Emerging Infectious Diseases and Antimicrobial Resistance
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Lecture – 11
Antimicrobial Resistance
A Global Threat and Importance of Antibiotic Stewardship Program

I am Dr. Kamini Walia and I coordinate the Antimicrobial resistance initiative at the Division of Epidemiology and Communicable Diseases at Indian Council of Medical Research. Today, I will be talking to you about why antimicrobial resistance is a global threat and the importance of Antimicrobial stewardship and its containment.

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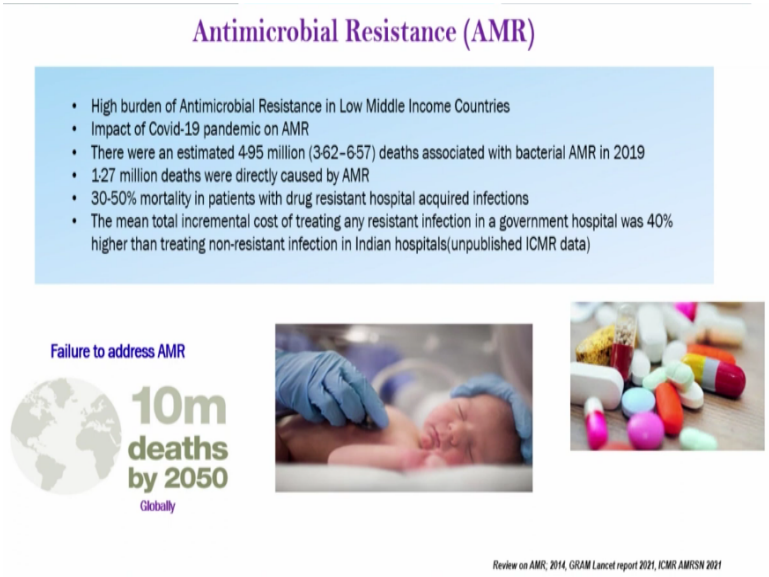

So Antimicrobial resistance there is a high burden of it in low middle income countries and following the Covid pandemic, there has been heightened concern around the increasing threat of antimicrobial resistance. As per one of the reports which was recently published this year, which documented the disease burden related to AMR from 2019, it was estimated that AMR claimed 4.95 million lives in 2019 out of which 1.27 million deaths were directly caused by AMR.

From our experience in Indian hospitals, we see that almost 30 to 50 percent mortality is caused in the patients who acquire drug resistant pathogens. At the same time, the mean incremental cost for treating drug resistant infection in government hospital in India was found to be 40

percent higher than the non-resistant infections in the Indian patients.

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So, what antimicrobial resistance is threatening is that it is threatening the advances that we made in the control of infectious diseases collectively, not just in our country but globally. Because of the high burden of AMR in low middle income countries, all our programs like malaria, HIV, tuberculosis they are getting affected. In addition, we are seeing the increasing burden of hospital acquired infections with drug resistant pathogens.

Which are now complicating even the simple treatments and procedures like cesarean sections, joint knee replacement or any other joint replacement surgeries. So, these pathogens are actually lurking in our hospitals as invisible threats, and they claim invisible lives. The reason I call them invisible is that there is no system which is currently recording how many deaths in our hospitals are happening because of the drug resistant infections.

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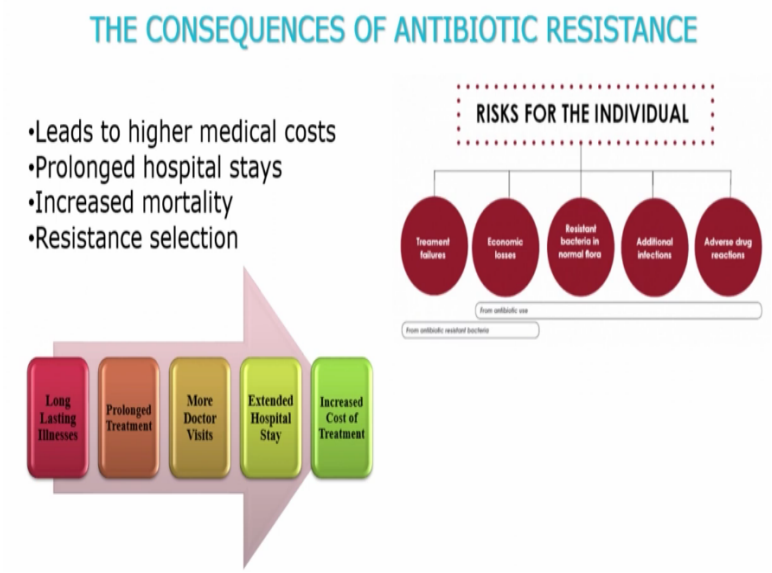

So, what are the consequences of antibiotic resistance? There are consequences both for the patient and for the healthcare system. It leads to higher medical costs for the patient. Many a times, the patients are meeting these costs from their pockets. Then there are prolonged hospital stays. There is increased mortality and there is also increased selection of further resistant pathogens, which amplify and increase the threat of infections in future.

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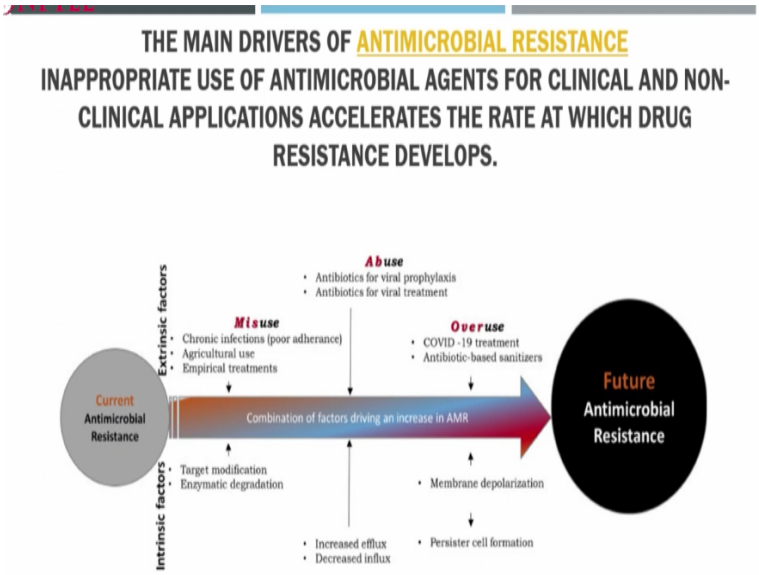

Now, what are the main drivers of antimicrobial resistance? There is one key driver of AMR and which is the inappropriate use of antimicrobial agents, whether clinical or non-clinical. They accelerate the rate at which the drug resistance develops which includes the misuse, abuse and

the overuse. COVID pandemic saw extensive overuse of antimicrobials and also added to it was hand sanitizers.

