucial in elucidating various aspects of the basic biology of influenza viruses and has also aided the development of candidate vaccine viruses (CVVs), in particular those derived from highly pathogenic avian influenza viruses such as H5N1 and H7N7 identified in poultry outbreaks and sporadically in humans.

This first method allowed the genetic manipulation of one influenza genomic RNA segment

at a time and depended on the use of a helper virus and a selection system to select for the newly generated recombinant (also known as ‘transfectant’) influenza virus, or against the respective RNA segment of the helper virus. A major breakthrough in influenza virus reverse genetics was achieved in 1999 when two groups independently published methods to generate influenza viruses entirely from cDNA, without the use of helper viruses and thus obviating the need for a selection system.

This literature review collates information on RG methods for influenza virus that are in the public domain and attempts to categorise them based on various technical aspects of these methods.

There are four types of influenza virus, termed influenza viruses A, B, C, and D. Aquatic birds are the primary reservoir of *Influenza A virus* (IAV), which is also widespread in various mammals, humans, and *Influenza D virus* (IDV) is found in cattle and pigs. IAV and IBV circulate in humans and cause seasonal epidemics, and ICV causes a mild infection, primarily in children. IDV can infect humans but is not known to cause illness. In humans, influenza viruses are primarily transmitted through respiratory droplets produced from coughing and sneezing. Transmission through aerosols and intermediate objects and surfaces contaminated by the virus also occur.

