Applied Environmental Microbiology
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Lecture – 49
Antimicrobial Resistance I

Dear students in today's lecture, we are going to talk about a very important environmental health and public health problem, even though this seems to be mostly an environment a public health problem. It has a very strong environmental component, because this particular issue, which is the issue of antimicrobial resistance and often, it is called as antibiotic resistance proliferates that is spreads and increases through environmental routes. And in fact, now we know that many of our man human activities and our engineered systems are contributing to increase in the levels of antimicrobial resistance.

Now, let us look at what is antimicrobial resistance. When we talk of antimicrobial resistance, we are talking about the ability of microbes to resist our attempts to kill them by using antimicrobials. So, antimicrobials are the drugs like antibiotics anti (Refer Time: 01:19) that kill our microbes. And we want to kill them because the ones we are targeting hopefully are pathogenic, but over time and we have been noticing that these pathogens are becoming resistant increasingly resistant to the drugs that we use to kill them or and basically the other way of saying this is the drugs we use for treating our diseases.

So, at the beginning of antibiotics, when antibiotics were discovered and then made on industrial scales, scale, the pathogens were susceptible or vulnerable to the drugs that we were giving them the antibiotics. However the question now is why are there as being becoming increasingly resistant. Now, when earlier they were vulnerable to antibiotics and the reason is that pathogens in general do not, were not resistant but they have acquired their resistance from other microbes.

Now, when we are talking about antimicrobial resistance, dear students I must tell you the antimicrobial resistance in itself is not a novel phenomena, in fact, few years ago a very nice study reported in a top known journal declared that even in an ancient cave that has not been touched by man or our activities. They found a wide diversity of antibiotic

resistance in the bacteria, why would that be so? Well, we know that many of our antibiotics and many of our antimicrobials are actually produced by bacteria and microbes themselves to use either to kill the competitor, so only that particular microbe can survive in the or the ones he likes it likes survive and the competitors die out. Or they also use these chemicals which we call antibiotics or antimicrobials as communication agent.

So, bacteria and microbes especially many bacteria we know have a wonderful system of quorum sensing. In quorum sensing the bacteria can sense each other's presence using chemical signals they can communicate about food source and about threat and so, basically they talk to each other using these chemical signals. For many bacteria, these chemical signals are antibiotics for and what we call antibiotics, because they are toxic for some other kinds of bacteria. So, in this case, the bacteria achieves two fold benefit by producing antibiotics, first it is able to talk and sense its own kind of bacteria ; and the other it is able to fend off the competing bacteria.

So, antimicrobial resistance is has been present since the inception of microbial life. Now, with human activities, we have enriched the levels of antimicrobial resistance. And also as we talked earlier microbes have the capacity to share genes to share their attributes. And as the microbes that are resistant have enriched, they have also shared greatly their resistance genes. And this has eventually resulted in an elevated levels of antimicrobial resistance in our environment and also in our clinics. And as such increasingly we have cases we have incidences of infections every year which are resistant to antimicrobial. So, let us look into antimicrobial resistance and the environmental aspect of it ok.

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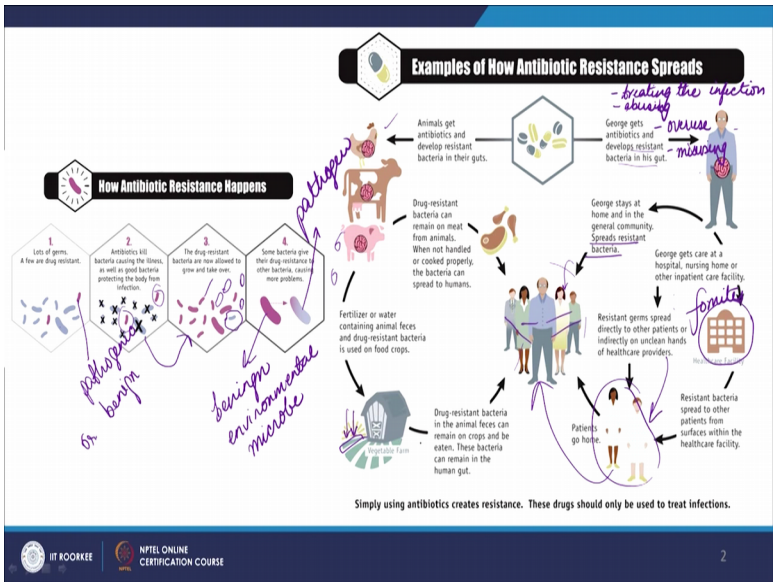

So, how does antimicrobial or antibiotic resistance happen. So, typically when we begin we begin with lot of germs. So, there are lot of microbes that are present in our community, environmental community or clinical community, and only few of them the ones here in purple are the ones that are resistant to the antimicrobial to the drug. Now, what happens is when we add, now, let us say this is what is happening in a person's gut. So, in our, this is the sample of our gut let us say, and in our gut very few my microbes are actually resistant to drugs, but they are not necessarily pathogenic. So, we cannot say that this is pathogenic microbe it actually, could be both pathogenic or benign; regardless of that it might have antimicrobial resistance in it.