Sometimes they were antibiotic supplemented hand sanitizers. So, all these would have led to development of drug resistant pathogens and we really need to maintain a close watch on how this particular field kind of changes with time.

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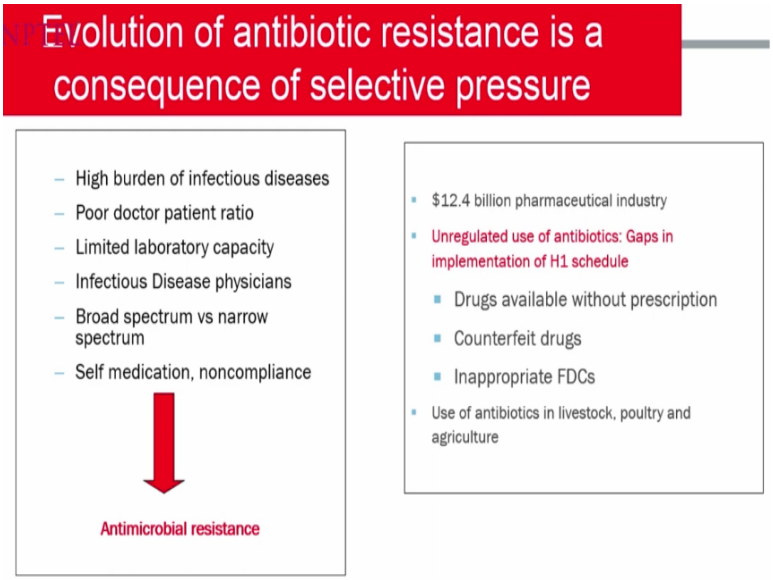

So, otherwise there are many factors in our healthcare system, both the social, the economic as well as the clinical factors which actually contribute to development of selective pressure, which results in development of resistance. We are a tropical country with the high burden of infectious diseases. There is poor doctor to patient ratio, limited laboratory capacity, all this are a reflection of poor investment in the healthcare system.

The ID physicians, clinical pharmacists, infection control nurses are essentially not there in most of the hospitals. Then we also use a lot of broad spectrum antimicrobials compared to the narrow spectrum antimicrobials, added to that is a patient behavior of self-medication, noncompliance. So, all these factors, the socioeconomic factors also contribute to development of resistance. Besides this, we are pretty big, 12.4 billion pharmaceutical industry.

The unregulated use of antibiotics is encouraged by the gap in the implementation of our

regulatory system. The drugs are available without prescription. Then there is a problem of counterfeit drugs, inappropriate fixed dose combinations and also extensive use of antibiotics in livestock, poultry and agriculture.

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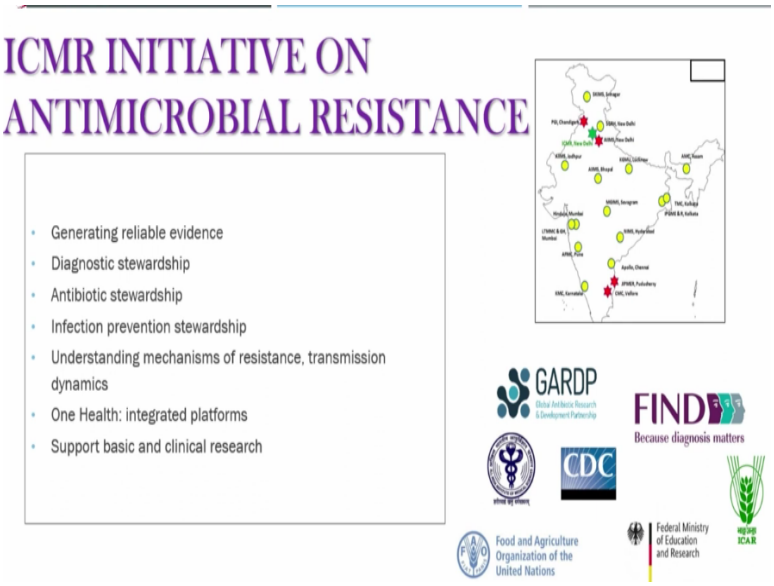

So ICMR's AMR initiative actually focus on generating reliable evidence, improving the diagnosis by strengthening the diagnostic stewardship, working with hospitals to create systems of antimicrobial stewardship, working with hospitals to strengthen the infection prevention and control practices, funding research on understanding mechanisms of resistance, transmission dynamics.

We work with the relevant stakeholders to create integrated One Health platforms as well as support basic and clinical research. We work with large number of hospitals within the country and also large number of international organizations on different aspects of AMR.

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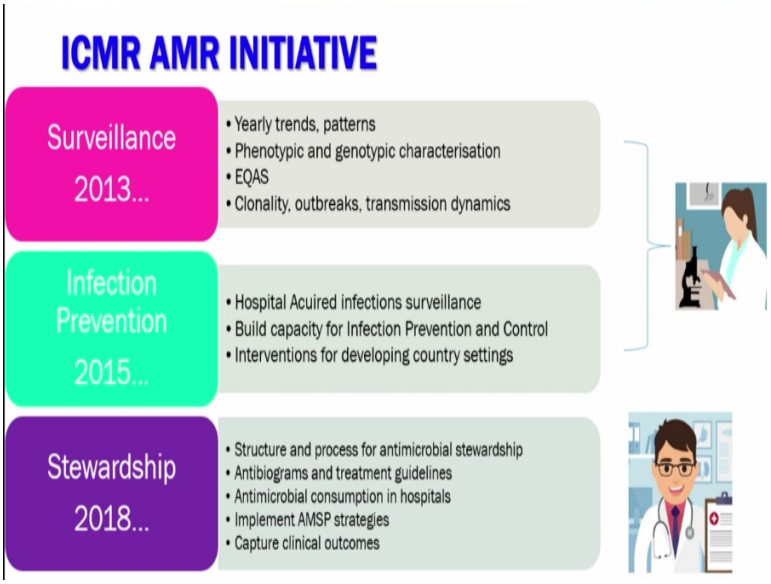

So the first initiative was the Surveillance initiative which started in 2013 and the aim was to capture the yearly trends and the patterns of AMR, undertake the phenotypic and genotypic characterization, external quality assurance system as well as track clonality, outbreaks and transmission dynamics. In 2015, we added to it the infection prevention control program. We set up a first hospital acquired infection surveillance in the country.

