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A COMPREHENSIVE REVIEW ABOUT THE PATHOGENESIS AND VIRULENCE OF DIFFERENT PATHOGENS

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Abstract - The world of diseases is a vast one with one disease differing from another disease in many ways, from the mode of action to the severity and lethality of the disease etc. For each disease there are mainly two underlying factors that decide the success or the failure of the pathogen causing the disease. These factors, that are discussed in this paper, are 'Pathogenesis' and 'Virulence.' Though these are the two main factors, with every pathogen the variance within themselves is vast. Not only do these factors allow us to have a better understanding of the disease itself but also gives information that is essential for working on a cure for it. In this paper, the two terms and what exactly is their role in diseases is discussed with relevant examples of four disease including two bacterium caused diseases and two virus cause diseases. These diseases are Anthrax, Tuberculosis, HIV/AIDS, Covid-19.

Keywords: Pathogenesis, Virulence, Infection, Tuberculosis, Anthrax, Covid-19, HIV/AIDS.

I. INTRODUCTION

When it comes to diseases there are a lot of factors that play a role in defining not only how the disease develops in the body but also till what extent or severity of the disease. For this, there are a lot of terminologies that are involved with this which are required to be defined in order to get a better understanding of the core concept of pathogenesis and virulence. Two of the most familiar terms of the world of diseases and probably the backbone of it are 'Host' and 'Pathogen'. A host can be defined as the organism or the body which supports or accommodates the growth and survival of a microorganism or a smaller organism. The host is the larger organism of the two organisms involved. The second terminology here is 'Pathogen'. Pathogen can be described as the organism due to which a disease is caused in the host. The process of the organism or pathogen growing in or on the host is often dubbed as infection which then leads to a disease [1]. Another key infectious disease terminology is there which is termed as 'Reservoir'. It can be defined as the natural location or place where the pathogen commonly resides. A reservoir can be living like an animal, within an animal or can also be a non-living object. An example for a living reservoir is the H1N1 virus found in pigs which leads to swine flu. In this example the reservoir is the pig. Another example for a non-living reservoir is soil where the presence of Clostridium tetani has been observed which causes the disease commonly known as tetanus. As for a water reservoir, there is a presence of Escherichia coli which can lead to diarrhoea and dehydration. Though there is a presence of pathogens in the reservoirs and can be a source of an infection or a place or a medium from where the host picks up an infection, but it is not necessary for the reservoir to always be the source of infection. The source of the infection, as mentioned above, is different from a reservoir. A reservoir basically is the place where one can find the pathogen naturally whereas the source of infection is the place where the host actually acquires the pathogen or microorganism from[2]. The reservoirs can be termed as the primary source of an infection. Apart from them there are also secondary sources which can lead to a host acquiring a pathogen or microorganism. These secondary sources can also be called vectors. As we know, vectors are the organisms that can spread diseases either from a reservoir to a host or from one host to another. A very prominent example of a vector is that of mosquitos that are the main carriers of Malaria. The vectors usually are not infected by the disease and are commonly the temporary vessels for the transport of the pathogen.

Now as we know that the pathogens are living microorganisms, so like every other organism they also need certain conditions and certain processes that are essential for their survival.

For these microorganisms to successfully cause an infection and lead to a disease in the host, microorganism initially requires a suitable environment for its growth and to reproduce. The main factors that revolve around the growth of the microorganism include:

- Temperature
- pH level
- Oxygen requirements
- Humidity

These are basically the four common and major factors for the growth of different pathogens and microorganisms, but the requirements of each factor can vary from organism to organism[2,3]. As much as these factors play a major role,

the microorganisms can also adapt through mutations to survive within the host more effectively and then promote its own growth. One example of the adaptation of the microorganism is facultative anaerobes. These are bacteria which utilise oxygen present in the environment but can also adapt to the anaerobic conditions and hence transform into anaerobic inside a host organism to survive.

