Themed Collection : Combating the Unseen

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Viral Pandemics Through the World History in a Biochemical Viewpoint

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Disease and illness have affected humans since the dawn of life. Some of these diseases might affect a considerable portion of the human population at once while some are limited to a minuscule number. As an example, a sudden episode of a simple food poisoning and HIV/AIDS can be considered. The latter is a widespread problem found throughout the globe at a given time while the food poisoning will be limited to the small group who ingested the food. This differentiation is of enormous importance because the approaches taken to manage the condition will vary with its spread. The words 'Pandemic' and 'Epidemic' are two words used in epidemiology to define the effect of a disease to the human population.

An epidemic is when a disease exceeds the usual prevalence of it in a given population, while being confined to the area defined by geographical borders. In order for it to become a pandemic, it should cross geological and political boundaries and be spread across the world.[1] Throughout history, pandemics have played a key role in shaping the world to the one we live in today. From them, infectious disease pandemics are more significant due to their contagiousness. As now we are facing a global level pandemic caused by a viral disease, looking back and understanding what happened during the past viral pandemics of the world would provide us with a valuable insight.

Before diving into the history, learning some basic concepts of virology will help understand the behavior of those disease patterns and the biochemical basis behind them. Viruses are obligate intracellular pathogens and generally are made of a protein coating and a core containing genetic material. They cannot carry out any biochemical reaction outside a host, and upon infection they hijack the host cell's metabolic processes for replication of their genetic material and the production of more viral particles. Antiviral drugs aimed in treating viral infections are most effective during the replication of viruses as they do not have any other crucial metabolic reactions like bacteria do, which are targeted by antibiotics. The main hardship faced in prescribing antiviral drugs is that symptoms start appearing later during a viral infection and by this time, most of the viral multiplication have taken place. In such an instance, antiviral drugs will have little to no effect in controlling the disease.[2,3]

Having a rough idea about the defense mechanisms in the human body against viruses is also essential in understanding biochemical basis of the therapeutic options used in treating viral infections. Main goal of host defense mechanisms is to slow the replication of the virus and then eradicate it from the system. Interferons (IFN) play an important role in this process. IFNs are glycoproteins which are secreted by cells that are already infected and these IFNs then diffuse to adjacent healthy cells to activate their genes to hinder the viral replication in them. Furthermore, IFNs activate Natural Killer cells which can kill already infected cells and thereby limit the spread of the virus. Two other important proteins involved in this process are antibodies and the complement system. Antibodies have the ability to bind with viral antigens on an infected cell and then make the cell more susceptible to the phagocytic activity of macrophages. Also, antibodies can directly bind with viral particles and inhibit their binding with host cell, and agglutinate viral particles, allowing them to be phagocytosed. Complement proteins can attack some viruses by damaging their protein envelopes. A type of cells involved in the immunity known as T cells can produce cytokines, which give rise to inflammation which in turn inhibit the viral replication, and they can also kill host cells containing the virus following recognition of viral antigens on cell surface.[4]

The Antonine Plague

The first known viral pandemic in history is the 'Antonine Plague', which mainly affected the Roman empire ruled by Marcus Aurelius in 166-180 A.D.

followed by another outbreak in 189 A.D. which also spread to Egypt. It is assumed that 7-10 million people died due to this pandemic and it is considered as a factor that contributed to the downfall of the Roman empire. A detailed account of this pandemic is not found in literary sources. The most accepted and trusted description of it comes from the texts of Galen, a well-known Roman physician and a writer. Galen describes the symptoms of the disease as fever, an exanthem (a rash involving the whole body) and diarrhea in some cases. The exanthem became black due to collection of blood in the blisters and the diarrhea was dark black in some cases due to bleeding in intestines.[5] These features are very much consistent with that of a hemorrhagic smallpox infection. Thus, researchers and historians widely agree to the fact that this pandemic might have been caused due to smallpox.[6]