We also initiated systematic training programs to build capacity for infection prevention control as well as both the programs on IPC and the stewardship. They focus at developing customized interventions which are relevant to the developing country settings which can be implemented in our country. Antimicrobial Stewardship, we added in 2018. One of the first few initiatives was to carry out training of the doctors on antimicrobial stewardship.

This was followed by establishing the structure and process of antimicrobial stewardship which included creating anti bigrams for hospitals helping them create their own treatment guidelines. We also created a system to capture antimicrobial consumption in these hospitals. Now, we are implementing MSP strategies including capturing clinical outcomes for drug resistant infections in our country. So, this will provide us a very valuable data, which will be based on evidence within the country setting.

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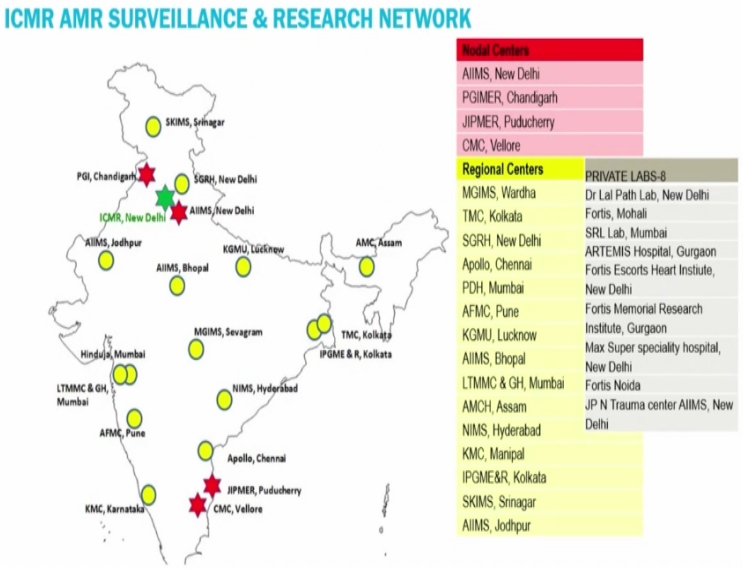

So, we work with almost 30 hospitals and labs across the country.

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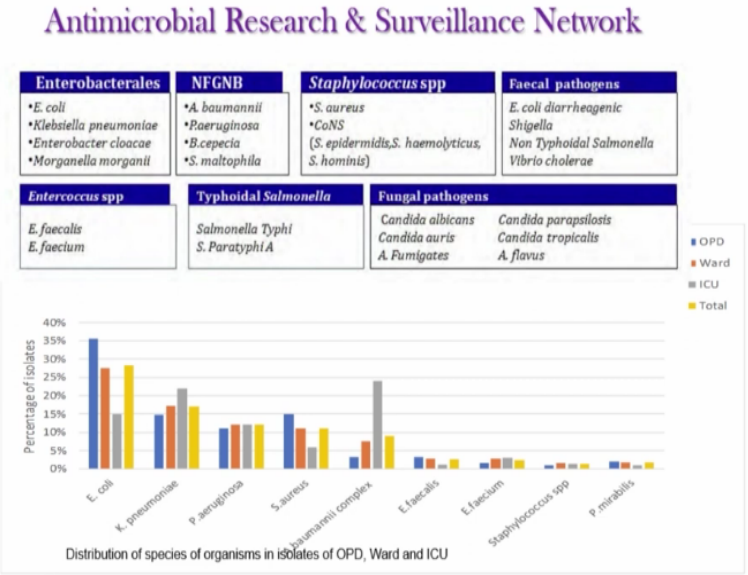

And these are the pathogens that we are focusing on. Enterobacterales, gram negative non fermenters, Staphylococcaceae, fecal pathogens like E. coli, Shigella, non Typhoidal Salmonella and Vibrio cholerae, Enterococcus faecium and faecalis, Salmonella Typhi and also a lot of fungal pathogens are now being reported by our network because we have systematically built the capacity of the hospitals in our network to report fungal pathogens. Yet, gram negative organisms cause the large proportion of drug resistant infections in our country and they are becoming very challenging to treat.

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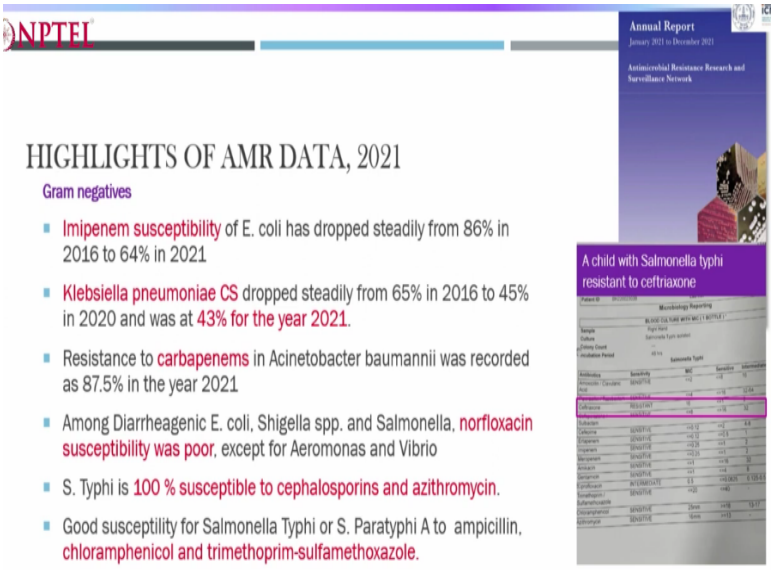

For example, the imipenem susceptibility for E. coli has dropped steadily from 86 percent in 2016 to 64 percent in 2021. Klebsiella pneumoniae carbapenem susceptibility has dropped from 65 percent in 2016 to 45 percent in 2020 and was at 43 percent for 2021. We publish this data every year and every year's report can be found on the ICMR website. So, resistance to carbapenems actually has been increasing by 5 to 10 percent every year for all these pathogens.

And Acinetobacter recorded resistance rates at 87 percent for the year 2021 which was very alarming. For the diarrheagenic pathogens we have, the data indicates that the norfloxacin susceptibility was poor. Salmonella Typhi they continue to remain susceptible to cephalosporins, azithromycin, chloramphenicol, Trimox, Co-trimoxazole as well as ampicillin. Once in a while, we do come across such reports as you can see in this report.