Another factor that plays a major role in the survival of a microorganism within a host is the nutrient source. As other organisms, the pathogens too require a source of nutrition in order to carry out life processes. Commonly, the nutrition is taken up by the host cells but when a pathogen or microorganism infects the body the pathogen now must compete with host cells for obtaining nutrition. For obtaining the nutrients, one thing that helps the pathogens or the microorganisms are the specific structures or substances that are produced by the pathogen itself. These are basically referred to as virulence factors.

Apart from the environmental factors and the source of nutrient another factor, possibly deciding the lifeline of the pathogen, is protection from harm. For a pathogen there can be many harmful things such as physical stressors or chemical stressors. But one of the most effective stressors within a host is the immune system. When a pathogen or a microorganism enters the body, there are two parts of the host's immune system that come at play[4]. The first is the non specific immune response or more commonly known as the innate immune response which acts as the primary line of defence against any pathogen or microorganism. The second part is the adaptive immune response which is more specific to an organism as compared to the innate immune response. In this, the immune response detects the pathogen and according to its specificity, after the detection the pathogen is removed by the immune response. Consequently, it becomes imperative for the pathogen to devise a suppressing mechanism in order to productively infect the host. Therefore in supposition, the environment factors, the source of nutrition and protection from harm are the key factors required by a pathogen or microorganism for essentially infecting or surviving within a host body.

The next step after the survival of the pathogen or the microorganism is the onset of infection leading to the eventual disease. After invading the body of the host organism, the process of infection sets in. This process takes four steps to complete[5,6].

The first step of this process is commonly dubbed as 'The Incubation Period'. This stage is characterised by the time period between the exposure to the pathogen or microorganism and the first emergence or development of the symptoms or signs of a disease and the. It is in this period where the disease is not contagious. The incubation period can be different or different pathogens. For some diseases like bacterium based it can be a few days for some viral diseases like for example HIV/AIDS, the incubation period can be a few years as well.

After the incubation period, the prodromal stage follows. In this stage of infectious disease, the host organism begins to show signs or symptoms, but the symptoms exhibited are not very specific to a certain type of disease hence resulting in unclear diagnosis. One example of this is that in a particular case, a host may exhibit the symptom of coughing. Coughing as a standalone symptom cannot be used to diagnose a specific disease hence it become unclear to give a proper diagnosis. At this stage, the disease that the host organism is now infected with becomes contagious and the intensity of the symptoms increases and is greater than the intensity of symptoms in the incubation period which is almost none.

Following the prodromal stage, the host undergoes the illness period. Though practically self-explanatory, in this stage or period the host begins to exhibit more characteristic symptoms or signs that point towards a particular disease. The intensity as well as the severity of the symptoms increases in this stage at a steeper rate as compared to the other periods or stages. After the symptoms or signs reach their maximum severity or intensity, the immune response is triggered which targets the symptoms and helps in levelling the symptoms out thus flattening the steep increase in the severity of the symptoms. Basically, the action of the immune response leads into the next stage.

Through the help of the immune response, the disease now moves into its final stage or period that is dubbed as the convalescence period. In this stage, the signs and the symptoms of the disease start disappearing over a period of time. Unfortunately, in some cases of different diseases, the symptoms of the disease can progress. In such cases the symptoms are no longer acted upon by the immune system hence increasing the severity and the intensity of the symptoms which can ultimately lead to death of the host.

A very prominent example to understand and summarise the four stages of a diseases can be given by studying the cases of Covid-19 infections. The incubation period in the cases of Covid-19 is of two to 14 days where the pathogen infects the host. Then the prodromal stage sets in where the patient start exhibiting symptoms like coughing or sneezing which do not directly point towards a specific disease unless tested. At this stage the host acts as a carrier as well, as the host becomes contagious. After this comes the illness stage where the symptoms like lack of taste and/or smell start appearing, and the pathogen starts affecting the organs as well. After this, the convalescence stage sets in where after different treatments can help in fighting the pathogen hence reducing the signs and symptoms. As observed, the Covid-19 related deaths have been more prominent in children and older people due to a weak immune system. Therefore, due to the lack of immune response the symptoms are not suppressed eventually leading to more damage to the organs especially the lungs and then leading to the demise of the patient.