Now, when I let us say, this person falls sick and they take some antibiotics. When we take antibiotics, antibiot, most antibiotics are quite broad spectrum which means that they have the ability to kill my to kill a wide spectrum of different kinds of microbes bacteria. And they are not very specific to the target pathogen that we have want to treat. And such as what they do is they kill the good bacteria as well as the pathogens hopefully. And now the problem is that these good bacteria were actually competing with the pathogens and keeping they were the internal system that was keeping a check on the pathogen consideration in the gut, but now because antibiotics have killed all these gray susceptible bacteria.

Now, the body is more vulnerable to infections and also we have killed all, but we have except for the microbes that are resistant. So, now, when the body will start being populated by gut, because now gut has out of food; So, whatever survivors are there, they will eat it rapidly and they will divide. Eventually, we find that we have the antibiotic resistance bacteria have overtaken the gut. So, the good bacteria there and the ones that were susceptible to antibiotics are dead and the gut is full of antibiotic resistant bacteria.

Now, this is where the problem begins. Let us say this is our pathogen that is causing the disease and let us say there was a pathogen survivor. Now, these enriched microbial communities that all of them have antibiotic resistance or antimicrobial resistance will be able to transfer their ability to the pathogen. So, this is what we say and a benign environmental microbe.

And now, it is able to transfer by a horizontal gene transfer. It is ability to resist the drug to the pathogen and this is where the problem begins, because as pathogen feasts on the body, it will increase in number and now no matter how much drugs I give the pathogen would not die out and it will rapidly populate the gut. So, these are all pathogens that are populating the gut know. The person will fall sick and more sick regardless of the persons dosage of the drug. Now, this is how antibiotic resistance begin.

Now, let us look at how it spreads. So, to begin to understand how it spreads, let us see let us start from here. These are our antibiotics in many countries including India, we have a very strong animal poultry and poultry farms they are very strong dairy and meat industry. Now, in dairy and meat industry, we often feed a prophylactic dosage of antibiotics to our cows, buffalo, goats, chicken. And the reason we do is this a twofold first to prevent any infection that will reduce the amount of our poultry products and thus cause economic damage. And we also give them doze of antibiotics, because now we know that our farm animals that are fed in including chicken that are fed sub therapeutic levels of antimicrobials.

So, sub therapeutical means the level of antimicrobial that is lower than the dosage. So, if in if the chicken were to fall sick and it were to be given 50 milligram of an antibiotic; instead of giving it 50 milligram, I will give a little much lower value of antibiotic like 10 milligram. So, I give 10 milligram of antibiotics to my poultry animals, pigs, buffalos,

cows and chicken, and when I do that I notice that their propensity to fall sick reduces and also they grow faster. So, there are two benefit is of giving prophylactic dosage of antibio microbials to chicken.

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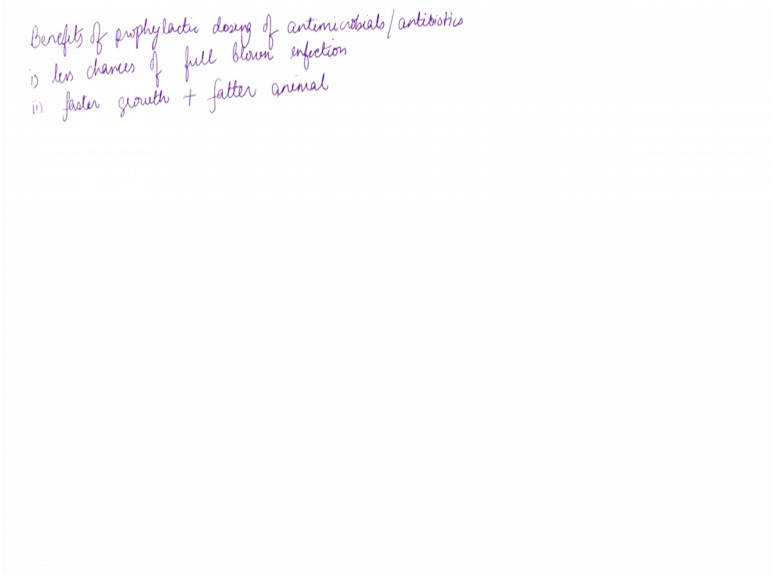