This is from a 10-year-old child reporting resistance to ceftriaxone. So, there is a need to continuously monitor how the pathogens are evolving and how this data should be utilized to guide treatment strategies across hospitals.

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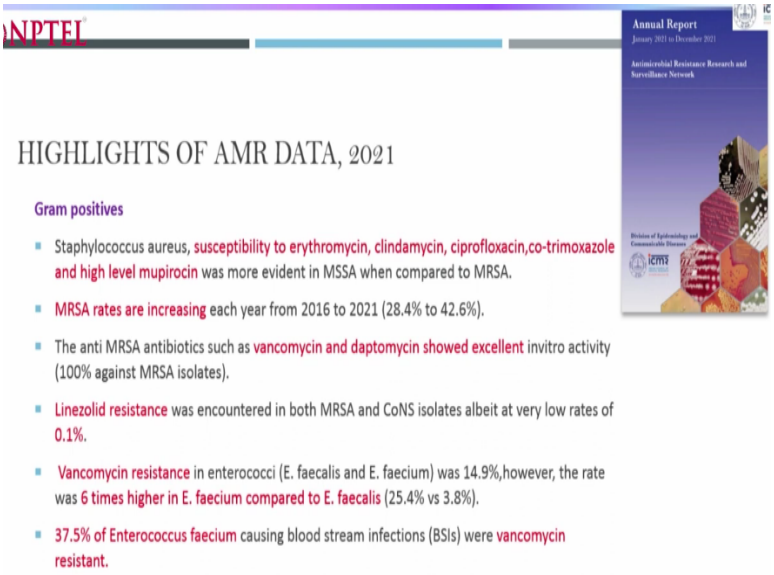

Staphylococcus aureus, the susceptibility to erythromycin, clindamycin, ciprofloxacin, co-trimoxazole and high level mupirocin was more than MSSA as compared to MRSA. MRSA rates have increased and they are increasing each year. Last year we recorded 40 percent MRSA out of the total stuff isolates. Vancomycin and daptomycin continue to show excellent activity. Linezolid resistance is increasing, although very low rates. Vancomycin resistance is alarming, it was around 14 percent or 15 percent, 6 times higher in Enterococcus faecium as compared to faecalis. So, Enterococcus is an important bug which should be monitored in future.

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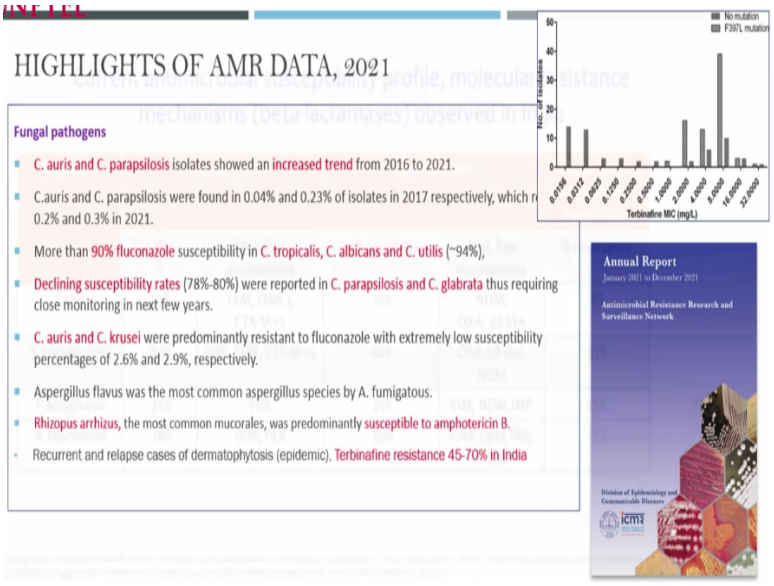

A lot of our centers are also reporting fungal pathogens now. The fluconazole susceptibility is

around 90 percent among Candida tropicalis, albicans and utilis. Declining susceptibility rates were reported in Candida parapsilosis and glabrata, Candida auris reporting rates have increased and they have very high resistance levels to fluconazole, an extremely low susceptibility of 2.6 percent. So, this is something that needs to be monitored.

And attempts should be made to identify Candida auris early so that the treatment can be guided accordingly. Otherwise, the only excessive use of antifungals will only contribute to the increasing problem of antifungal resistance. Rhizopus arises the most common mucorales predominantly susceptible to amphotericin B. There are recurrent and relapse cases of dermatophytosis which are reported and terbinafine resistance is almost at 45 to 70 percent in India.

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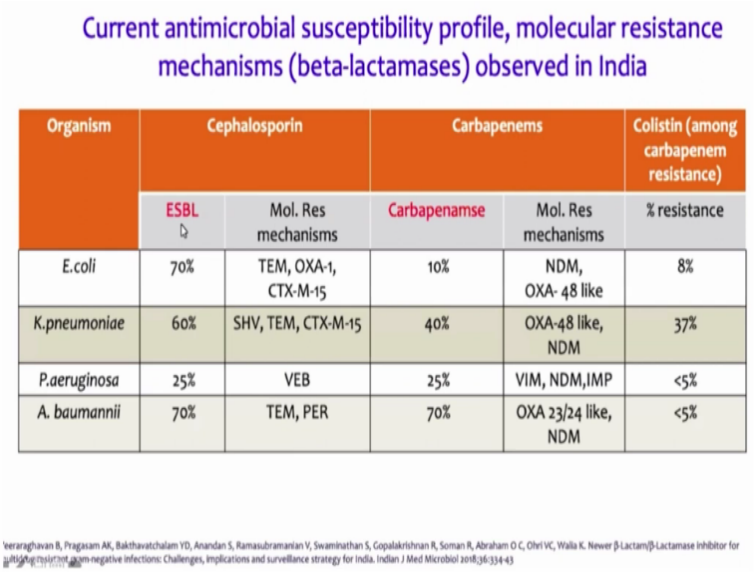

We also look at the mechanisms of resistance. These are the mechanisms of resistance which are currently operated in four important pathogens which is E coli, Klebsiella pneumoniae, Pseudomonas aeruginosa and Acinetobacter baumannii. And E. coli has recently acquired penicillin binding protein three and many of the drugs which are in the pipeline or which are to be introduced in India recently will not be effective against these mechanisms of resistance. So, it is very important to continue to characterize the mechanisms of resistance that are prevalent in the country so that helps us in deciding the treatment strategies for our patients.