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Now once the pathogen has infected the body, the question becomes how fast does an infection proceeds through the host. It can be observed that with every disease the progression rate of the disease differs massively. There are three main factors that determine as well as influence the rate of infection in a host.

- Resistance of host: This basically concerns with the resistance offered by the host which can be the barriers existing within the host like skin, mucous, acid in stomach etc. The other resistance towards the pathogens is provided by the immune system. Which help in fending off infections. The response initiated by the immune system upon the pathogen or microorganism infection can be either specific to the microorganism or pathogen or it can be innate. Other responses can also include the adaptability and resistance of the host towards a pathogen.
- Virulence of the pathogen: This fundamentally refers to the damage or harm the pathogen can actually inflict upon the host after entering and infecting the host. The higher the damage causing ability the greater the rate of infection.
- The volume of microorganisms present: It refers to actually how many cells or particles of the microorganism or pathogen is present within the host. A single cell cannot lead to disease and it will require a no of cells of its own kind. For example, in HIV the virus particles after taking over the DNA replication process after invading a T-Cell duplicate themselves and generate many units of its own kind to infect the other cells which then leads to the disease.

The no of microorganisms or pathogen particles present in the host can actually be quantified to study them. They are of two basic types dubbed as 'Infectious Dose 50 (ID_{50})' and 'Lethal Dose 50 (LD_{50})'. The ID_{50} refers to how many pathogenic particles or how many units of its own kind need to present within the host in order to cause the particular disease in about 50% of the hosts. The LD_{50} indicates how many pathogenic particles of the microorganisms are needed in order for the disease to prove to be lethal in around 50% of the hosts. The lower the infectious dose number, the greater the chance of the pathogen being more harmful to the host, the greater the lethal dose number the greater the chance of the disease being deadly to the host[2,6].

The virulence factors as mentioned above are nothing, but products present within the pathogen or 'intrinsic' products which increase the harmfulness of the pathogens or in other words they increase the pathogenicity as well as the virulence of the pathogen. These virulence factors can be soluble products like enzymes, toxins etc or they can also be structural products like pilus or fimbriae present on the surface of the pathogen. Now these virulence factors actually reside deep inside the cell of the pathogen. In bacteria, the virulence factors are found in parts or segments of the DNA of the pathogen within the chromosome of the bacteria or the plasmid of the bacteria which essentially encode the virulence factors. These small areas within the bacterium where the DNA sequence or segment has the characteristic structure and sequence along with virulence factors of the pathogen are often dubbed as the 'pathogenicity islands' due to the cluster of the factors. These islands then make a gene product within the pathogen which all have a different function like acting as a toxin or increasing the survivability etc in order to make the pathogens more harmful to the host. Well, these factors can increase the pathogenicity in a few different ways.

Firstly, they can help in the adhesion of the pathogens or microorganisms within the host and then allow it to colonize host cells. This can be performed through the structural products as mentioned above. These structures can be pilus, capsule proteins, spike proteins in viruses etc.

Secondly, they can help in invading other cells or tissues in the host in order colonize and multiply. So not only do they help in aiding the first infection but can also help in spreading the infection into different cells. This can be through different enzymes or toxins that can be produced in the pathogen.

Thirdly, one very common factor observed in different pathogens is 'Exotoxins'. Exotoxins are made up of proteins that released or secreted by the bacteria given away into the environment. These toxins are mostly soluble in their nature and can have difference in their structures. They act upon the other target cells or even tissues by travelling or moving away from the initial infected site. Due to the different variants of the toxins in the aspect of their shape, these can have and exert many different effects upon the cells and tissues of the host. These are very harmful to the host as these are very much toxic and can be exceptionally lethal even in the smallest amount of dose and can deliver very harmful and even life-threatening effects on the host. One very prominent and easily observable example of an exotoxin is 'Botulinum toxin' or more commonly known as 'Botox'. This is an exotoxin which is produced by the bacteria 'Clostridium botulinum' and it acts as a neurotoxin which means that this toxin prevents the neurotransmitters from being discharged which leads to the neurons from functioning properly. Ultimately due to the low to nil activity, this can lead to paralysis in high doses. This toxin is used in the make up industry in a very diluted form which helps in paralysing the muscles of the person's face hence, preventing any wrinkles or creases from forming. These toxins demonstrate high endurance towards heat and are able to endure in great temperatures. These are produced and released by bacteria which are gram positive in nature.