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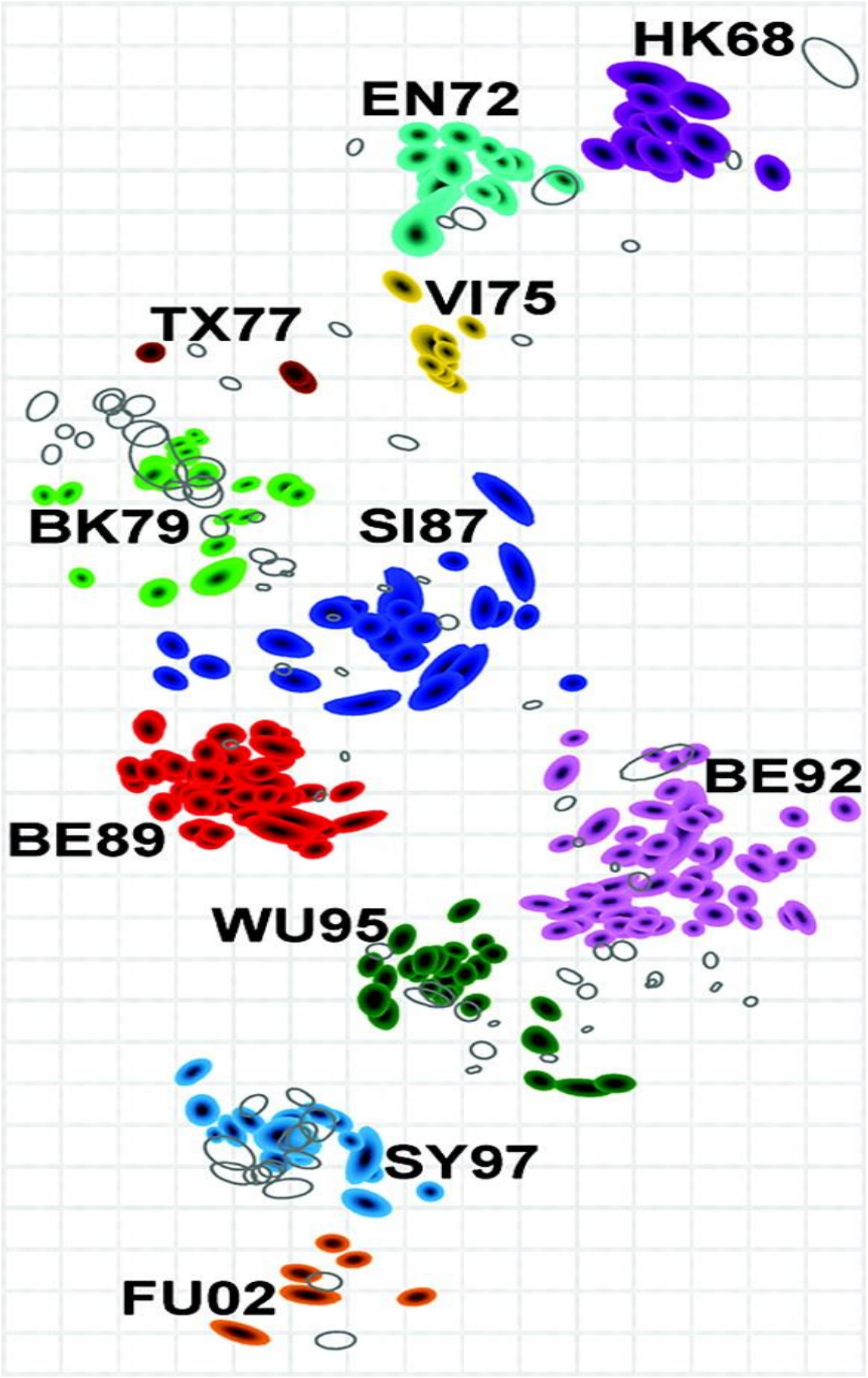
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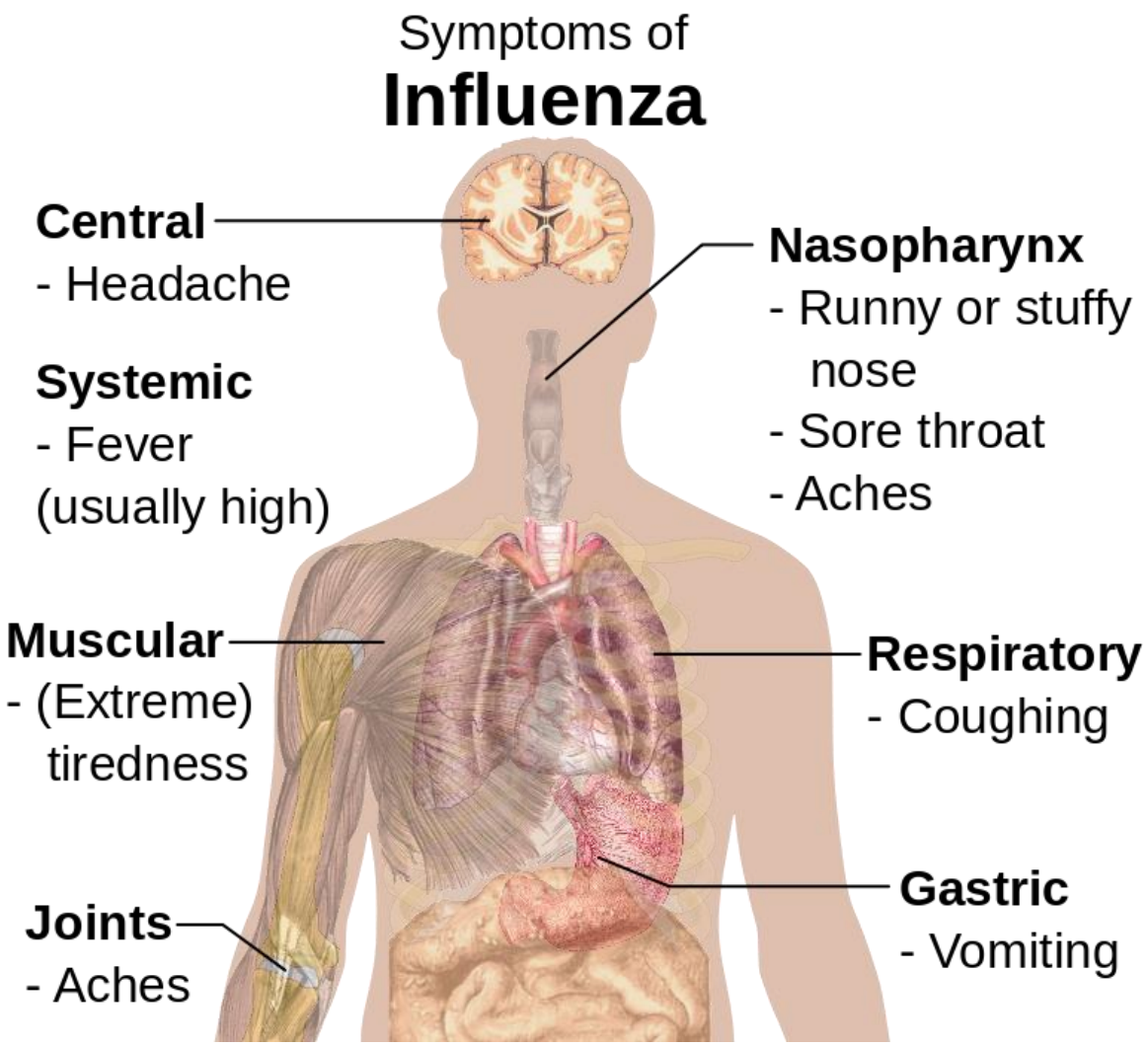
Chapter 3