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Table I: Difficult to treat drug resistant pathogens in Indian hospitals

	Group I	Group II	Group III
Pathogens	• Carbapenem Resistant Enterobacterales • Carbapenem Resistant *A. baumannii* • Drug resistant *Salmonella* Typhi • *Candida auris*	• ESBL producing Enterobacterales • Multidrug resistant *P. aeruginosa* • Vancomycin-resistant enterococci, • Azole Resistant *Candida* spp	• Methicillin Resistant *Staphylococcus aureus* • Azole resistant *Aspergillus fumigatus* • Amphotericin B resistant *Aspergillus flavus* • Drug-resistant *Stenotrophomonas maltophilia* • Colistin Resistant Enterobacterales • Colistin resistant *Acinetobacter* spp.
Action required for containment	Aggressive action	Sustained action	Continuous monitoring and prevention efforts

Now, based on the data for last 4-5 years, these are the priority pathogens for India. Carbapenem resistant Enterobacterales, carbapenem resistant Acinetobacter baumannii, drug resistant Salmonella Typhi and Candida auris, they require aggressive action. Similarly ESBLs, vancomycin-resistant enterococci, azole resistant Candida they require sustained action and we need to continuously monitor the MRSA azole resistant Aspergillus, Amphotericin B resistant Aspergillus flavus, drug resistant Stenotrophomonas maltophilia, colistin resistant Enterobacterales as well as colistin resistant Acinetobacter species.

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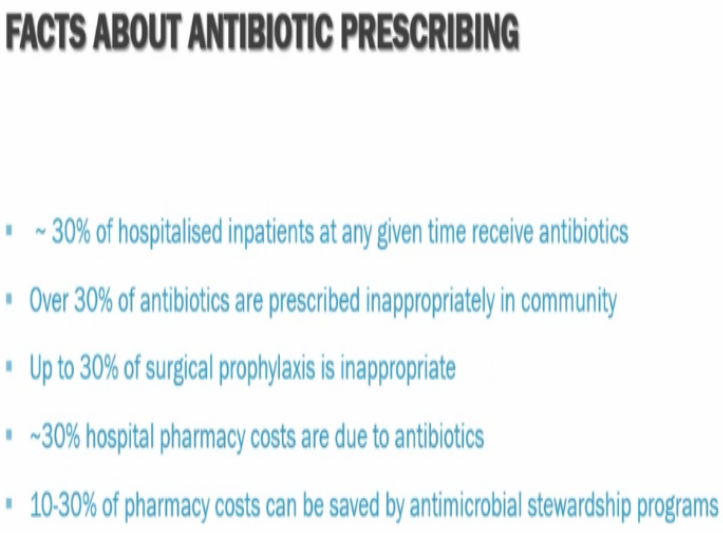

Now we are going to digress a little bit and see what kind of practices prevail as far as

antimicrobial prescribing is concerned in our country. So, these are the global figures, 30 percent of the hospitalized inpatients at any time receive antibiotics when they are in the hospital. Over 30 percent of these antibiotics are prescribed inappropriately in community, 30 percent of surgical prophylaxis is inappropriate, 30 percent of pharmacy costs are due to antibiotics and 10 to 30 percent of pharmacy costs can be saved by a good antimicrobial stewardship program.

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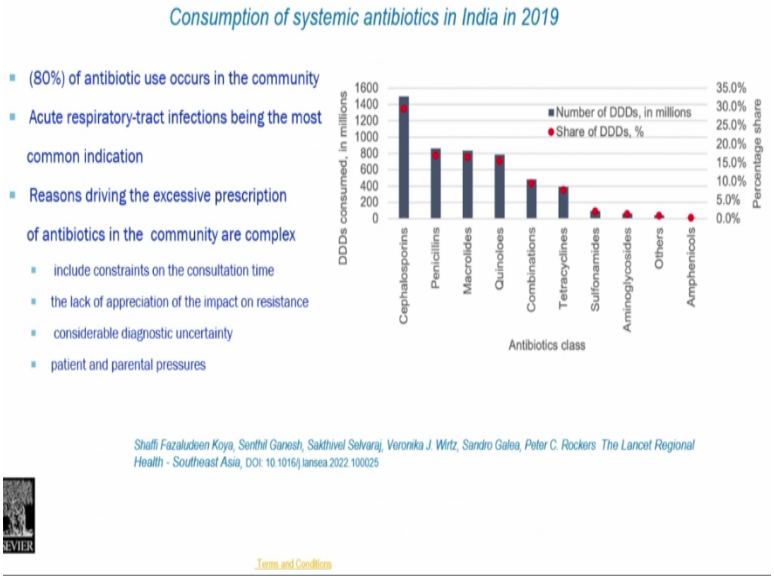

What we see is that in our community 80 percent of the antibiotic use occurs there and acute respiratory infections are the most common indication. And there are many reasons which drive antibiotic use in a community which includes constraints on the consultation time of the physician, lack of appreciation of impact of the resistance, this is most common in the physicians as well as in the community.

Considerable diagnostic uncertainty because of the poor laboratory infrastructure, absence of point of care diagnostics and then all kinds of patient and parental pressures to prescribe antibiotics. Now, the bar diagram on the right side shows the consumption of antibiotic in India and as you can see the physicians in India, they love to prescribe cephalosporins. The broad-spectrum antimicrobials are effective against both gram positive and gram negative.

And if you would break this down cephalosporins into the generation wise you would see that higher generation cephalosporins are also prescribed a lot.

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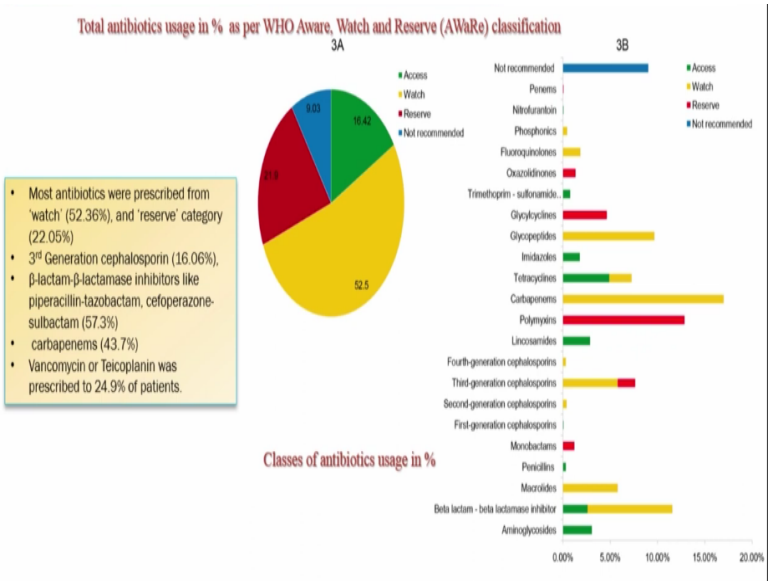

We also saw this happening during the COVID times. What we saw was that most of the antibiotics were prescribed are broad spectrum antibiotics from the Watch and Reserve group of WHO classification and the piperacillin- tazobactam, carbapenem, vancomycin they all were prescribed indiscriminately in the hospitalized COVID patients.