Fourthly, another toxin produced as a virulence factor is 'endotoxin' which is commonly produced and released by bacteria which are gram negative in nature. These are a part of the Lipopolysaccharide which are confined to the outer membrane of the bacteria. The endotoxin that is released by this is called Lipid-A. One major positive thing about the

endotoxin, from the perspective of the host, is that the toxins are only released when the bacteria dies or 'lyses' as compared to the exotoxins which are produced by the bacteria during the course of its life cycle[3,5].

Another virulence factor and a particularly difficult one is called improving the development of the biofilm. A biofilm is basically a cluster of microbes or pathogens that are held together in a group by the sticky secretions of the microbes which can be polysaccharides or carbohydrates. These biofilms can be a cluster of the same microbes or different microbes. This film helps the microbe or pathogen by increasing the physical resistance of the microbe or pathogen. These films are very hard to cure as they can become resistant to not only the antibiotics but also the immune response. This resistance allows the microbes to do more harm to the host. This resistance is not restricted to only one microbe or pathogen present within the film but is passed to all the microbes present within the film.

The microbes or pathogens can also become more resistant to the immune responses of the host. They can become physically resistant to the attachment of the immune cells on the pathogen or microbe, some factors can help avert detection by persisting and concealing in a better manner inside the host. Some can also produce 'decoy proteins' which can help the pathogen bind with the antimicrobial compounds granting the microbe or the pathogen to function normally[1,6].

II. PATHOGENESIS AND VIRULENCE OF ANTHRAX

One of the major diseases that have been observed over the years and has drawn a lot of attraction towards it is Anthrax. This disease is initiated by the bacteria called 'Bacillus anthracis'. This bacterium is generally gram positive in *nature* and has the capability to create spores. The spores produced by it are very dormant in nature and have many pathogenic factors which allow them to be resistant to various harmful stimuli present around it. The spores are actually able to survive for longer periods of time and they have high temperature resistance as well. The bacterium commonly infects the host through the spores. These spores can invade the host through three main ways. One way is to enter the host through the gastrointestinal route which can be through infected food or water. Another one is through inhalation where the spores may be suspended in the air. Lastly another way of the spores invading the host is through cutaneous route where the spores can be present on the surface of the skin of the host which is then absorbed by the host thereby starting the infection. Within the host these produce vegetative bacteria rapidly through germination. They also have the ability to divide rapidly and they can also encode for the virulence factors which can include exotoxins called 'anthrax toxins' which aide the bacteria in evading the immune response and to spread itself within the host in a systematic manner[7,8].

The exotoxin that the bacteria produce is commonly called the 'anthrax toxins.' They are cluster of three polypeptides that together form two different toxins. These toxins are called 'Lethal Toxin(LT)' and 'Edema Toxin(ET)'. These toxins share a common component for the role of receptor binding which is known as the 'Protective Antigen (PA)'. This allows and helps in the transport of the toxins through the body[9]. The cellular pathways of the host is targeted by these toxins which results in inhibiting the host immune response hence increasing its lethality. The PA as mentioned above, generally has four domains which helps in the process of binding of the toxins. The four domains are as follows:

- Domain 1: This contains a specific sequence which upon binding of the PA to the cell receptors is cleaved by the proteases present on the surface of the cell. This process allows a PA fragment which is capable of endocytosis to oligomerise into octamers or even heptamers to form the binding sites for the toxins[10,11,12,13].
- Domain 2: This helps in the translocation of cargo by helping in forming the beta-barrel core of the pore[14,15].
- Domain 3: This plays a major role in the interactions, specifically protein-protein, in the oligomer with the help of the hydrophobic regions present in this domain[16].
- Domain 4: This domain is solely responsible for binding of the receptor[17].