So, there are two benefit is of giving prophylactic dose of antimicrobials to poultry; one is that less chances of full blown infection which will hamper my economic profit, and the second is they grow faster. So, owing to these two advantages we want to give a sub therapeutic dose of antibiotics or antimicrobials to our animals. However, following the same old logic that we talked about earlier here that in a community when we give them antibiotics or antimicrobials, the susceptible organisms will die leaving behind the resistant ones, and then the resistant will colonize the gut. And even if some other susceptible ones enter the body and start colonizing it, their resistance one would be very happy to share their resistant genes.

So, over time what we notice is that the animals who are getting the antibiotics develop resistant microbes in their gut. Now, the other thing is here we are giving sample of George. So, this young hero develops takes antibiotics and develops resistant bacteria in the gut. Now, why would this person take antibiotics, what is the benefit for him to take it. First, he might be sick, so he wants to take it for treating the infection. Ideally, this is the case we know what the disease is and we know what antibiotic would work well and how much dosage is required, and we give just that amount of dosage to the human

being. But what often happens specially in countries like India where it is very easy to buy drugs in fact, many antibiotics are over the counter drugs. So, if you feel like you are down with diarrhea or some other disease that requires antibiotic, you can go to a medical store and buy antibiotics.

As such more often than not; more than 80 percent of time we notice that the antibiotics were not really required. For example, personally I know people who have had antibiotics for headaches where clearly there is no link between headache and the bacterial, any bacterial infection. So, as such we are abusing; abusing the availability of antibiotics in our medical stores in our market. And when we do that we needlessly enrich the population which is antibiotic resistant in our environment. The other reason why George would take an or the human being would take antibiotics is overdosing over use.

So, for example, the doctor had prescribed the person to take antibiotics for a week, but the person decides now I am going to take it for a longer time, so that I am sure I do not get the infection. Now, the more we overuse it we will see how later it becomes another problem, but the more we you take antibiotics and the longer duration, we take the more good we are at selecting for only resistant microbes.

And then the next thing we can do is abusing, overusing and misusing. Now, misusing would include conditions when the person really requires an antibiotic, but we are giving him a wrong antibiotic. So, the pathogen that was supposed to be killed by some other antibiotic is now developing resistance to this new antibiotic, and the good bacteria are dying. So, the infection is getting worse. So, abuse, overuse, misuse and the new treatment of infection or the fourth scenario in which antibiotics will be eaten by the human being.

Often with cheap availability of antibiotics and poor awareness in the public abuse, overuse, misuse are much more common than treating the infection. As such over time the human being develops resistant bacteria in his gut. Now, here is the thing now this person lives in the community and when they live in the community they excrete or wherever we live we do excretion and that excretion you know through different portals will eventually land up in wastewater treatment plant or will land in our drains in our septic tanks on our roads on our fields depending on the where the human being is

pooping and what is how our solid waste management is. And as such we start spreading resistant bacteria in the community.

So, the family members and the friends of this particular human being after the resistant bacteria have enriched in his stomach will also start getting exposed to resistant microbe which will, if they are also abusing drugs then there the stomach the good susceptible bacteria will die out and only resistant bacteria will be enriched. Now, the other thing is maybe the human being now is really sick and then goes to a nursing home or a hospital to take care. Now, when this person is being treated in the hospital his samples have been collected, his wounds are being treated now in this particular case it is also likely that this person will spread disease to other patients.

So, hospitals is a very or very tricky and very sensitive location because in hospitals we use a very high dosage of disinfectants and have very high dosage of antibiotics. Most of the patients who walk into the hospital are on some or other antimicrobial, and because of that the people who come there have this kind of condition which is the good bacteria have died out, and the resistant bacteria increasing. And also many a times people have surgical wounds or other wounds and or they are collecting body samples. And if it is not being done carefully then the person is likely to spread it to other patients who already have compromised immune system and whose good bacteria have already died out because of use of antibiotics.

Now, this person who has been overusing, abusing or misusing antibiotics will spread the resistant microbes to the other patients in the hospital. Will also spread the will also in fact or put the microbes deposit microbes on the surfaces of the infrastructure in the healthcare right. So, for example, let us say I have a wound in my hand and that wound has a staphylococcus aureus infection in it and it so happens that I have been overusing, abusing and misusing drugs or I am just unlucky enough that the staphylococcus aureus is resistant already. In any way for any reason, but the infection law is resistant to the drugs that I was taking to treat it. Now, if I go to a hospital and that the cotton gauge is used for cleaning my wound and then for disinfecting and other purposes, now all these cotton gauge etcetera, they have the resistant microbes on they are resistant pathogens on it.