HISTORY OF EVOLUTION INFLUNZA VIRUS



Symptoms

The time between exposure to the virus and development of symptoms, called the incubation period, is 1–4 days, most commonly 1–2 days. Many infections, however, are asymptomatic. The onset of symptoms is sudden, and initial symptoms are predominately non-specific, including fever, chills, headaches, muscle pain or aching, a feeling of discomfort, loss of appetite, lack of energy/fatigue, and confusion. These symptoms are usually accompanied by respiratory symptoms such as a dry cough, sore or dry throat, hoarse voice, and a stuffy or runny nose. Coughing is the most common symptom. Gastrointestinal symptoms may also occur, including nausea, vomiting, diarrhea, and gastroenteritis, especially in children. The standard influenza symptoms typically last for 2–8 days.

Symptomatic infections are usually mild and limited to the upper respiratory tract, but progression to pneumonia is relatively common. Pneumonia may be caused by the primary viral infection or by a secondary bacterial infection. Primary pneumonia is characterized by rapid progression of fever, cough, labored breathing, and low oxygen levels that cause bluish skin. It is especially common among those who have an underlying cardiovascular disease such as rheumatic heart disease. Secondary pneumonia typically has a period of improvement in symptoms for 1–3 weeks followed by recurrent fever, sputum production, and fluid buildup in the lungs, but can also occur just a few days after influenza symptoms appear. About a third of primary pneumonia cases are followed by secondary pneumonia, which is most frequently caused by the bacteria *Streptococcus pneumoniae* and *Staphylococcus aureus*.

Causes

The main three types of influenza virus that cause illness in people are named A, B, and C. Influenza A and B viruses cause seasonal epidemics of disease almost every winter in the United States, while influenza C causes only mild respiratory symptoms and is not thought to cause epidemics, according to the CDC. The influenza A virus is broken down into subtypes, and both A and B are broken down into strains for classification.

While there are many types of flu, it is important to note that the "stomach flu" isn't actually a type of influenza. It is actually gastroenteritis, an inflammation of the lining of the intestines caused by a virus, bacteria or parasites.

Also, avian influenza (bird flu, H5N1) is a flu virus that typically only affects birds. It is very rare for a human to contract it, and only around 700 cases of this bird flu in humans have been reported from 15 countries since 2003, according to the CDC. It is most often contracted directly from birds and is usually not spread from human to human like most types of influenza.

Another type of rare bird flu, called H7N9, first appeared in people in China in 2013. Since then, the virus has caused several hundred human infections per year in China; but there was spike in cases from 2016 to 2017, when 766 human cases in China were reported. The H7N9 virus also does not appear to spread easily between people.

History of evolution of influnza virus

It is impossible to know when an influenza virus first infected humans or when the first influenza pandemic occurred. Possibly the first influenza epidemic occurred around 6,000 BC in China, and possible descriptions of influenza exist in Greek writings from the 5th century BC. In both 1173–1174 and 1387, epidemics occurred across Europe that were named "influenza". Whether these epidemics and others were caused by influenza is unclear since there was no consistent naming pattern for epidemic respiratory diseases at that time, and "influenza" didn't become completely attached to respiratory disease until centuries later. Influenza may have been brought to the Americas as early as 1493, when an epidemic disease resembling influenza killed most of the population of the Antilles.