Role of Toxin in Pathogenesis:

It is understood that the toxins of anthrax play major roles in two phases of the infection. During the early stage of the infection, as a survival tactic, the bacterium, in order to evade the immune response, it directly targets the immune response[18]. This also helps in the distribution of the bacterium throughout the host. Through this systematic method of distribution, the bacterium is capable of targeting various tissues and thereby increase the lethality of the of the disease. The early neutralizing of the immune response of the host is a very essential process in order for the bacterium to spread within the host[19]. One way through which the host has developed a fighting mechanism is through the absence of the receptors of the PA on specific tissues in the body[20,21]. For example, if such receptors are not present on the myeloid cells, the host shows resistance to the infection. Hence it becomes essential for the toxins to target the immune response of the host[22]. The toxins produced by the bacterium target the pathways which play a major role in the functioning of the immune response ultimately affect all the cells in the host[23]. Due to the dire nature of the toxins, the first and most affected cells are the dendritic cells, the neutrophils and the macrophages which are also initial responders of the immune system in the host. These affected

cells then undergo the process called lyses which leads to the death of the cell. The toxins also inhibit quite a few major processes which further shields them from the immune response[24]. Preventing the signalling of MEK, responses of proinflammatory cytokine along with the interaction and recruitment of the immune cells is also hindered. This leads to the malfunction of the capability of the phagocytes and macrophages to eradicate the bacterium[25,26].

Determinants of Virulence Factors and Capsules:

In the bacterium a capsule, which is a negatively charged sheath which is antiphagocytic in nature, of 'poly-D-glutamic acid' is present which helps in protecting the bacterium from the immune response of the host[27]. This capsule is essential as it plays a major role in the transport of the bacteria through the host. The CapD which is present within the operon is a gene which encodes a 'putative capsule depolymerase' also renders the bacteria to be less virulent[28]. It is assumed that this happens because the gene is required to catalyse the 'polyglutamate' into 'peptidoglycan.' Therefore, the strains which show the deficiency of the are fundamentally free of the capsule[29,30].

III. PATHOGENESIS AND VIRULENCE OF TUBERCULOSIS

Another common disease which is caused due to the pathogen type of bacteria is Tuberculosis. This disease is caused by the bacteria called 'Mycobacterium tuberculosis.' The severity as well as the lethality of the infection of this disease is very much unpredictable and is governed by environmental factors as well as the reaction of the immune system. Just like the Anthrax causing bacterium, 'M. tuberculosis' has a virulence gene as well[31]. These help code for enzyme producing factors as well as other virulence factors which play a major role in the process of interaction within the host. These are also responsible for damage caused by pathologically during the infection[32]. This bacterium does not have the classic virulence factors but in turn have two genes which are 'Virulence associated genes' and 'Virulence lifestyle genes.' The first gene present in the pathogen is the 'virulence associated gene' which is associated with virulence which code for factors which help in the regulated expression of the genes associated with virulence and also, through translational modifications, help in the activation of the virulence factors. The second gene present is the 'virulence lifestyle genes' which play a major role in the survival of the bacterium within the host by cyphering for virulence factors like dodging of the immune response of the host and also helps in colonization of the pathogen. One special thing about this bacterium is that its virulence can be measured in a quantitative manner as it can be linked directly to the transmission of the disease. There are three main factors through which help aide this process are as follows:

1. The bacteria's ability to survive the response of the immune system of the host.
2. The bacteria's competence and capability to cause damage to the lungs.
3. The ability of the bacteria to be effectively transmitted into another host.