If it is thrown in trash can or somebody mishandles it or I just go and wipe the surfaces now I have developed formites in the hospital. The floor or the surface in fact even the door handle, the scissors all of them are potential surfaces where the antibiotic resistant microbes and pathogens may have been deposited.

Now, let us say it is the door handle, when I am opening the door I brush off through my wound or through my skin where I have some antibiotic resistant staphylococcus aureus sitting. And when I opened the door using the door handle that microbe is antibody resistant staphylococcus aureus pathogen is deposited on the door handle. Next time a patient walks in and then the patient will pick up the infection. So, this is for mind the surfaces when we touch them before sick because the pathogen has been deposited on them. So, either way more patients fall sick. And when more patients fall sick when they go back to their community or when they interact with their family members or visiting them in the hospital, they make them also be exposed to resistant microbes.

Now let us come back to our animals. Now, these animals have resistant microbes in their gut. Now, many a times we use their manure their poop for example, definitely in India we use cow dung as manure when we used it and also chicken droppings. So, when we use their fecal matter for from a manure and fertilizer, what we are doing is we are depositing on our farms, agriculture farms you are depositing antimicrobial antibiotic resistant bacteria and pathogens also perhaps. Now, as a result the food we eat the soil that is here is now getting populated by antibiotic antimicrobial resistant organisms.

Now, if there is a rain event or if there is a just irrigation event then the water also will carry antimicrobial resistant microbes which now can be transport transported through environmental routes, and they will eventually expose to other people also. Also the people who eat this food let us say raw will also get directly exposed to the exposure to the antimicrobial resistant microbes. So, this is an example of how antimicrobial resistant spreads. It also it all starts with overuse, abusing, misuse of antibiotics which in there in case of human or in case of animals.

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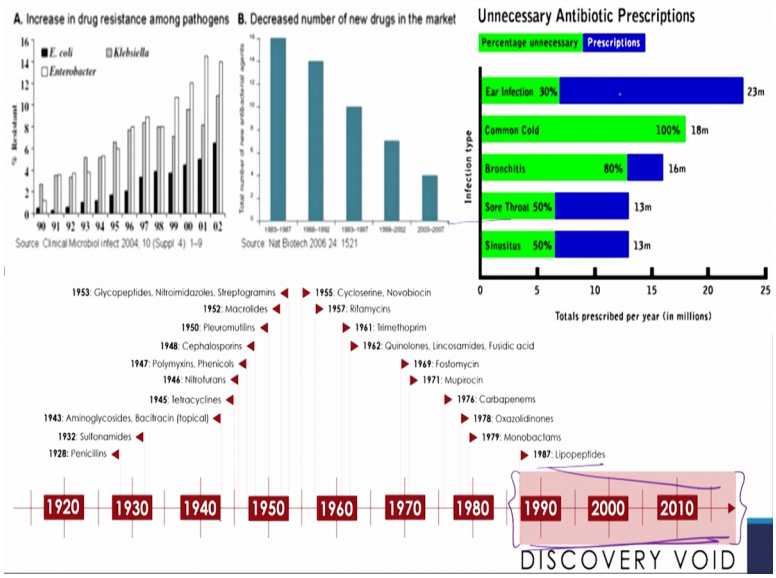

Now, let us look at this here. So, on the left side here, we have a rough diagram on how antimicrobial resistance in ecoli, enterobacter and klebsiella, all three of them are potential pathogens depending on what kind of ecoli etcetera it is. We notice how the resistance has increased to overtime. So, it is a consistent increase in the resistance in ecoli, consistent increase in the resistance in klebsiella in an intra vector. Now, if you look this is from 1992 to 2012, now this particular diagram is showing how the number of new drugs in the market have been consistently decreasing from 1983 to 2007. And the picture ahead is even more decimal in the last ten years.

So, this is pretty sad as we are we are antibiotic resistance is increasing, but new antibiotics we are not able to discover them. This is bad because that say if microbes are resistant to an old antibiotic if you discover a new one we can use a new one. I will give an example earlier in India say plov ciprofloxacin was a very commonly used prescribed antibiotic. Over time the doctors found out that the may infections were not responding to ciprofloxacin treatment the reason being perhaps and now we know actually the reason was that microbes the pathogens were resistant to ciprofloxacin, they had acquired this resistance.