Smallpox, which is considered to be eradicated now, was caused by variola virus belonging to the Orthopoxvirus genus. It consists of a small genome with 186 kbp and is known to exclusively infect humans with an incubation period of 14 days. It is widely thought that the first spread of smallpox among humans occurred in the southern parts of the African continent.[7] Main treatment method used to control smallpox was vaccination, followed by Edward Jenner's breakthrough findings. These vaccines contained a prototype orthopoxvirus named vaccinia virus. Modern formulations of the smallpox virus vaccine contain either highly attenuated vaccinia virus or non-infections subunits of it like DNA or protein envelopes in contrast to the live vaccines used before. The purpose of the vaccine is to provide prophylaxis, where it acts to increase the immune response of the body through the development of antibodies, T cell response and cytokine profiling that will enable the body to fight against a future smallpox infection. Furthermore, there are antiviral drugs which were suggested to be used in the treatment of smallpox yet have not been tested clinically since these were developed even after the last smallpox outbreak. Cidofovir and Tecovirimat have been tested in animal models and are known to inhibit viral DNA polymerase and prevent its replication, and inhibit protein envelope respectively. Since the eradication, research done on smallpox has been on a minimal level and thus novel treatment methods to control it are not explored in detail.[8]

Smallpox of the New World

The next recorded viral infection outbreak of world history also was due to a smallpox infection epidemic in Japan from 735 – 737 A.D. This did not spread in to neighboring countries to be declared as a pandemic. Smallpox caused a pandemic again in the 16th century and this is commonly known as the smallpox outbreak of the new world. This pandemic started in 1520 with an expedition from Cuba to Mexico with the intention of hoarding the gold and other riches of the Aztec empire. Among the crew of the ship was an African slave who had smallpox. Since the native Aztecs did not have any previous exposure to the disease, there was no immunity against it among them and it is recorded that more than half of the population died due to it. From the coastal area it spread inland and at least half the population living in Mexico succumbed to it and this assured the success of the conquests done by Cubans. From Mexico, the disease spread into the Inca empire in Peru allowing the small band of Spaniards from Cuba to easily claim victory against them. Afterwards, it continued spreading to Caribbean islands, Central America and Chile, being responsible for the deaths of millions of natives. This even spread into the interior of Brazil later through the missions of conversion by Jesuit missionaries. The Spaniards showed a resistance to smallpox due to their childhood infections in the 8th century through the introduction of the disease to their homelands through Moors. This enabled them to easily overcome the plagued natives and conquer their lands for themselves. Smallpox continued to spread through the South American continent until the early 19th century, when vaccination was established against it.[9]

1781-1782 flu pandemic

Influenza marks the next great viral pandemic of the world. The first pandemic of influenza lasted from 1781 to 1782 in the European countries. It is assumed to have started in Russia and then moved towards west across Finland, Germany, Hungary, Vienna to the British Isles. It even spread to the Mediterranean countries, Italy, France, Spain and Portugal by the August of 1781. This pandemic posed a low mortality rate, while only the elderly population and the ones who already suffered from respiratory illnesses were at risk of death. Yet, it is assumed that at least three-fourth of the population of

whole Europe fell ill owing to this influenza pandemic by the first half of 1782. Although the exact identity of the causative virus is unknown, scientists conclude it is different from the viruses which caused the next influenza pandemics of 1889-1890 and 1918-1919 as this illness spread through the continent during the summer and spring whereas other influenza pandemics thrived during winters. Thus, it is a matter of debate among historians whether this pandemic is actually an influenza infection or some other viral infection which caused respiratory symptoms.[10]

Russian flu

Following yellow fever epidemics in Hispaniola, Philadelphia, New Orleans and then a Measles outbreak in Fiji, then came the next viral pandemic of Influenza in the years 1889-1890. This also began in central Asian regions which then belonged to the Russian empire and then gradually spread all over Europe except for Ireland, Northern Great Britain and Sardinia. Furthermore, it spread through ships to United States, Toyo, Hong Kong, Singapore, India, South America, Africa and Egypt. Even though exact figures are unknown, assumption is that at least one third of the world population caught the disease during that period. Causative virus of this 'Russian Flu' pandemic is also uncertain since virology was still a developing field those days.[10]

