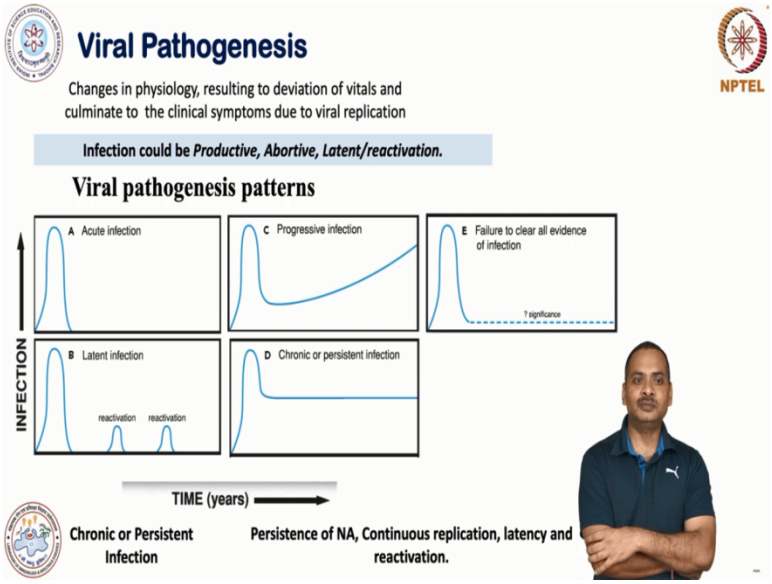
Host-Pathogen Interaction (Immunology)
Prof. Himanshu Kumar
Laboratory of Immunology and Infectious Disease Biology
Department of Biological Sciences
Indian Institute of Science Education and Research (IISER), Bhopal

Lecture - 57
Host-Virus Interaction

So, today we will begin this host pathogen interaction and this is in real sense this is host pathogen interaction and today in this session I will discuss about the host virus interaction and their co-evolution. So, try to understand this is the viruses also keep on evolving and the host is also keep on evolving. And today I will give you few of theise concept and I will also discuss one very landmark experiment which was performed that shows that this viruses and host both are co-evolving. Initially the virus is extremely fatal and after few years it turned to be less fatal.

(Refer Slide Time: 01:24)



So, let us begin with this session and before going to more details I would like to explain what is the virus infection. So, virus infection is a simply transfer of viral genome into the host cell ~~vacuum~~, as you know very well that viruses are obligatory parasite. When they do not have a host, they are non-living and as soon as they come in contact with the living host or living cell then they replicate and then they hijack the host cellular machinery.

And then they make a copy and then replicate and then that causerves the disease. And how you define the disease that is a little interesting, let the virus replicate, it is no problem. Let it replicate but when they replicate in higher number, they change the physiology of host they perturb the homeostasis of the host where this problem arise then we start defining it as a disease. When they change their physiology that result to the deviation of vitals.

Vitals means the replication is so much that now they are changing the physiological parameter the vital parameters. For example, they can make a more they can skew the body temperature, they can change the physiology in respiratory system that will start producing more mucus and all those things. They will hamper the oxygen retention capacity of the blood. So, these are the vitals.

So, when this replication is so much then they will change the vital signatures and then we start calling as a viral disease. So, this is clinically visible and the patient or the individual experience, all these changes in physiology. And this is happening why because of viral replication because virus is replicating too much. And when they replicate it is obvious that they are taking our resources, you know that they hijack.

So, it means they are taking our resources and making their own copies and due to that the problem arises. So, there are varieties of kind of infection, so infection as I told you it is a just transfer of genome into the cell and when this transfer of genome is taking into the genome is taking place then the cell has mainly three kinds of responses or this genome will cause three kinds of effects.

One could be productive, means when this genome is transferred into the living cell or the host cell, at that time they will start replicating making a more copies. So, that we call it as a productive, productive infection it could be abortive, genome is there but somehow the host response is in such a way that this genome is somehow degraded or removed or something or this genome containing cells were eliminated, so that we call it as a abortive infection.