Then we started using ofloxacin, which the microbes even those who were resistant to ciprofloxacin could not resist. And then we could treat the infections successfully.

Then what happened with time was the microbes also acquired resistance to ofloxacin, and now we are using (Refer Time: 21:01). So, we are moving from one drug to another just to lay the catch on game with the microbes who are increasingly getting resistant to the drugs we are using. So, for this we require that as a anti microbial resistance increases, our rate of discovery of antibiotics should also increase, but that is not what is happening, if you look at this top left panel, antibiotic resistance is increasing antimicrobial antibiotic new drugs are decreasing all righty.

This is another timeline of how we have detected different kinds of antibiotics from 1928 the discovery of penicillin to 1987 depth of peptides. And after 1987, our the trend has declined. So, see no new antibiotics from 1990 to 2010 and forward. No ,new some significant new drug that can be used as a successful antibiotics on a large scale without serious impact on health. So, now, and now we do have the last line of antibiotics like vancomycin etcetera. But they are now we also have resistance against vancomycin by the way, but they have serious side effects for the patient. So, we do not want to use them early on.

So, you notice here there was a peak of discovering antibiotics from 1940s to 1980 early 1980, but since then it has been read here. In fact, one of the guidelines of World Health Organization currently is to push the pharmaceutical industry to for research and discovery of normal antibiotics. Now, the question is why would they not want to discover or spend money in new antibiotics when antibiotic resistance infection is increasing and is a demand for new antibiotics. The reason is that drug design, drug delivery and testing requires lot drug design in it is testing and approval requires lot and lot of funding, and lot of many years of research to that need to be put in. And it so happens that right now this is not very profitable for the pharmaceutical industry to invest money in researching new antibiotics.

Now, if you look here I was talking about earlier how the major cause for antibiotic resistance and environment are abuse, overusing, misuse of antibiotics. So, this is a very nice picture and this is a global information. So, what we have here is a total prescription in per year in millions. And if you note that the green one is the unnecessary prescription and the blue one is what was actually necessary.

So, if you look at the ear infection we have 23 million in prescriptions per year of which there are 70 percent or 80 genuine they need the drug thirty percent of additional we can get rid of them. If you look at common cold common cold caused by virus. Then look here my dear students, if it is a viral infection, what is the point of giving an antibiotic except that in antibiotic would get rid of the good microbes which compete against our the pathogen and make the person more susceptible to further infection.

So, this is 100 percent pres antibiotic prescription for common cold is excessive. So, we have 18 million excessive prescription every year. For bronchitis again only 20 percent actually require antibiotics or they require help, but not antibiotics. So, again here we have an very serious case of abuse. Sore throat sinusitis same thing half of the cases it is not required. Now, in a country like India where pathological pathology labs are not very accessible to majority of the public the this is the figures look even more grim than this ok.

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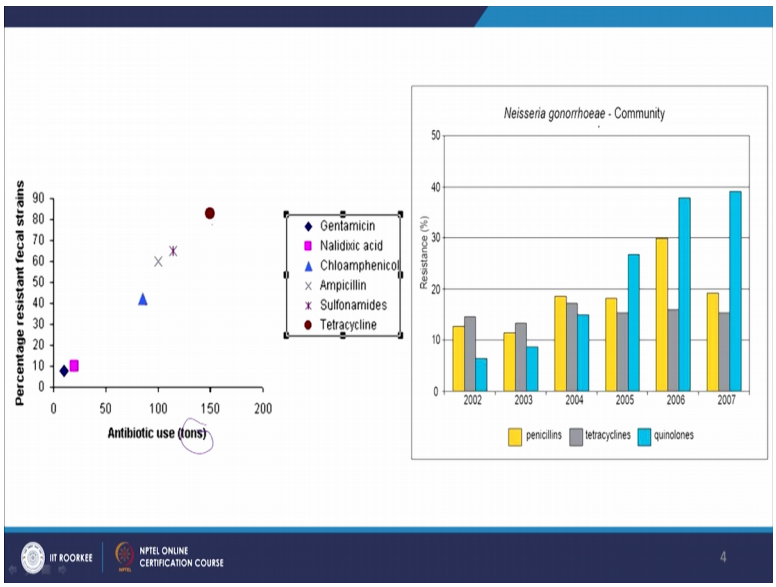

Now, let us look here now we know that the microbes when we eat antibiotics they enrich in antibiotic resistant microbes. Now if you on the global scale also, we know that the antibiotics for which we use more, we also have higher percentage of resistant microbes against them. For example, we have a tendency to use tetracycline it is a lot. So, because we used tetracycline much more than we use gentamicin, chloramphenicol

this is where I am felling call, this is gentamicin, and this is tetracycline we use it a lot more. So, the percentage resistant in the fecal strain are also very high.