The infection, at first, caused by the bacterium is primarily across the respiratory pathway[33]. The most common cells that are infected by the bacterium are the 'alveolar macrophages' and due to the infection, there is a rise in the 'inflammatory signals' which thereby increases the number of additional macrophages and also the monocytes which in turn get infected. Though the inflammation process is essential for controlling the infection in the earlier stages, it can lead to extensive damage to the tissues. The bacteria has the ability to make use of the inflammatory signals of the host. One key features of the pathogenicity of the bacterium it its ability to contaminate and as well as persist within the macrophages therefore to analyse the virulence of the bacterium and its variants during the initial stages of the infection such primary macrophages are used[34]. These are more useful in natural settings or during 'in vivo' but can be problematic to reproduce to adequate quantities for experiments on virulence. There are two main molecules that are involved in the virulence and pathogenesis of the bacterium. These molecules belong to the category of 'mycobacterial lipids' and are found in the cell wall of the mycobacterium which is rich in the lipids and has great physical as well as chemical properties[35]. The two molecules are as follows:

- 'Lipoarabinomannan (LAM)': It is a 'glycolipoconjugate' which is composed through an anchor 'Mannosyl Phosphate Inositol (MPI).' It is a diverse capping of motifs species and is a polysaccharide backbone[36].
- 'Lipomannan (LM)': It is a 'multiglycosylated lipid'. The 'LAM' and the 'LM' exist within the cell wall of the mycobacterium[37].

As compared to the other microorganisms or pathogens, the bacterium directly infects as well as inhabits in the immune cells. The bacterium also has the capability of living within the heterogenous and dynamic environment of the phagosome of the macrophage[38]. The bacteria uses a lot of approaches in order to escape the microbial acting processes of the macrophage which includes 'fusion of phagosome and lysosome', 'conscription of the hydrolytic lysosomal enzymes', 'fabrication of the reactive oxygen/nitrogen species', 'antigen presentation' and 'apoptosis.' These functions when disrupted in turn disrupts the immune response of the host[39]. The process of the phagocytosis is an active process which is dependent on the interaction between the various receptors that are expressed upon the macrophage.

The bacterium has the main mode of action of acting as a parasite and making the phagosomes the host. This is done

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through the process of inhibition of the maturation of the phagosomes into phagolysosome. Now this process has two main contributing factors that allow the bacterium to perform this arresting of the phagosome. There are two phosphatases involved which are the 'PtpA' and the 'SapM.' The former binds to a hydrogen subunit of the 'V-ATPase' so that it can 'dephosphorylate' the substrate which is the 'vacuolar protein[40].'

Another key feature of this bacterium is that the bacterium is resistant to 'reactive nitrogen species (RNS)' and the 'reactive oxygen species (ROS).' This is done through the enzymatic activity of the 'NADPH Oxidase (NOX2)' This is a complex of multiprotein enzymes and in response to the process of phagocytosis it is activated which allows the transfer of the electrons across the membrane. Along with this there is another contributing factor which is the 'inducible Nitric Oxide Synthase (iNOS)[41].' This ability of the bacterium to survive stressor produced by the redox reaction within the host and it's ability to synchronize the expression of its virulence factors and the metabolic pathways are the major factors that contribute towards survival as well as the success as a disease causing pathogen[42].

IV. PATHOGENESIS AND VIRULENCE OF HIV/AIDS

This disease has become an epidemic upon our world due to the special mechanism of its pathogen which makes the disease problematic to find a cure for it as well as to deal with it. What makes this disease and pathogen different from other diseases is that the disease itself is not what kills the host but in turn pre-existing or other diseases are what that kill the host. The main pathway of the infection is through the bloodstream also dubbed as the circulatory pathways. The main modes of exposure to the virus is though exchange of body fluids from an infected person or through applying used or shared needles. When the virus invades the host, the virus which contains two single strands of RNA make the 'macrophages' their main target which are often dubbed as the 'HIV Factory' once infected. The single strands invade the macrophages and through the help of an enzyme, which is present in the virus itself, called the 'reverse transcriptase' converts this RNA into the DNA or the 'HIV DNA.' This 'viral DNA' then incorporates itself into the DNA of the host which is then replicated through various cycles of replication of DNA. These cells then release the 'viral mRNA' which there after give instructions to the ribosomes for the production of proteins which aide the virus. After the virus has a sufficient amount of viral strands, it targets the 'helper T-cells.' Thereby reducing and eventually inhibiting the immune response that is offered by the host[43]. When the 'viral DNA' is being incorporated, due to the increased number of mutations in the virus there are errors in the genetic code making it difficult to find a cure for the disease.