Another is latent activate a latent infection, so when this genome is transferred into the host cell, then genome is present in such a way that cell will not experience any kind of infection. They are somehow, evade the sensing mechanism of host cell, they remain in the cell, either they will replicate extremely slow or if this is not needed then they will just sit in the cell and wait for right time.

Right time is when there is a change in homeostasis of the host or somehow the defense mechanism is little hampered by some or other mean there could be a several means by which the immune system can be perturbed. Then this will reactivate and cause the productive infection or then that will cause the symptom or disease. One very good example is HIV, HIV is something like that.

When they in fact the host will not know and for quite a long time, they are present in latent form, in pro viral form, the genome is integrated into the host genome everything is very nicely hijacked, nicely hijacked of this host system. So, they will go slowly replicate and then they make a it is a retrovirus you know that. So, this makes RNA to DNA and this DNA will integrate into the host genome and they will just lie in the cell.

And when there will be some perturbation, then this will make the more copies of viruses. So, this is a very good example of latent infection and then there will be a reactivation. So, viral pathogenesis patterns are there are several kinds here you can see that there is a acute infection. So, the virus which is infecting the host cell and replicating in very high number and that immediately affect the vitals of the host.

So, we or sometime it affect very severely that may cause the fatality. So, we call it as a acute infection. There is a similar term known as chronic or persistent infection, so here the host immune system also learned how to control this virus to some extent. And there will be a virus in the cell but it will be not so much that it will drastically affect the vitals or vital signatures. So, we call it as a chronic infection.

The persistence of this nucleic acid will be there, there will be a continuous replication, sometimes they will remain in latency sometimes there will be a reactivation there will be episode of change in vitals. Another is latent infection which I have already explained you there will be a the genome will remain in the cell and when there will be a right situation then that will reactivate.

There is a progressive infection, there is when the virus infects the host cell, initially there will be a very high intensity of a change in vital and that result to the severe damage to the host. But after sometime this replication will go down and then there will be a progressive and steady and progressive increase in viral infection. Initially the host will overcome this infection but later on the virus will slowly and steadily progress. So, that we call it as a progressive infection.

Chronic or persistent infection it is I have explained, so there will be a some kind of arrangement between virus and host, its arrangement means virus is also not able to overtake the host immunity and immunity is also not able to take over this virus. So, there will be some equilibrium stage where the virus will be also there and immunity will be also there and the change in vitals are not so significant, it is a persistent kind of thing.

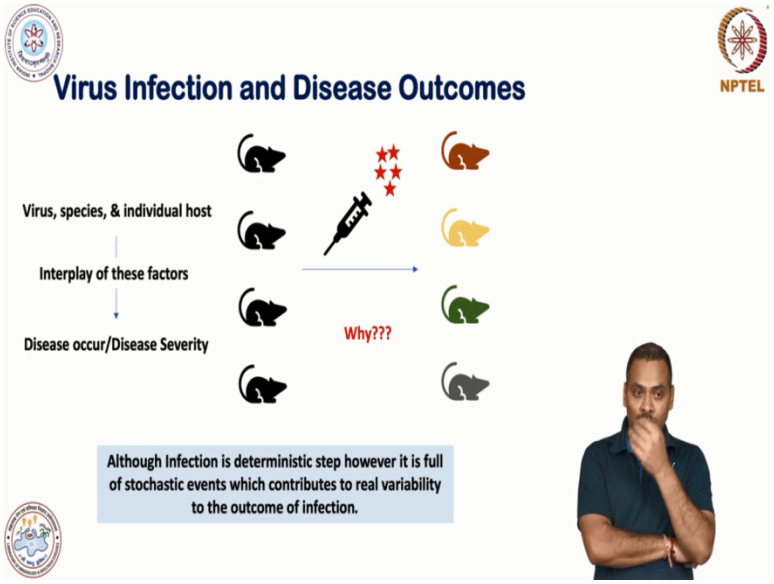
So, we call it as a chronic or persistent infection. There could be a failure to clear all evidences of infection, the virus is a sometimes very smart some. In some cases, they will disappear from the system, for example the virus is infecting say epithelial lining. So, after there is a high peak of infection, they cause severe damage to the epithelial lining and then they will reach to the blood and suddenly this will disappear. Why? There could be several reasons.