So, we have up to 80 to 90 percent of fecal strains that are resistant to tetracycline. On the other hand, gentamicin is not used very commonly and that is the percentage resistance is also low. So, basically what we are hearing here in this particular plot is that if a community consumes one particular antibiotics at much higher levels, then the probability of finding microbes that are resistant to that particular antibiotic in the microbiome of the person is very very high.

Now, if you look here penciling tetracycline and konini over the years from 2002 to 2007, 5 years, within 5 years the percent resistance in Neisseria gonorrhoeae which is a sexually transmitted disease has increased quite so much specially for Pennsylvania and Cannolis.

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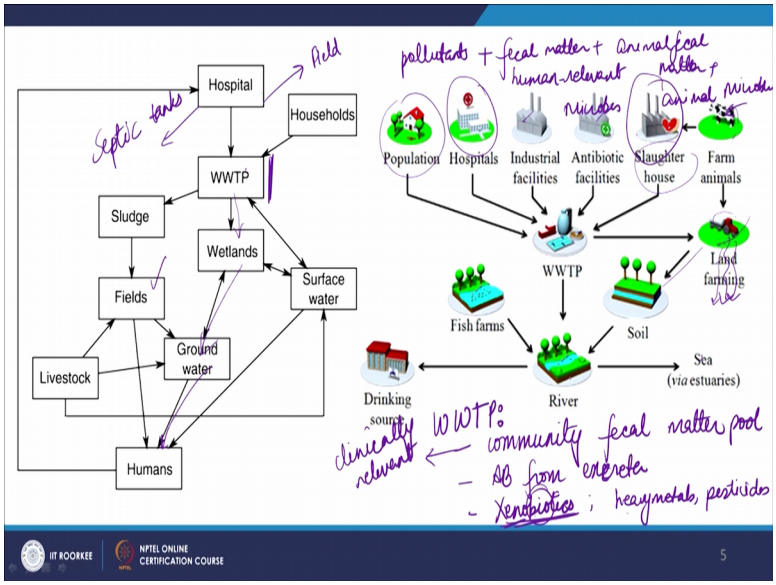

Now, this is how does antimicrobial resistance let us say the human being or the animal has been overusing, misusing, abusing antibiotics and has enriched antimicrobial resistance in its body. How does it transfer from one person to another, from one community to another. And nowadays it is been noticing from one country to another. Well, let us start from here humans are the ones consuming the antibiotics that they are the ones that are producing them and they are the ones falling.

So, let us say we have humans who fall sick. These sick humans will go to hospital in hospital they get antibiotics they become rich in antibiotic resistant gut microflora. So, the microbiome in their gut is now resistant to antibiotics. And ideally when they excrete, the executor goes to wastewater treatment plant which is not necessarily the case in India. In India if you draw the same diagram for India, we will have one arrow going to septic tanks. And then the open drain will have another arrow going to filled open defecation right, then they will have their own diagrams ok.

So, the, but ideally the excreta goes to waste water treatment plant, a wastewater treatment plant also received the household wastewater which includes kitchen grey water, and includes excreta the fecal matter from bathroom. Now, the wastewater treatment plant, once it has treated the water it releases the water in wetland. And there are recent studies showing that antibiotic or antimicrobial resistant genes or the genes that are that confer antimicrobial resistant to microbes, do not die necessarily in this water treatment plant in fact, many times they get enriched relative to the entire bacterial population.

So, now, they go to wetland and now the wetland will give the share this resistant microbes with groundwater which the human beings will drink and fall sick, but then will also share the surface water which humans might use as draw drinking water source and falls sick. The then the wastewater treatment plant the other thing that is produced is sludge. Now, the sludge is either applied in fields or it is dried and then burnt off. If it is applied in field, again it will affect the groundwater which will affect human health.

The other thing is instead of using humans consuming the instead of humans consuming the antibiotics, we also have beside human consuming antibiotics we have livestock and giving antibiotics. Life stripe livestock drop them manure their droppings in the field and then that affects the groundwater quality and that affects the human. Same thing here the livestock will swim in the surface of surface water body is like we have buffaloes enjoying the mud in wet mud near poor wetlands. So, now, they will also in fact, or populate the surface water bodies with resistant microbes. Similarly, the groundwater the field will eventually contribute to the groundwater contamination.

As a result we noticed that waste water treatment plant is our primary gate where we can put an end to antimicrobial resistance spread from the human perspective. The livestock

perspective the easy way would be because we cannot control the grazing of animals in we should not and how way how invade the poop is very hard to control. What we can do is we can put an end to prophylactic utilization of antibiotics for fattening the poultry and also for making sure they grow faster.