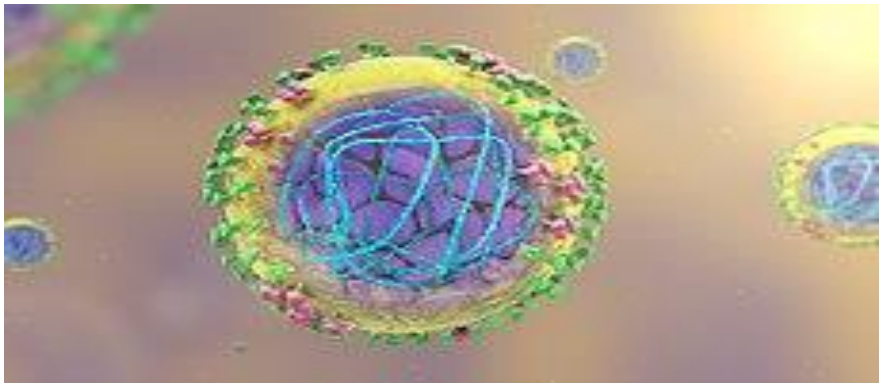
The first convincing record of an influenza pandemic was chronicled in 1510; it began in East Asia before spreading to North Africa and then Europe. Following the pandemic, seasonal influenza occurred, with subsequent pandemics in 1557 and 1580. The flu pandemic in 1557 was potentially the first time influenza was connected to miscarriage and death of pregnant women. The 1580 flu pandemic originated in Asia during summer, spread to Africa, then Europe, and finally America.[] By the end of the 16th century, influenza was likely beginning to become understood as a specific, recognizable disease with epidemic and endemic forms. In 1648, it was discovered that horses also experience influenza.

Influenza data after 1700 is more informative, so it is easier to identify flu pandemics after this point, each of which incrementally increased understanding of influenza.The first flu pandemic of the 18th century started in 1729 in Russia in spring, spreading worldwide over the course of three years with distinct waves, the later ones being more lethal. The second flu pandemic of the 18th century was in 1781–1782, starting in China in autumn. From this pandemic, influenza became associated with sudden outbreaks of febrile illness.[] The next flu pandemic was from 1830 to 1833, beginning in China in winter. This pandemic had a high attack rate, but the mortality rate was low.

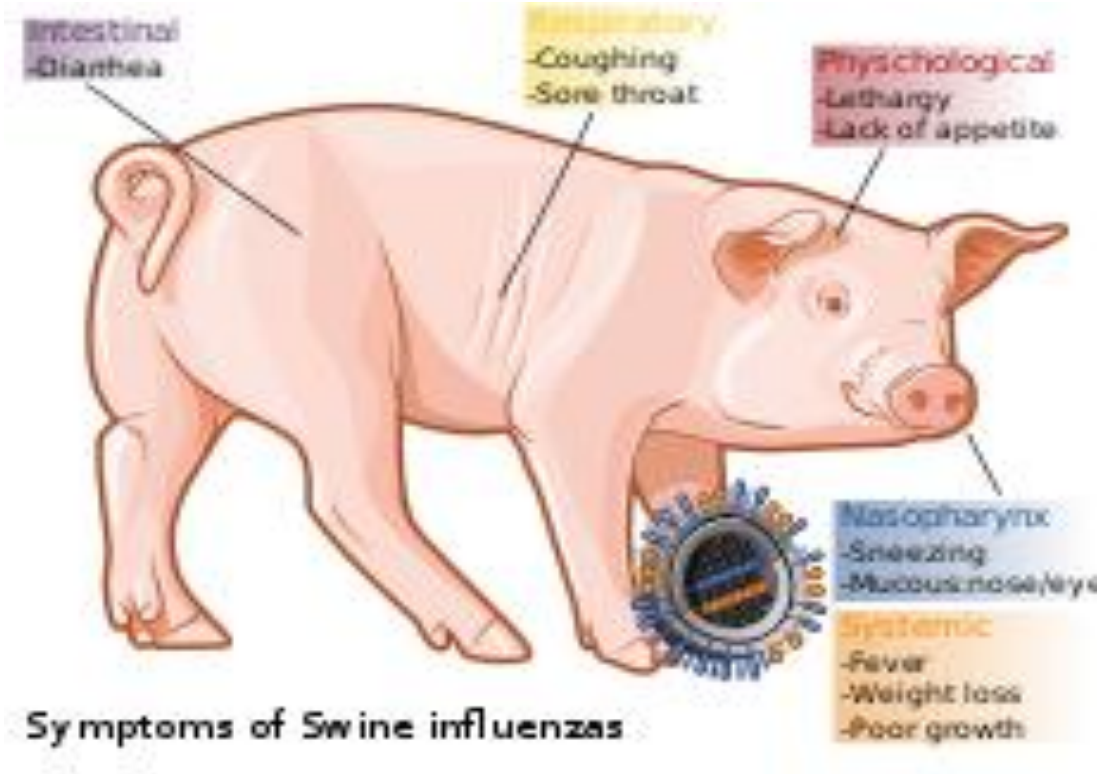
The 1918 influenza pandemic was the most severe pandemic in recent history. It was caused by an H1N1 virus with genes of avian origin. Although there is not universal consensus regarding where the virus originated, it spread worldwide during 1918-1919. In the United States, it was first identified in military personnel in spring 1918.