One is that they somehow gain the assess in neuronal system which is having a blood-brain barrier. And either they will present over there or they will be hiding from the immune system and they will be present in some place where there will be a not so active immunity. So, they will be not generally present in blood or epithelial cell as I explained you that if the virus has a tropism to the epithelial cell or they are infecting to the epithelial cell.

Then initially they will be present in epithelial cell, they will replicate more in number, they will cause the severe problem but suddenly this will disappear, they may hide somewhere. However, we do not know what precisely is going on and what is the significance of this because if it is hiding and not causing disease then what is this meaning. But if you see in philosophical way, then it is a very good equilibrium stage.

It is like you live and I live something like that, it is like a virus is basically not killing the host if it will kill the host then virus cannot also survive. So, this is a very good arrangement kind of thing, so this is all about the viral pathogenesis.

(Refer Slide Time: 14:02)



Here I would like to say that when there is a infection to the host, then the outcomes are not always same. Here I am just showing one simple experiment, here you have a black colour syngeneic micemouse, same genotype is same, same age, same sex everything is same. And you are infecting this group of mice by particular virus, here you can see there is a syringe I am depicting the infection and the stars are viruses.

So, when you do the experiment, the outcome is always quite different. I will explain you why, here you can see that one mice is severely affected, another is just moderately affected, some may be not at all affected. So, the different colour I just wanted to depict as a severity of

infection if you see the dark brown that is more severely affected, yellow means just a bit, green is almost nothing and the grey colour mice is almost no effect.

So, why it is like that? So, that is very interesting to understand I will explain you this is happening because of the infection process although we have controlled everything age sex everything is same virus is same. All those infection is a deterministic step however it is full of a stochastic event I will explain you, which contribute to the real variability to the outcome of infection. Let me explain what is this stochastic event.

So, stochastic even means the it is a random event, so when you introduce the virus in these animals in same way you have introduced the virus in same way absolutely same protocol everything. So, when you do this thing then it is a very random process when you inject the virus maybe it will go in such a way in some cases it will be severely hampered the viral replication in some cell in some case.

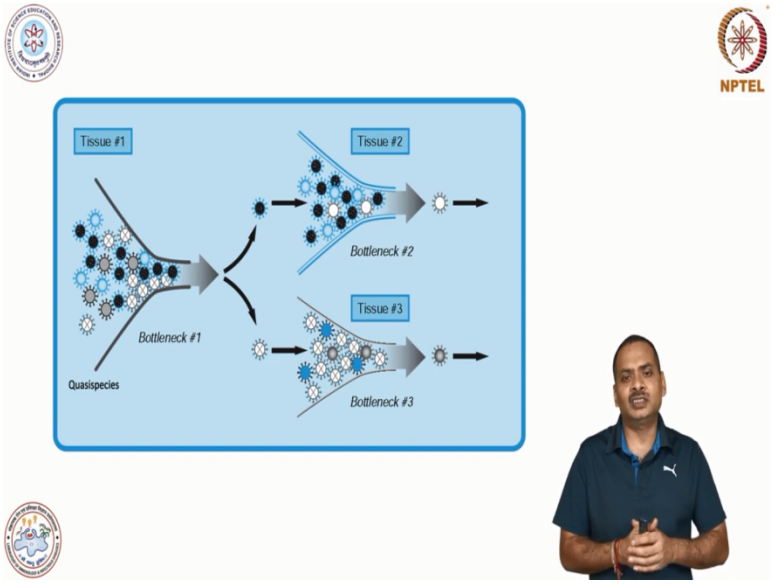
In another case it will supportive to the virus infection. So, it is a highly random process I will explain you much better in with in a subsequent slide over there I have some schematic. Just try to understand it is a highly random process. For example, this virus is having a more infectivity in epithelial cell but not in muscle cell. So, when you introduce the virus in one case it will go more in it will infect more in epithelial cell.

But in another case, it will this virus will go more in the muscle cell. For example, it is a very random and arbitrary example. So, in case of epithelial cell, it will cause more severity if it is going in muscle cell it is causing less severity. So, you can understand there is a huge variation, it is a just I tell you the cell type, there could be a signalling, there could be a different things. So, due to this huge variability the outcome will be also quite variable.