Now, here is a wonderful diagram showing the importance of wastewater treatment plant in antimicrobial resistance. The wastewater treatment plant is a very unique place why is it unique, first it is the community pool of fecal matter ok. So, the so we what we get here are very rich microbial communities that our gut microbial communities, because the entire communities fecal matter is collected together. The other thing we can also because this is the case though it is very nutrient rich fix sees a very nutrient rich bacterial often. So, these microbes are perhaps very happy enjoying the food.

The other thing is when people consume antimicrobials or antibiotics a very small proportion is actually absorbed in the body. A lot of it is and the one that is absorbed in the body is some good portion of it is actually excreted in the urine. So, we have urine and poop which actually do not sometimes antibiotics do not transform even when they are excreted out.

Waste water treatment plant also receive antibiotics from excreta of human beings. Many a times people have bad habit is and they actually directly pop the pill inside the inside the pot. So, we they receive direct antibiotics. Now, we have a coverage very rich microbial community from the community in the community fecal matter, all of them are clinically and really clinically relevant and also relevant to human health because they were from human bodies.

Now, they we also had a lot of antibiotics and we also a lot of other xenobiotics. Now, xenobiotics is a way of saying objects that bio life has not seen before xeno is the foreign something that is foreign to life on earth. So, we had novel drugs that life is not used to. Then we also have heavy metals pesticides and other things now these things are important to write down because they trigger they trigger expression of antibiotic resistance ba my bacteria might have ability to have proteins that give an antibiotic resistant, but might never express it. Now, put heavy metals in there and it turns that it turns the regulation on and they start expressing resistance to both antibiotics into heavy metals.

So, this is why wastewater treatment plant is considered as the one point most important point and the gate keeper for spreading the antibiotic resistance because wastewater treatment plant will receive community pool from or fecal matter from a large population they also received the wastewater from hospitals.

Now, remember hospitals already enriched in antibiotic resistance most of the people, and they do not they are not very rich in other microbes. See other thing that happens in wastewater treatment plant is there in under in activated sludge we increase the biomass a lot. So, the biomass is very much and then what we have is that the microbes they are in very close proximity with each other and they can share their genes very quickly and successfully very fast. So, the resistance travels from a resistant microbe to a susceptible microbe very fast within a wastewater treatment plant.

The other thing is industrial facilities, antibiotic facilities. What they do is they give it a lot of xenobiotics which again trigger promotion and trigger and promote antibiotic resistance. Next, we also have slaughterhouses that send a wastewater to way typical waste treatment plant. Now, the issue here is that less water waste often contains guts of the animals that have been slaughtered; and as a result they have lot of animal microbiome.

And now we have a very funny condition in wastewater treatment plant where we have pollutants the trigger resistance in antimicrobials against microtubules we have fecal matter. So, we have human man human relevant microbes which could be clinical pathogens also. The other thing we have is heavy metals and other contaminants of all including pollutant. Then we also have animal fecal matter an animal microbiome.

Now in the slaughterhouse, we get animals from the farm animals which are being fed antibiotic resistance. So, fatten them up to make them grow faster. So, you can slaughter them faster. And thus not only do they when is their slaughter do they affect the quality of water in wastewater treatment plant and how much antibody resistance genes it has. But also they do droppings in the on the grass and when they drop of the grass, we have land farming, soil, fish farms, river, drinking water, sea. So, this entire chain that comes here.

So, in land farming, we can do lead be they can be leaching of antibiotic resistance to the ground there could be a you know people children might be playing here and when they

play here they might get a scrap or two. And now they are antibiotic resistant microbes sitting here which might infect the children. The other possibility is that as I mentioned if it rains and not only percolation down the earth, but also the runoff so, but land farming will affect the soil which will also might also affect the river. And then the wastewater treatment plant open empties itself in the river, so now, all of these actually affect that quality of water in the river ok.