Spanish flu

Soon after that, one of the most serious pandemics of history occurred with a record of at least 50 million deaths in its wake. Later on, the causative virus for this pandemic was identified as an influenza virus. Thus, before going into specifics of it, having an understanding about the general structure of an influenza virus will be important. Influenza viruses are of 4 types; A, B, C and D, with influenza A viruses being the most common. These viruses are enveloped viruses with an RNA strand as their genetic material. The envelope is derived of host cell lipids and there are three viral proteins in it. The genomic RNA strand is organized into 8 segments. Haemaglutinin (HA) is the viral protein that is needed to attach to a host cell and there are about 18 types of HA in existence. Neuraminidase is needed to cleave the sialic acid molecules on the host cell surface and thereby allow the newly replicated viral particles to be released from a host cell. 11 types of neuraminidase have been identified currently. There are two types of M proteins, M1 which is a matrix protein and M2. M2 acts as a selective channel for protons and this allows the interior of the virus to be acidic and prevent complex formation between the genome and M1 proteins. This helps the viral genome to be transferred into the host cell nucleus. These viral proteins are again needed for the incorporation of the newly replicated genetic material into new virus particles. Immune system identifies these viral proteins as antigens and produces immune reactions against them.

Subtypes of Influenza A viruses are named according to their neuraminidase and haemaglutinin types (eg: H1N1, H5N1 etc.). Two other concepts that are important with regards to influenza viruses are 'Antigenic shift' and 'Antigenic drift'. Antigenic shift occurs due to exchange of genome segments between subtypes of influenza A viruses. This ultimately results in a virus with completely new combination of antigens and thus previously immunized population will also be susceptible for infection. In antigenic drift, slight mutations occur in the antigens and this is known to happen in Influenza viruses A, B and C types. This results in a slightly modified strain of an existing virus, against which a considerable proportion of the population may show immunity.[11]

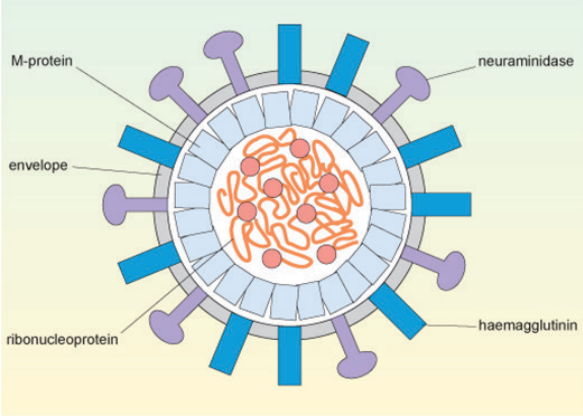

Figure 1: Schematic diagram representing the general structure of an influenza A virus

The 1918 Influenza pandemic is known to be caused by an H1N1 subtype of influenza A virus which is closely related to the influenza virus which caused swine flu recently. It is thought that influenza viruses have been transferred to pigs from its natural reservoir, birds and

pigs, who act as the intermediate host, then acquired the viral infection from humans also. Then these strains underwent genetic segment reassortment (antigenic shift) and formed a new subtype with novel antigens causing the large number of infected cases in humans. This pandemic came in three major waves affecting North America, Europe and Asia. Apart from normal influenza symptoms (which are similar to common cold symptoms), this infection caused pneumonia conditions owing to its high virulence and the ability to replicate throughout the full extent of the respiratory system.[12]

Since antiviral drugs were not yet developed by the time of this pandemic, governments around the world took measures to mitigate the spread of it by encouraging people to wear masks, spraying antiseptics in public places, closure of schools and public institutions and promoting hygienic practices among populations. Some governments even announced quarantine periods and thereby managed to reduce the number of cases.10