So, here I am trying to explain you the virus species individual host everything is different although, it is a syngeneic mice is genetically same. Maybe in some minds the metabolism is in different states and all those things. So, there is a huge variability and this interplay of these

factors the virus, the host factor, the viral factor, all those things result to the different disease outcome or infection outcome.

(Refer Slide Time: 18:45)



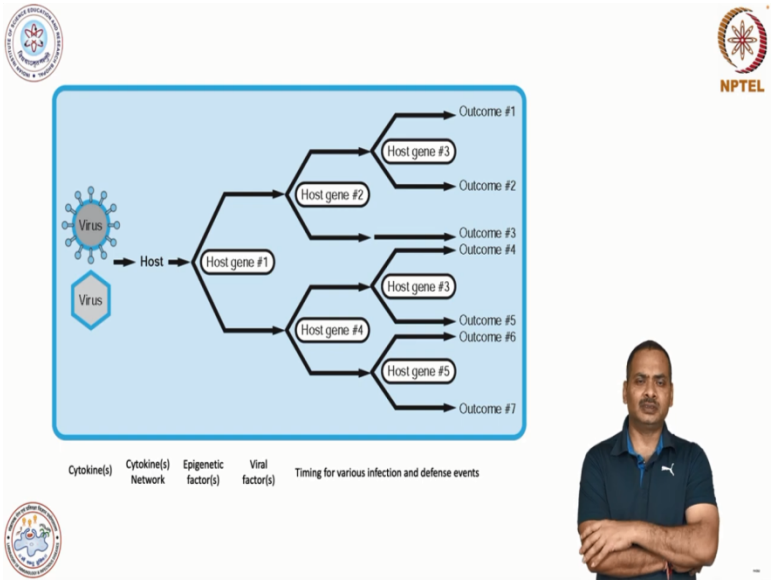
So, here I am just showing you one schematic, here you can see that I am it is just a model try to understand. So, virus when I am giving the virus to the host. So, here you can see that virus itself is a it is a mixture of genetically variable. I will explain you why it is genetic variable you know that viruses replicate using the polymerase. And most of these virus polymerases they do not have a correction ability proofreading we technically we call it as a proof-reading.

They do not have a proofreading mechanism and if it is there it is not very good. So, that is why when virus infect the host cell then they are keep on varying so this is a property of virus. So, they will be keep on varying~~wearing~~ and that is why we use one term here you can see that there is a term known as quasi species, it is a mixture of virus, so not one kind of virus. Here that I have depicted in this schematic, this is a mixture of virus.

So, when you inject into the host here you try to understand what is bottleneck. So, bottleneck is nothing it is a basically a different resistance, bottleneck means resistance, resistance means it could be immune resistance it could be cellular resistance, there is a huge kind of immune resistance, so these are the bottlenecks. So, when you introduce then maybe one this quasi mixture will one kind of virus will follow another pathway, another kind of virus.

Although it is same but it is different genetically different that will follow another root. And in that route, there will be a different kind of bottlenecks; there are different kinds of resistance. So, that is why the outcome will be different.

(Refer Slide Time: 21:14)



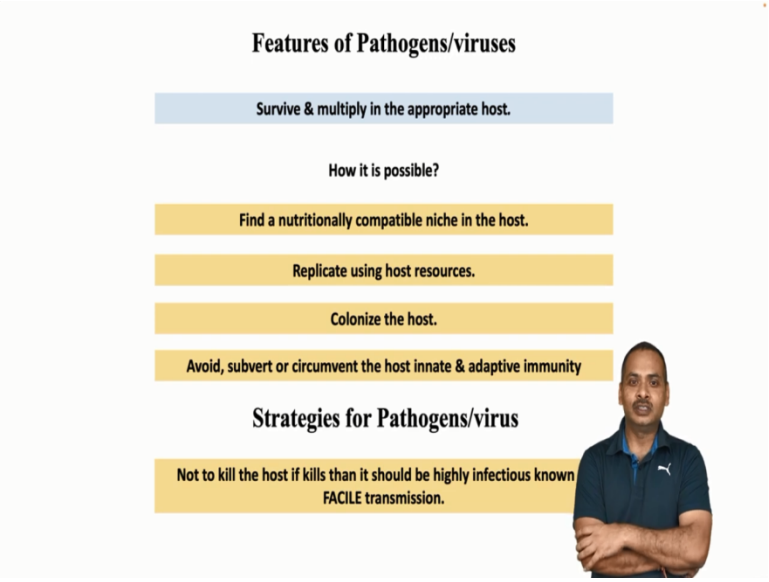
So, here I have a much more refined thing, so here you can see that this is a quasi-species of virus both are virus same virus if you want to say. But they are different genetically different and this is a host there is a host gene this virus will interact with the host gene 1, host gene 2, 3, 4 like that 5. So, there will be huge variation, let us take it this host gene maybe cytokine some cytokine network there could be some epigenetic factor viral factor timing for various infection and defensive event.