One key term that requires to be defined in order to get a better understanding of the virulence of this pathogen is 'heritability.' It can be labelled as the amount of variation in a phenotype pf the pathogen which is in turn credible for the difference in the fundamental genotype[44]. Another term that comes in play for this pathogen is 'viral load.' This basically refers to the load or the quantity of the virus in the body after the infection which is quite high during the early phases of the infection as the virus reproduces and multiplies in order to be more transmissible throughout the body. After a while the immune system able to stabilize the infection through the development of 'specific cytotoxic T cells.' This limit is commonly called the 'HIV set point viral load (HIV-1 SPVL).' In case of the 'HIV set point viral load', heritability can be defined as the amount of variation in a phenotype pf the pathogen which is in turn credible for the genetic factors of the virus which heavily impact the factor of how severe the disease will be, if left untreated[45]. The 'HIV-1 SPVL' and 'heritability' are closely related to the liaison between the value of the trait in the transmitter or host and the receiver. The greater the heritability of the of SPVL, the more will be the severity [46]. Though there is no concrete evidence for the affecting virulence factors of the virus the two main factors that are believed to play a role in this are:

1. The genetic features of the virus that control the reproducing capability of the virus[47].
2. The genetic features of the virus that help in influencing the capacity of the virus to induce the activation of the immune system[48].

One quantifiable factor that can correlate to the virulence of the virus is the 'replicative capacity(RC)[49].' It is the average of the number of cells that are infected by another infected cell along with ample access to the target cells due to the lack of the immune response of the host. Evasion mutations with minimal RC are prone to evolve in a host when the 'selection strain' applied by the immune system is greater than that of the intrinsic selection for the escalating RC. The process of the initiation of the CD4 cells can also be considered as a category for the determining factor of the virulence of the virus which is a very important and crucial process that occurs in the initial stages of the infection. The 'viral load' is not only the most commonly utilized analytical statistic of the progression of the disease, but it is also correlates positively with the infectiousness of the disease[50].

The repeated mutation of the virus is a very prominent part of the life cycle of the virus and is able to develop resistance to drugs in a short period of time. The mechanism of the pathogenesis of this pathogen require to be in sync with the 'multilevel selection' of the host which allows the virus to adapt easily within the host. This requirement is very crucial and there are three possible mechanisms which explain this.

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- Slow evolution of the replication capacity of the virus: The mutation rate of the virus is very high and rapid, but this does not emphasize that the virulence factors of the virus also evolve rapidly. The fitness within the host can be greatly convoluted which could lead to a reduction in the rate of the mutations. Along with this the high capacity of the mutations of the virus may not reach the continued elevated occurrences, if they are inherently greatly immunogenic, or for the reason that they are favourably affected by acquired immunity and as a result of their supremacy during the early stages of the infection[51].
- Lesser selection in the host for the 'viral load': It is feasible that there are certain viral factors that greatly influence the viral load but are impartial with respect to the host fitness, and therefore do not evolve swiftly within the host. Due to the absence of the host fitness, the virulence of the pathogen increases. The difference in the rate of the initialisation of the target cells can be a major source of these variations. If the virus triggers target cells in a systematic manner, then any strains of the virus that stimulate the cells offer a benefit of replication which is not constricted to the single strain but in turn all the strains, to such extent that all the cells are offered with extra target cells[52].
- The impact and spread of the initial viral strains: Another explanation of this mechanism can possibly be superior spread of the viruses that haven't undergone several cycles of replication in the host, either because the spread occurs during early phases of the infection. The response of the virus would be similar to the differentiation between the 'soma' and the 'germ line' and hence can be a useful strategy[53].