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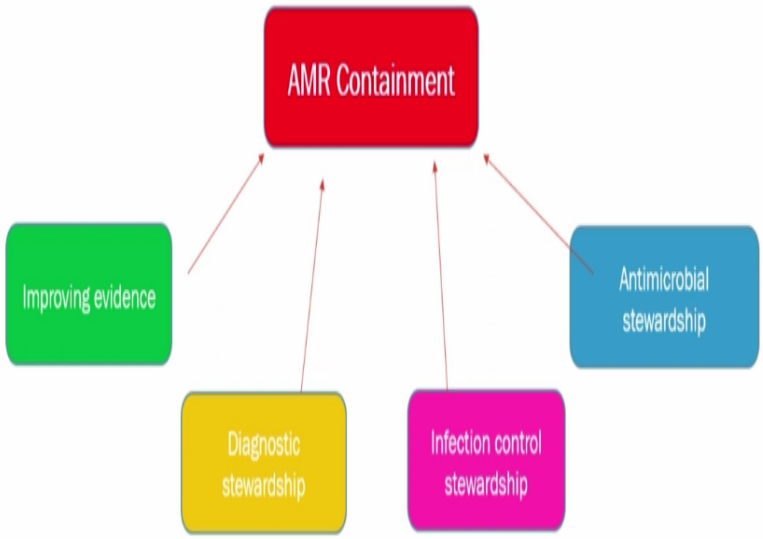

Now how can we move towards AMR containment? The first and foremost is improving the evidence on the ground which we are already working on. Improving the diagnostic stewardship and infection control stewardship. Without these two, antimicrobials stewardship cannot stand on

its own. Because for physician to prescribe antimicrobials responsibly, he would need a diagnostic test report which he can trust like what is the pathogen that is there in the infection and also what is the infection rate within a hospital or in a community.

Most of the time, what we see is that antimicrobials are being prescribed to compensate for a poor infection control whether it is in a community or whether it is in a hospital. Whenever the physicians do not trust the hospital's infection control system, they are more likely to prescribe more than two or three antibiotics to his patient because no physician wants to lose the patient.

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So antimicrobial stewardship is essentially a coordinated set of interventions which are designed to improve and measure the appropriate use of antimicrobial agents by promoting selection of optimal antimicrobial drug regimen including the dosing, duration and the route of administration.

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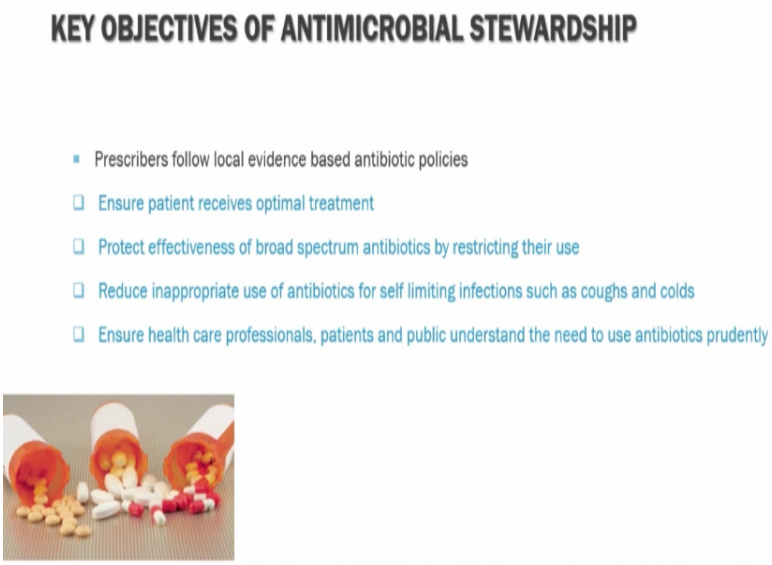

So, the antimicrobial stewardship practice ensures that the patient receives an optimal treatment. It also aims to ensure the effectiveness of broad spectrum antibiotic by restricting its use in the long run. Reduce inappropriate use of antibiotics for self-limiting infections like cough and cold. Ensure that healthcare professionals, patients as well as public they all understand that antibiotics need to be used responsibly and prudently.

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Now, the Australian Commission on safety and quality healthcare they prescribe following four practices which should be considered and which are considered desirable as per the available resources. Education of prescribers, pharmacists and nurses about good antimicrobial prescribing

practice, use of point-of-care interventions, streamlining of and de-escalation of therapy, dose optimization or parenteral to oral conversion.

Using of IT systems such as electronic prescribing with the clinical decision support or online approval systems and annually publishing the facility specific antimicrobial susceptibility data and this is the most important and every hospital should try to have their own antibiogram and have an antibiotic policy based on those antibiograms.

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Now, antimicrobial stewardship for a long time was considered only the microbiologist's business, but the microbiologist's role is only limited to providing antibiogram for local antibiotic policy. Beyond that, administrators need to provide the logistic support, the doctors need to prescribe antibiotics following local policy, nurses have to monitor the antibiotic administration in a timely manner.

Prompt review, therapeutic drug monitoring and adverse reaction monitoring as well as a very important role in infection control and the pharmacists are needed to ensure antibiotics are prescribed as per policy, provide prompt review and advise on therapeutic drug monitoring results.