So, due to this the outcome will be very much different. Now you can understand that when there is a any infection it is not for any particular infection, when the individual is infected with SARS Covid 2 someone although we all are human. Of course, there is a lot of genetic variation but still we are all human but some human or some individual they show different severity and some individual are just very healthy.

So, although here there is a one very big variable is there the human genetics is very different but here, I am talking about the same genetic animal but the outcome will be very much different.

This we observe in our experiment when we conduct the experiment with mice, we get this kind of variable or variation in the result.

(Refer Slide Time: 23:01)



So, now I will talk about what is these features of pathogen and virus why these guys cause disease because virus is a non-living entity or even a pathogen is a another for example bacteria there although they are living but they need to survive. So, what is the aim of any species? The aim of a species is continuity of a species, they want to replicate, they want to make their own copy, they want to reproduce.

And make their own copy in order to continue their life the continuity of life is the key aim of any living entity. So, pathogen or viruses they survive and multiply in appropriate hosters they want to live, so in order to live they have to infect so this is the aim of any pathogen or virus and how it is possible. So, human or any animal they are very good source of food. There will be a good the host is a nutritionally rich and compatible niche in the host.

So, this is a very compatible environment for the pathogen, so you try to see from pathogen point of view, do not see from host point of view. So, if you see the pathogen they just want to live and in order to live they infect the host means human or animal and then in order to when they grow more than that cause the disease. It is not intention of pathogen to kill the host, I will show you there is a one very beautiful experiment.

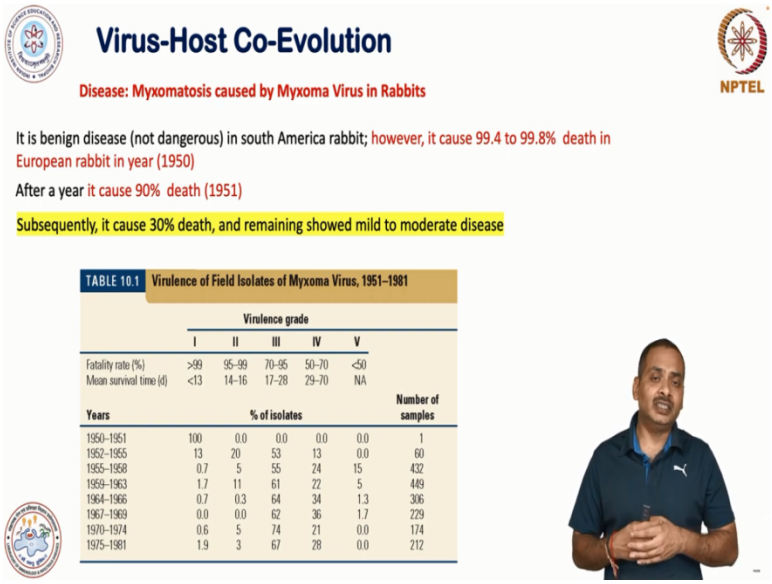
So, they can replicate using host resources the nutrition and all those things they can colonize on the host. So, we are basically house for the pathogen try to understand from pathogen point of view, they want to live, they want to replicate, they want to colonize. So, but host is always having a defense mechanism they the innate immune system and adaptive immune system they we do not want that they should grow on us.