V. PATHOGENESIS AND VIRULENCE OF COVID-19

A new disease has gripped everyone which is again caused by a virus. Covid-19 has become the latest addition to the long list of viral diseases that have impacted everyone with the difference being that it has turned into a pandemic. Being a virus, the issue persists with the high mutation rates and different variants evolving over time. The mode of propagation of the virus is through respiratory pathways mainly through the particles suspended in the air which makes it difficult to control and regulate the spread of this disease.

The infection caused by the virus occurs in different stages where different responses in the host are triggered. This infection is having three stages to its process of infection[54]. The three stages are as follows:

- Initial Stage (Asymptomatic state): This stage can last form anywhere between 2 to 14 days. This is also termed as the 'incubation period of the virus.' The virus enters the host through inhalation and within the nasal cavity it binds with the 'epithelial cells' where it starts replicating[55]. The main receptor in the host for this is virus is the 'ACE-2.' Within the conducting airways of the host the key and the initial cells that the virus infects are the 'ciliated cells.' The immune response of the host, which is innate in nature, is limited and there is a regional spread of the virus. The infections are now communicable, though the 'viral load' can be low. The RT-PCR rate of the 'viral RNA' is essential in the prediction of the 'viral load' of the virus[56].
- Response of the upper airway and the conducting airway: After the initial incubation of the virus, the pathogen spreads further than down the respirational route all along the conducting routes, which leads to the triggering of the immune response of the host's immune response which is more vigorous in nature[57]. This disease is now manifested in the host.
- Ground glass infiltrates, hypoxia and ARDS progression: It has been observed that around 20% of the cases of this disease have progressed to this stage which eventually leads to the development of the 'pulmonary infiltrates.' Some cases also develop severe symptoms in this stage. Depending upon the nature of the infection, a host being symptomatic or asymptomatic can make a difference in the morbidity and fatality rates of the infection. After the pathogen reaches and infects the 'alveoli type-2 cells' These alveoli that are infected are 'peripheral' and 'subpleural' in nature. The pathogen transmits to the other type-2 cells, thereby releasing a large amount of the particles of the virus. These cells then undergo the process of apoptosis. The end result of this process is the pulmonary toxin which is self-repeating in nature[58].

There two major virulence factors that are specific to this virus. There is a very distinctive 'Furin-cleavage site(FCS)' in the virus which is structurally similar to the similar 'novel coronaviruses' which have been responsible for previous epidemics and pandemics[59]. Another common factor between the two is the cell receptor which was mentioned above called the 'ACE-2.' What makes this variant of the virus different from others is the 'FCS' which contains a 'multi-basic amino-acids' present at different intersections of the spike proteins of the virus. Patients who have had more severe symptoms also showcase an elevated immune response through the course of action of the infection[60]. The spike like proteins present on the virus help in the process of the invasion of the host cell and the evasion of the response of the immune system as well. These spikes catalyse the fusion between membrane of the host cells and the membrane of the virus for the process of infection[61,62]. There is a belief that the spike proteins exist in two different conformational states within the cells of the host which plays a major role in the development of the vaccines against the

virus which mainly target the spike protein of the pathogen[63]. A conformational change in the spikes after it has undergone the fusion with the cell membrane of the host can lead to the nullifying antibodies not forming in the host[64].

VI. CONCLUSION

The diseases talked about above show that there are a lot of underlying factors that influence every little aspect of a disease. All four diseases differ in a great way in terms of their infection and how the pathogen is transmitted. There are genetic factors involved with every disease as each pathogen can develop resistance towards the stressors that the host may offer as well as the environmental stressors. By achieving a better understanding of the genetic factors there is a lot of potential and possibly offering another outlook at tackling such diseases and researching upon them. Along with this, the multi-disciplinary nature of the field allows greater scope for the transfer of information and techniques to analyse the pathogens and controlling the spread at early stages. With the increasing number of diseases in the world and the meteoric advancement in the technology aiding betterment in the research industry there is a fruitful future of this field in the coming years.

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