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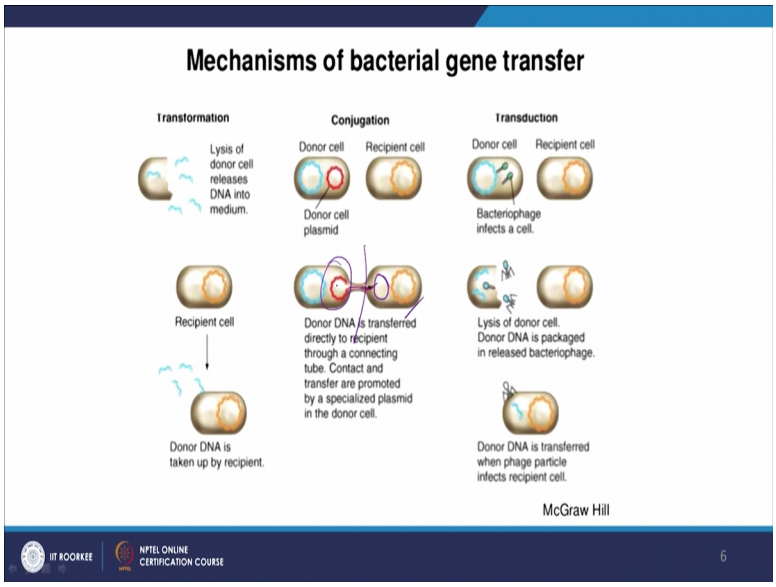

Now, I have been talking about transferring genes, sharing genes and if this is a revision from a previous lecture where we talked about different ways in which microbes share horizontal genes horizontally. One is transformational is conjugation and then via transduction. Transformation is when a bag migrate bacteria opens up pore in it is cell membrane to pick up an extracellular DNA. So, what they do is they pick up an extracellular DNA, and then they are happy, and they are poor closes again maybe.

The other is conjugation in conjugation they are two kinds of cell donor cell and recipient cell. So, the donor cell will now what it does is it, it opens the pillars comes into contact and then donates it donates the extra chromosomal material here they wanted to be shared to this. So, now, what we will have is this will come here or maybe at times there is just extends here, and this makes a copy of it; either case this will acquire the quality present in this extra chromosomal plasmid. Many a times we notice that antimicrobial resistance is actually present the plasmid, in that case it is very important

for us to stop this, so that the susceptible bacteria nor do not become resistant. Next is transduction which is carried through bacteria or through bacteria files or viruses. We have talked in depth about them ok.

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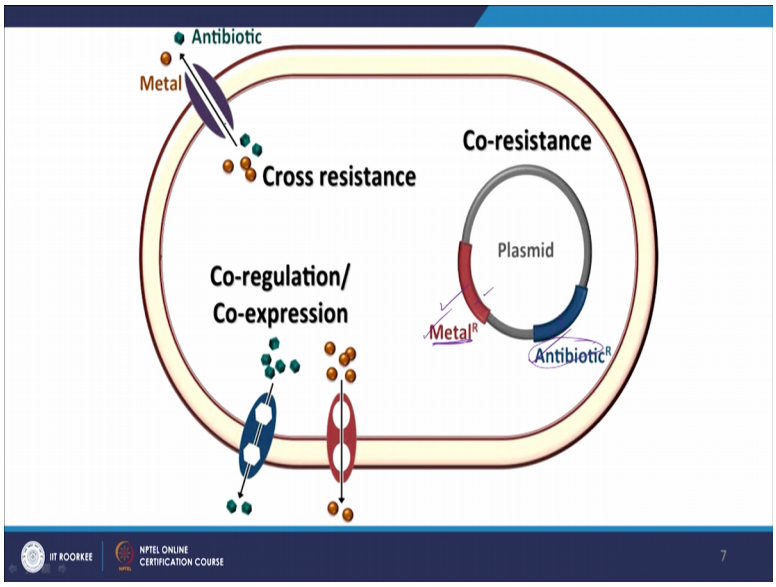

And this is another thing I would like you to know is cross resistance co resistance and co regulation co expression. So, in cross resistance, what we have is if microbes are have an ability to kick something, some other pollutant out of their body and that helps them survive and they use the same mechanism. So, mechanism that helps them resist some other contaminant is also helping them resist antibiotics, this is cross resistant. So, these efflux pump allow cell to kick out the metal and they use the same pump to kick out antibiotics together, they are happy antibiotics do not hurt the metals do not hurt them. So, example of cross resistance.

In co resistance let us say metal and antibiotics their genes that are resistant that give resistance to metals and give resistance to antibiotics are in the same plasmid or are next to each other same operand. When this gets expressed this also gets expressed. So, if a microbe operon community, community is exposed to heavy metals and this is triggered then that community will automatically become resistant to antibiotic are also this is co-resistance.

Now we have co-regulation and co-expression in which when proteins are helping to protect it from one particular in contaminant they also trigger proteins that will help it

another it against another contaminant. So, in this case, the efflux pump is not the same, but they both are regulated and expressed together. So, dear students this is all for today. In next lecture, we will continue antibiotic on talk on antimicrobial resistance and particularly focus on how it pertains to India.

Thank you very much.