So, avoid and subvert or circumvent the host innate and adaptive immunity they develop all those weapons but the pathogenic factors. So, this pathogenic factor is needed to the pathogen in order to survive in the host, so it is a very close battle between the pathogen and the host. We do not want they should live and they want to live because they cannot survive anywhere. So, they have to, so try to understand.

So, strategy for pathogen and viruses are, so overall aim of the pathogen is not to kill the host because if they will kill then they will not replicate, so they always want in an equilibrium position. So, if they will kill for example if there is infection and that will immediately kill the host. So, what will happen? In that situation they cannot replicate. So, then those pathogen has a capacity they hoop to the new healthy host.

As quickly as possible in order to again the aim is continuity of life. So, this is a little philosophical view of pathogen and host.

(Refer Slide Time: 27:18)



Now I will show you this virus host co-evolution. There is a disease known as myxomatosis caused by a myxoma virus in rabbit. This virus is causing a benign disease not, so dangerous in South America rabbit. However, when this virus means in the rabbit from South America, they will live happily with this, there will be no problem absolutely no problem but if this virus infact the European rabbits, then that will cause severe fatality about 99.4 to 99.8 rabbits will die.

For example, if you have 100 rabbits European rabbits and these rabbits are infected by this virus, then they quickly die most all will die. So, there is a experiment people, it is a very old and but very beautiful experiment. So, what would they have done? They have this is a practical example also it was happened. After a year it occurs so initially there is a 99 fatality but if they keep on infecting then the fatality is reduced it is about 90 percent in 1951 the next year.

And subsequently it came at equilibrium stage only 30 percent death was there and this 30 percent death remains show very mild and moderate disease they do not cause very severe disease. So, here you can see the data you can understand this there is a virulence grade this is more than 99 percent fatality if the grade is one if the grade is 2 then 95 to 99 percent. If the grade is 3 like 70 to 95 percent like that, you can go through that.

But overall outcome of this experiment is that initially there will be a massive fatality and this fatality will reduce with a subsequent infection.

(Refer Slide Time: 29:51)

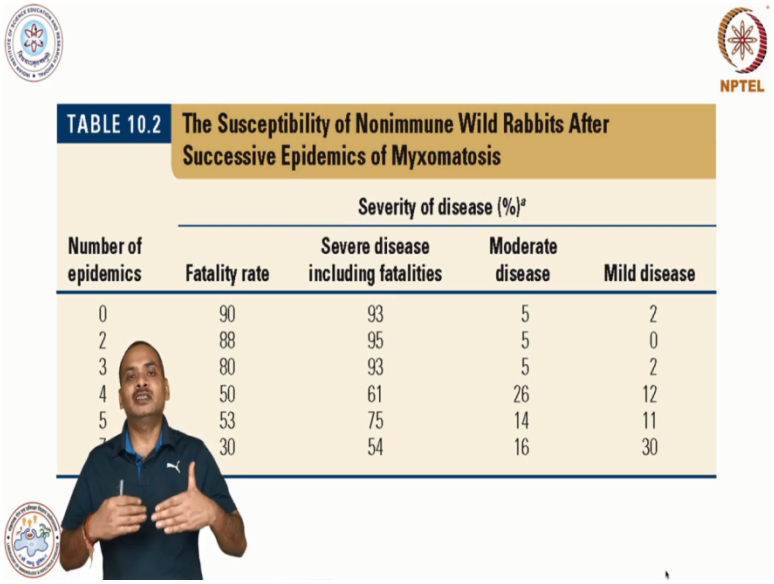


TABLE 10.2 The Susceptibility of Nonimmune Wild Rabbits After Successive Epidemics of Myxomatosis