It is estimated that about 500 million people or one-third of the world's population became infected with this virus. The number of deaths was estimated to be at least 50 million worldwide with about 675,000 occurring in the United States. Mortality was high in people younger than 5 years old, 20-40 years old, and 65 years and older. The high mortality in healthy people, including those in the 20-40 year age group, was a unique feature of this pandemic.

While the 1918 H1N1 virus has been synthesized and evaluated, the properties that made it so devastating are not well understood. With no vaccine to protect against influenza infection and no antibiotics to treat secondary bacterial infections that can be associated with influenza infections, control efforts worldwide were limited to non-pharmaceutical interventions such as isolation, quarantine, good personal hygiene, use of disinfectants, and limitations of public gatherings, which were applied unevenly.

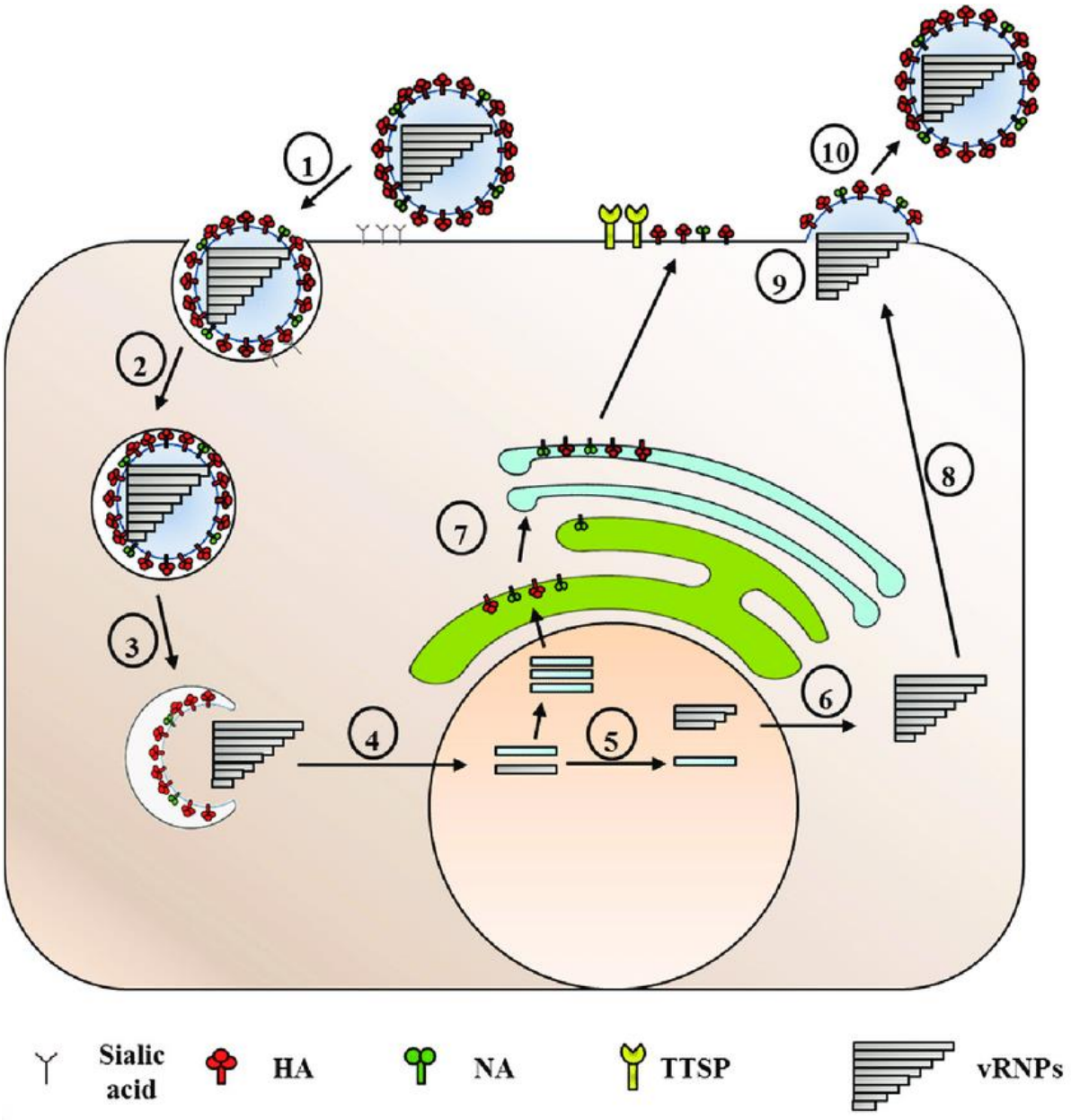


Structure of H1N1 virion



Symptoms of Swine influenzas

Life Cycle of Influnza Virus



Life Cycle

The viral life cycle begins by binding to a target cell. Binding is mediated by the viral HA proteins of the cell membrane. For N1 subtypes with the "G147R" mutation and N2 subtypes, the NA protein can initiate entry. Prior to binding, NA proteins promote access to target cells by degrading mucous, which helps to remove extracellular decoy receptors that would impede access to target cells. After binding, the virus is internalized into the cell by an endosome that contains the virion inside it. The endosome is acidified by cellular vATPaseto have lower pH, which triggers a conformational change in HA that allows fusion of the viral envelope with the endosomal membrane. At the same time, hydrogen ions diffuse into the virion through M2 ion channels, disrupting internal protein-protein interactions to release RNPs into the host cell's cytosol.

The M1 protein shell surrounding RNPs is degraded, fully uncoating RNPs in the cytosol. RNPs are then imported into the nucleus with the help of viral localization signals. There, the viral RNA polymerase transcribes mRNA using the genomic negative-sense strand as a template. The polymerase snatches 5' caps for viral mRNA from cellular RNA to prime mRNA synthesis