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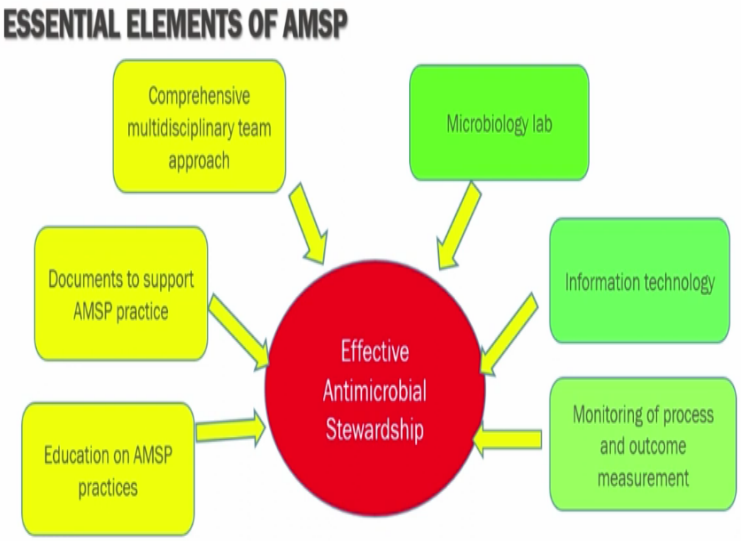

Now, these are the key elements of antimicrobial stewardship. There has to be a microbiology lab, there has to be an IT system which will be helpful in dissemination of resources like antimicrobial stewardship guidelines, treatment guidelines which a hospital has, then a system to monitor the process and outcomes that should be measured to monitor the process and its implementation.

A comprehensive multidisciplinary team is needed as I mentioned in my previous slide. Then there should be resource materials to support AMSP. If the doctor does not have a policy to fall back on, what is he going to prescribe and based on what and education and awareness of the hospital staff on antimicrobial stewardship has to be a continuous process.

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These are the two key pillars of antimicrobial stewardship strategies. First is the prospective audit and feedback. This is when a doctor is supported to prescribe whatever he wants to prescribe, but within 24 hours, he has to justify why I am prescribing this particular medicine and he is also provided feedback by the pharmacist on an ID physician on his prescription. The second is formulary restriction and pre-authorisation. Under this system, no doctor can prescribe a certain drug something like a colistin.

Most of the hospitals like to add colistin formulary restriction without having approval from the senior person or someone who has been delegated this responsibility. This is sometimes not favored well in the Indian hospitals as it restricts the autonomy of the doctors to prescribe medicines and prescriptive audit and intervention and feedback is actually more practiced and more favourable, but it is again a very resource intensive exercise.

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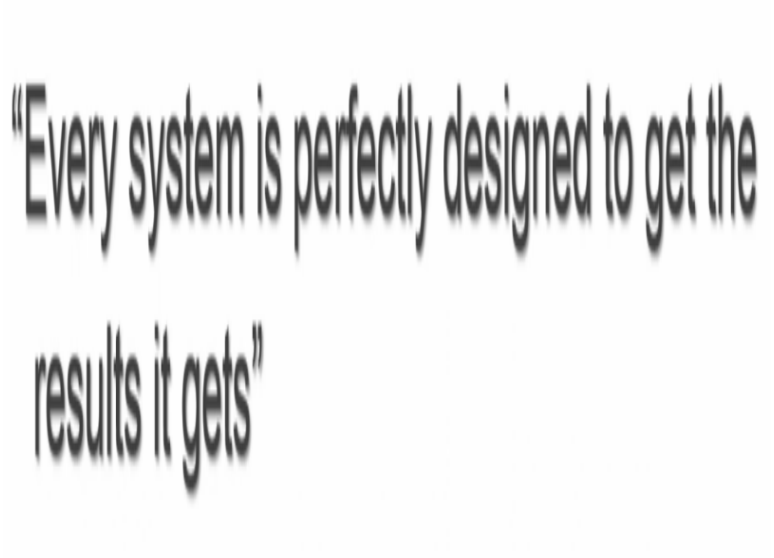

Not every system is perfectly designed to get the results that it gets.

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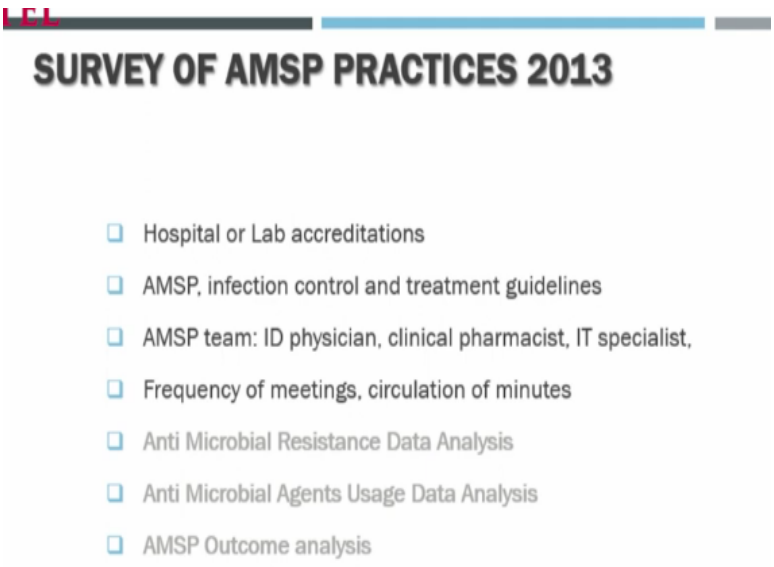

What we found in our survey that we undertook in 2013 was that many hospitals we surveyed, almost 26 hospitals, for availability of accreditations, AMSP, infection control and treatment guidelines, whether the AMSP teams were available. And even when these committees were available, how frequently did they meet? Did they undertake the AMR data analysis? Did these hospitals analyze their antimicrobial usage data analysis or did they undertake the AMSP outcome analysis?

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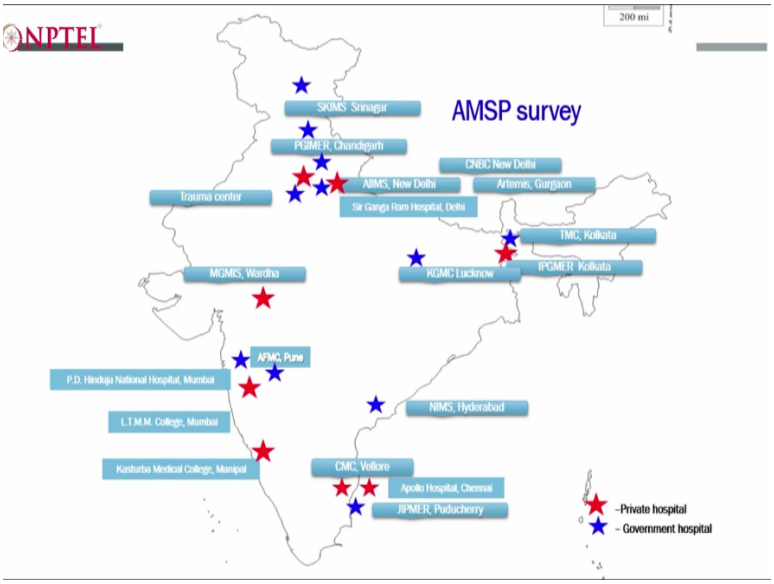

These are the hospitals, many private and government hospitals participated in it.