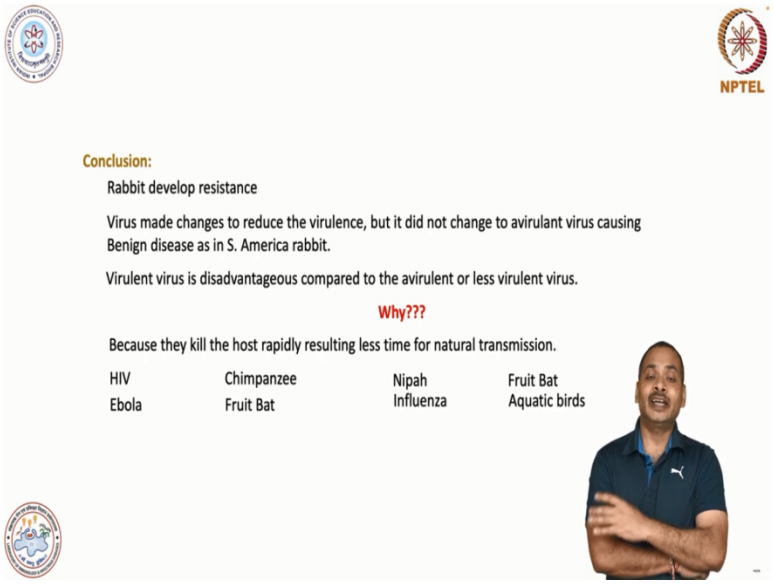
Number of epidemics	Severity of disease (%)[a] Fatality rate	Severe disease including fatalities	Moderate disease	Mild disease
0	90	93	5	2
2	88	95	5	0
3	80	93	5	2
4	50	61	26	12
5	53	75	14	11
	30	54	16	30

Here you can see that how it is happening. So, number of epidemic here you can see there is a initially there is a first epidemic there will be a lot of fatality about 90 percent and very few had a mild disease but most of them died. In second you can see that the fatality is reduced and at towards end at seventh epidemic it is just a 30 percent fatality and there is a 30 percent individual they developed a mild disease.

So, this is a I want to tell this philosophy that pathogen does not want to kill the host because host is a house, host is a food, host is everything. But initially when they come then they cause the fatality in order to show their means some somehow, they are it is a not good because a lot of fatality it is not good so that is why they come in equilibrium stage. Generally, they cause fatality when they jump from one species to another species.

In this experiment also you have seen that this virus is living very happily in South African American rabbits. But as soon as they come to the European, they cause the fatality and after a while after several years they reached to the equilibrium stage.

(Refer Slide Time: 31:42)



So, the take home messages or conclusion from this work is, so rabbit develop the resistance. So, rabbit also developed some resistance, they develop some mechanism in order to clear this virus infection. Virus also made changes to reduce the virulence, because if it will cause more virulence, then he will the virus will not have a host in order to replicate to make their copies. But it did not change to a-virulent virus they did not change.

It is a completely virulence was not zero but they reduced the virulence causing benign disease as in South America rabbit. Virulent virus is a disadvantage that what I was explaining disadvantage compared to the a-virulent or less virulent virus. So, more virulent is not good for virus why, because they kill the host rapidly resulting less time for natural transmission. So, if they will kill very quickly, they will not get another host quickly they will not get another host.

So, that is why there, it is a disadvantageous. There is some example that some of the disease which we can see in modern world also. They some of the infection is extremely fatal, why? Because they jump from one species to human for example HIV, HIV came from chimpanzee, HIV is basically present in chimpanzee and then this virus hooked to the human. Ebola virus, they came from fruit bat, Nipah virus this also came from fruit bat.

Influenza which caused a massive pandemic in 1918, this virus basically came from aquatic birds. And you know very well that the SARSs CoV2, SARs CoV2 is also came from some wild

cat from China, the name of cat is Civet cat. So, they change the affinity for angiotensin converting enzyme to2, there was a two mutation there is a one very beautiful paper if you have a extra interest you can take a look. It was published in cell I do not remember the year.

They reported that so initially they were infecting the Civetseaweed cat the wild cat in China. So, this virus they made a two mutations which changed the two amino acid and then this the SARS CoV gain more affinity to the human angiotensin converting enzyme. And then that was that caused the fatality fortunately at that time it was controlled. And after that you know the SARS CoV2, it is also considered that this came from some wild animal from China I do not know precisely.

So, here you can see that when the virus jumps from one species to another species then they causell the fatality. So, this is all about the host virus interaction and co-evaoluation and with this I will stop here and in next session I will discuss about the innate immune response against the viruses, thank you.