and the 3'-end of mRNA is polyadenylated at the end of transcription. Once viral mRNA is transcribed, it is exported out of the nucleus and translated by host ribosomes in a cap-dependent manner to synthesize viral proteins.] RdRp also synthesizes complementary positive-sense strands of the viral genome in a complementary RNP complex which are then used as templates by viral polymerases to synthesize copies of the negative-sense genome. During these processes, RdRps of avian influenza viruses (AIVs) function optimally at a higher temperature than mammalian influenza viruses.

Newly synthesized viral polymerase subunits and NP proteins are imported to the nucleus to further increase the rate of viral replication and form RNPs. HA, NA, and M2 proteins are trafficked with the aid of M1 and NEP proteins to the cell membrane through the Golgi apparatus and inserted into the cell's membrane.

Viral non-structural proteins including NS1, PB1-F2, and PA-X regulate host cellular processes to disable antiviral responses. PB1-F2 aso interacts with PB1 to keep polymerases in the nucleus longer. M1 and NEP proteins localize to the nucleus during the later stages of infection, bind to viral RNPs and mediate their export to the cytoplasm where they migrate to the cell membrane with the aid of recycled endosomes and are bundled into the segments of the genome.

Progenic viruses leave the cell by budding from the cell membrane, which is initiated by the accumulation of M1 proteins at the cytoplasmic side of the membrane. The viral genome is incorporated inside a viral envelope derived from portions of the cell membrane that have HA, NA, and M2 proteins. At the end of budding, HA proteins remain attached to cellular sialic acid until they are cleaved by the sialidase activity of NA proteins. The virion is then released from the cell. The sialidase activity of NA also cleaves any sialic acid residues from the viral surface, which helps prevent newly assembled viruses from aggregating near the cell surface and improving infectivity. Similar to other aspects of influenza replication, optimal NA activity is temperature- and pH-dependent. Ultimately, presence of large quantities of viral RNA in the cell triggers apoptosis, i.e. programmed cell death, which is initiated by cellular factors to restrict viral replication.