Asian flu

Year 1957 marked the emergence of another influenza virus pandemic, which was named 'Asian flu' owing to its origin in China. The causative virus was identified as subtype H2N2 and it subsequently spread throughout the world by September of that year. This pandemic caused more than 1 million deaths among the people who contracted it, and this also had the ability to cause primary influenza virus pneumonia similar to that of the 1918 pandemic. Identification of the virus subtype led to the development of a vaccine against it. Yet the limited amount produced, and low efficacy rendered the vaccine useless in changing the course of the natural progression of the disease.[13]

Hong Kong flu

Another pandemic influenza emerged in 1968. This was first reported in Hong Kong as a large epidemic and thus it was given the name 'Hong Kong Flu'. Virus subtype H3N2 was identified as the culprit. Since only the HA antigen has been changed when compared with Asian Flu virus, spread of the virus was affected by pre-existing N2 immunity among populations. This pandemic was responsible for about 1 million deaths worldwide and the H3N2 virus subtype continues to infect humans as the seasonal influenza while regularly undergoing antigenic drifts.

Swine flu

Again, another strain of influenza virus A, hit the world as a pandemic in 2009, giving rise to the A(H1N1) 'Swine Flu' which first emerged from populations in California and Mexico. Molecular studies done on the genetic material of this virus have shown it has been derived from the combination of several viruses of human, avian and swine origin, that have been circulated in pigs. Gradually the disease spread to 214 countries by April 2010 and it was noticed that mostly the younger population was at risk of infection (60% of patients were 18 years or younger). This observation was explained by the existing immunity in the elderly population who has been exposed to the seasonal flu virus strains. Exact number of infected cases are unknown because mostly the diagnosis was done clinically due to the laboratory diagnostic facilities being limited. However, it is estimated that around 200,000 people died as a consequence of the infection. In most cases the infection was limited to mild flu symptoms while it developed into primary viral pneumonia, respiratory failure and death in some cases. Transmission of the virus was mainly through respiratory droplets of infected people and formites (surfaces with which these respiratory droplets have come into contact). Vaccines were rapidly developed as a treatment method and this included inactivated whole viruses, subunit vaccines and live-attenuated vaccines. Despite the rapid production, manufacturers were unable to cater to the needs of the population all around the world. Thus, vaccination was targeted for groups at high risk including health care workers and pregnant women.14 To understand the effect of antiviral drugs towards this pandemic, first we will go through the principles of antiviral therapy.

Antiviral drugs mainly target different components of the structure of viruses and inhibit them to prevent the replication and infection. Amantadine and rimantadine are two antiviral drugs which are only effective against influenza A viruses. These drugs target the M2 channel protein of the virus and inhibit it, thereby inhibiting transfer of viral genome into the host. For these drugs to be effective, they should be given early in an infection. Another issue with them is the development

of resistance in vruses against them. Viruses which develop resistance against rimantadine becomes resistant against amantadine also and vice versa. Another type of such treatment option is neuraminidase inhibitors. These inhibit the neuraminidase proteins of the virus and thus prevent the release of newly synthesized viral particles from the host cell. Zanamavir and oseltamivir are examples of this category and unlike M2 inhibitors, these can treat influenza B infections as well.[11] In the 2009 A(H1N1) pandemic, oseltamivir was found to be an effective treatment option when given within 36 hours of infection whereas the virus showed resistance against rimantadine and amantadine.

SARS

Prior to the last influenza pandemic of 2009, a small-scale pandemic was caused by a novel coronavirus. This was named as Severe Acute Respiratory Syndrome (SARS) and the causative coronavirus was known as SARS-CoV. Disease outbreak was first noticed in China in November 2002 as an atypical pneumonia. An infected physician from China who stayed at a Hong Kong hotel infected 16 guests from different countries and this led the disease to be spread over the world. As the end result, 8096 cases of SARS were reported from 26 countries with 774 mortalities.