Dignosis

Diagnosis based on symptoms is fairly accurate in otherwise healthy people during seasonal epidemics and should be suspected in cases of pneumonia, acute respiratory distress syndrome (ARDS), sepsis, or if encephalitis, myocarditis, or breaking down of muscle tissue occur. Because influenza is similar to other viral respiratory tract illnesses, laboratory diagnosis is necessary for confirmation. Common ways of collecting samples for testing include nasal and throat swabs. Samples may be taken from the lower respiratory tract if infection has cleared the upper but not lower respiratory tract.

Influenza testing is recommended for anyone hospitalized with symptoms resembling influenza during flu season or who is connected to an influenza case. For severe cases, earlier diagnosis improves patient outcome.[] Diagnostic methods that can identify influenza include viral cultures, antibody- and antigen-detecting tests, and nucleic acid-based tests.

Viruses can be grown in a culture of mammalian cells or embryonated eggs for 3–10 days to monitorcytopathic effect. Final confirmation can then be done via antibody staining, hemadsorption using red blood cells, or immunofluorescence microscopy. Shell vial cultures, which can identify infection via immunostaining before a cytopathic effect appears, are more sensitive than traditional cultures with results in 1–3 days. Cultures can be used to characterize novel viruses, observe sensitivity to antiviral drugs, and monitor antigenic drift, but they are relatively slow and require specialized skills and equipment.Serological assays can be used to detect an antibody response to influenza after natural infection or vaccination. Common serological assays include hemagglutination inhibition assays that detect HA-specific antibodies, virus neutralization assays that check whether antibodies have neutralized the virus, and enzyme-linkedimmunoabsorbant assays. These methods tend to be relatively inexpensive and fast but are less reliable than nucleic-acid based tests.

Direct fluorescent or immunofluorescent antibody (DFA/IFA) tests involve staining respiratory epithelial cells in samples with fluorescently-labeled influenza-specific antibodies, followed by examination under a fluorescent microscope. They can differentiate between IAV and IBV but can't subtype IAV.

Rapid influenza diagnostic tests (RIDTs) are a simple way of obtaining assay results, are low cost, and produce results quickly, at less than 30 minutes, so they are commonly used, but they can't distinguish between IAV and IBV or between IAV subtypes and are not as

sensitive as nucleic-acid based tests. Nucleic acid-based tests (NATs) amplify and detect viral nucleic acid. Most of these tests take a few hours, but rapid molecular assays are as fast as RIDTs. Among NATs, reverse transcription polymerase chain reaction (RT-PCR) is the most traditional and considered the gold standard for diagnosing influenza because it is fast and can subtype IAV, but it is relatively expensive and more prone to false-positives than cultures. Other NATs that have been used include loop-mediated isothermal amplification-based assays, simple amplification-based assays, and nucleic acid sequence-based amplification. Nucleic acid sequencing methods can identify infection by obtaining the nucleic acid sequence of viral samples to identify the virus and antiviral drug resistance. The traditional method is Sanger sequencing, but it has been largely replaced by next-generation methods that have greater sequencing speed and throughput.

Chapter 4

OBSERVATION

Observation

You are being given this information and these instructions because you participated in the U.S. response to domestic outbreaks of avian influenza.

As part of your work, you may have been around bird flu viruses. Infected birds shed avian influenza virus in their saliva, mucous and feces. Human infections with bird flu viruses can happen when enough virus gets into a person's eyes, nose or mouth, or is inhaled. This can happen when virus is in the air (in droplets or possibly dust) and a person breathes it in, or when a person touches something that has virus on it then touches their mouth, eyes or nose. Rare human infections with some avian viruses have occurred most often after unprotected contact with infected birds or surfaces contaminated with avian influenza viruses. However, some infections have been identified where direct contact was not known to have occurred.

The Centers for Disease Control and Prevention (CDC) believes the risk of infection with AI viruses is low. Because human infections with these viruses are possible, however, all people participating in avian influenza outbreak response efforts should be monitored for illness for 10 days after their last possible exposure to infected birds or potentially-contaminated environments, even if exposure to the sick birds was minimal or if personal protective equipment (PPE) was worn appropriately. State and local health departments are helping with this monitoring effort and they may contact you while you're observing your health. By following the instructions below, you can help ensure that you receive prompt medical evaluation, possible testing and appropriate treatment if you become ill with signs and symptoms that could be due to AI virus infection. Thank you for your contribution to the AI domestic response effort.