Coronaviruses are large spherical viruses with an envelope formed by a lipid bilayer. In this envelope, viral structural proteins M, E and S are located. Within the envelope lies the nucleocapsid, which is formed by N proteins bound with single stranded RNA genome of the virus. These viruses are responsible for about 30% cases of common cold and upper respiratory tract infections that occur naturally. SARS-CoV is thought to be an unrecognized animal coronavirus which gained virulence against humans with mutations over time. A considerable number of first reported cases were from animal or food handlers in China and bats are thought to be the natural reservoir of this virus. SARS reported to have affected all age groups and both genders similarly. However, it is notable that 22% of infected cases were health care workers. SARS is considered to have low transmissibility and it is spread through respiratory droplets and formites. Common features of the infection were fever, body aches, cough and breathing difficulties with pneumonia, while upper respiratory symptoms were uncommon.

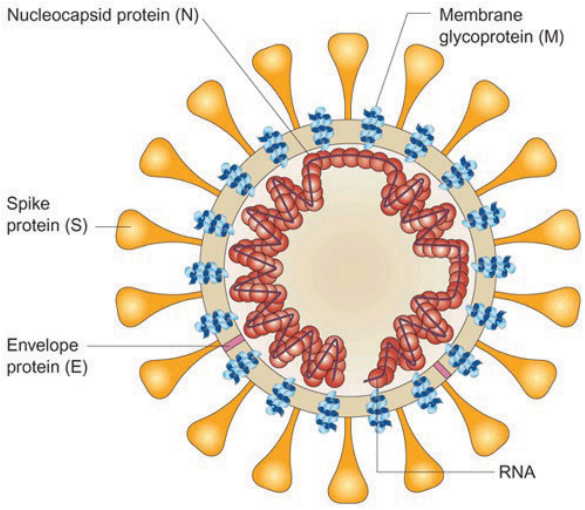

Figure 2: Schematic diagram representing structure of SARS-CoV

Diagnosis of SARS was done by the analysis of upper respiratory tract secretions or plasma component of the blood of suspected cases. Detection of virus under electron microscope after growing them in fetal rhesus monkey kidney cells led to the identification of virus particles consisting of a corona or a halo around it and hence the name, coronavirus. Viral RNA detection was done using Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) and this method is known to be 100% specific for the detection of infection. Immunologic assays such as ELISA and immunofluorescence microscopy was done to detect virus specific antibodies in the plasma. Definitive treatment methods are not available for SARS. Synthetic interferons were shown to be effective in inhibiting the virus and an antiviral named ribavirin was used to treat the infection, which had the ability to inhibit viral replication. Yet, soon it was discontinued from treatment as it showed many side effects among the patients using it. Mainly adjuvant therapy such as inti-inflammatory agents were used in the symptomatic treatment of the disease.[15]

MERS

After a decade of the first coronavirus pandemic, a man in Saudi Arabia developed an atypical pneumonia and died of it. Upon examination of his sputum, another novel coronavirus strain was identified, and this was

named Middle East Respiratory Syndrome Coronavirus (MERS-CoV). This infection gradually spread from the Middle East to other countries via travelers and by April 2016, there were 1,728 confirmed cases in 27 countries with 624 deaths. Similar to the SARS-CoV, MERS-CoV also has a very large RNA genome. Despite the long RNA strand, accumulation of harmful mutations to the virus is kept at check by the proofreading mechanisms available in coronaviruses. Even though usually bats are the natural reservoir of MERS-CoV like coronaviruses, serological studies done on Middle East animals have shown that camels were found to be harboring the virus as well as MERS-CoV specific antibodies. Thus, it is widely accepted that camels act as a natural reservoir for MERS-CoV. The symptoms and clinical features of both SARS and MERS are extremely similar and the diagnostic techniques used were also the same. There is no clinically proven therapy for MERS-CoV; thus, symptomatic treatment and supportive care is given to patients. There are several vaccines which are currently tested on non-human primates against MERS-CoV.[16]

By the time this article is written, a novel coronavirus is affecting the whole world and it is the largest pandemic originated during this millennium. Like all the previous pandemics, this will also gradually diminish after following its natural course. Yet, we can never be certain, but only hope, that may this be the last viral pandemic we will have to experience in our lifetime.

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