Treatment

There is no highly effective treatment for H5N1 flu, but oseltamivir (commercially marketed by Roche as Tamiflu), can sometimes inhibit the influenza virus from spreading inside the user's body. This drug has become a focus for some governments and organizations trying to prepare for a possible H5N1 pandemic.On April 20, 2006, Roche AG announced that a stockpile of three million treatment courses of Tamiflu are waiting at the disposal of the World Health Organization to be used in case of a flu pandemic; separately Roche donated two million courses to the WHO for use in developing nations that may be affected by such a pandemic but lack the ability to purchase large quantities of the drug.However, WHO expert Hassan al-Bushra has said:

"Even now, we remain unsure about Tamiflu's real effectiveness. As for a vaccine, work cannot start on it until the emergence of a new virus, and we predict it would take six to nine months to develop it. For the moment, we cannot by any means count on a potential vaccine to prevent the spread of a contagious influenza virus, whose various precedents in the past 90 years have been highly pathogenic".

Animal and lab studies suggest that Relenza (zanamivir), which is in the same class of drugs as Tamiflu, may also be effective against H5N1. In a study performed on mice in 2000, "zanamivir was shown to be efficacious in treating avian influenza viruses H9N2, H6N1, and H5N1 transmissible to mammals".[] In addition, mice studies suggest the combination of zanamivir, celecoxib and mesalazine looks promising producing a 50% survival rate compared to no survival in the placebo arm.[] While no one knows if zanamivir will be useful or not on a yet to exist pandemic strain of H5N1, it might be useful to stockpile zanamivir as well as oseltamivir in the event of an H5N1 influenza pandemic. Neither oseltamivir nor zanamivir can be manufactured in quantities that would be meaningful once efficient human transmission starts.In September, 2006, a WHO scientist announced that studies had confirmed cases of H5N1 strains resistant to Tamiflu and Amantadine. Tamiflu-resistant strains have also appeared in the EU, which remain sensitive to Relenza.

Treatment of influenza in cases of mild or moderate illness is supportive and includes anti-fever medications such as acetaminophen and ibuprofen, adequate fluid intake to avoid dehydration, and resting at home. Cough drops and throat sprays may be beneficial for sore throat. It is recommended to avoid alcohol and tobacco use while sick with the flu.Aspirin should not be

used to treat influenza in children due to an elevated risk of developing Reye syndrome. Corticosteroids likewise are not recommended except when treating septic shock or anunderyling medical condition, such as chronic obstructive pulmonary disease or asthma exacerbation, since they are associated with increased mortality.[1] If a secondary bacterial infection occurs, then treatment with antibiotics may be necessary.

Prevention

Reasonably effective ways to reduce the transmission of influenza include good personal health and hygiene habits such as: not touching your eyes, nose or mouth; frequent hand washing (with soap and water, or with alcohol-based hand rubs); covering coughs and sneezes; avoiding close contact with sick people; and staying home yourself if you are sick. Avoiding spitting is also recommended.

Although face masks might help prevent transmission when caring for the sick, there is mixed evidence on beneficial effects in the community. Smoking raises the risk of contracting influenza, as well as producing more severe disease symptoms. Thus, according to the laws of mathematical modelling of infectious diseases, smokers raise the exponential growth rates of influenza epidemics and may indirectly be responsible for a large percentage of influenza cases. Since influenza spreads through both aerosols and contact with contaminated surfaces, surface sanitizing may help prevent some infections.

Alcohol is an effective sanitizer against influenza viruses, while quaternary ammonium compounds can be used with alcohol so that the sanitizing effect lasts for longer. In hospitals, quaternary ammonium compounds and bleach are used to sanitize rooms or equipment that have been occupied by patients with influenza symptoms. home, this can be done effectively with a diluted chlorine bleach.

Social distancing strategies used during past pandemics, such as closing schools, churches and theaters, slowed the spread of the virus but did not have a large effect on the overall death rate. It is uncertain if reducing public gatherings, by for example closing schools and workplaces, will reduce transmission since people with influenza may just be moved from one area to another; such measures would also be difficult to enforce and might be unpopular. When small numbers of people are infected, isolating the sick might reduce the risk of transmission. According to studies conducted in Australia and Japan, screening individuals for influenza symptoms at airports during the 2009 H1N1 outbreak was not an effective method of infection control.

Chapter 5

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