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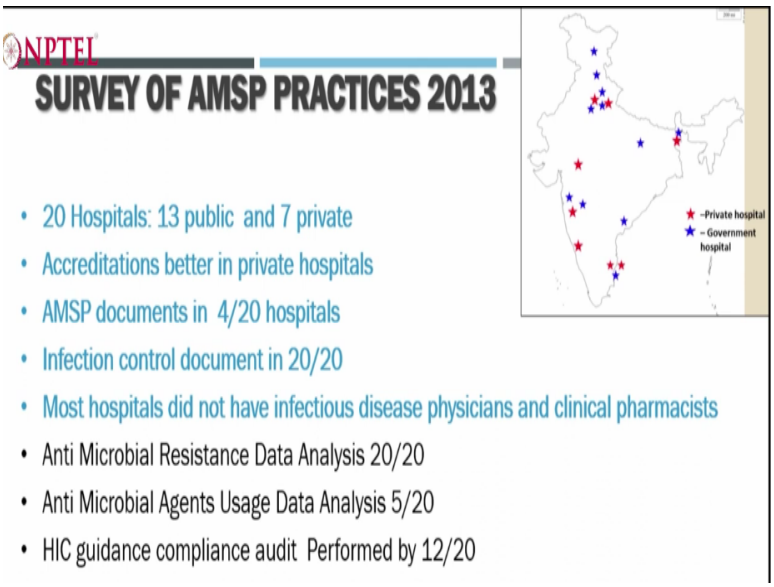

What we found that accreditations were better in private hospitals maybe because that is their requirement to deliver the kind of services that they do. AMSP documents were found only in 4 hospitals, all of them were private. Infection control document was available in all the hospitals. Only private hospitals had ID physicians and clinical pharmacists and most common government or any government hospital did not have that.

Antimicrobial resistance data analysis was being done by all the tertiary care hospitals who

participated in this program. Antimicrobial agent usage data analysis was being done only by 5 out of the 20 and HIC compliance audit was performed only by 12 out of the 20 hospitals.

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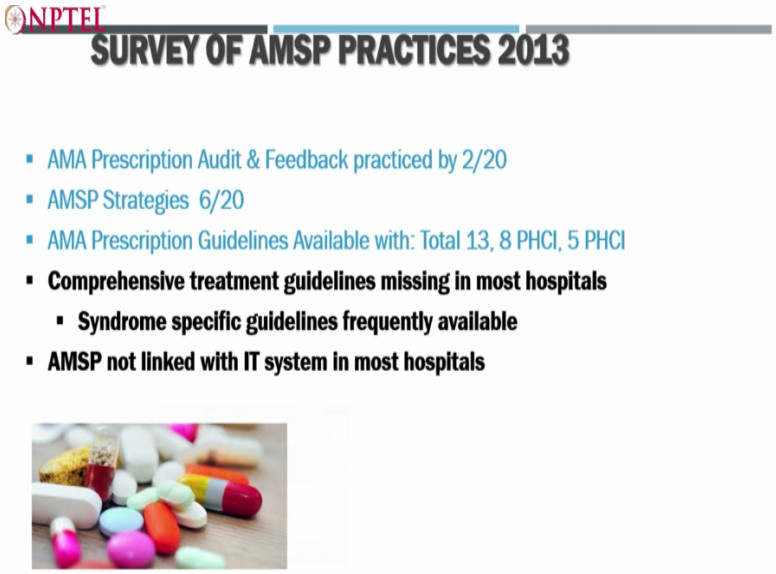

Now, the key pillars of AMSP practice which I discussed just now, the prescription audit and feedback was being practiced only by 2 out of the 20. And other AMSP strategies which were very different were being practiced only in 6 out of the 20 hospitals. AMA prescription guidelines were available with total 13 hospitals out of which 8 were private and 5 were government hospitals and comprehensive treatment guidelines were missing in most hospitals, although syndrome specific available guidelines were available. AMSP was not linked with an any IT system in most hospitals.

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So following this ICMR initiated systematic capacity building program for antimicrobial stewardship. We invited a 5-member team from all hospitals which included an administrator, a physician, a microbiologist, a clinical pharmacist and infection control nurse. We trained this 5-member team from each hospital on AMSP.

We did 5 workshops across the country and almost trained more than 60 medical colleges and hospitals, both from government and private on AMSP. So, in a nutshell almost 3 to 400 staff were trained and with a small funding we initiated AMSP projects in ICMR-AMR network. The latest treatment guideline was published in 2019.

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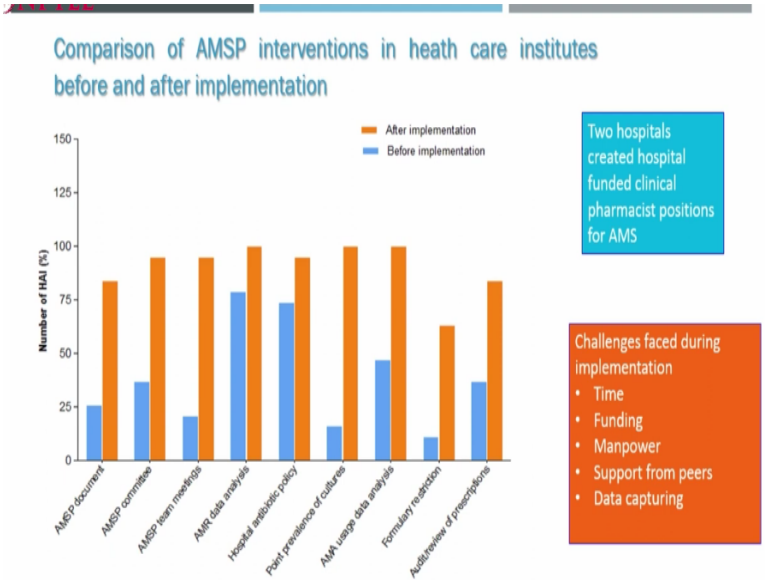

And what we found was that there was significant improvement in the practice of antimicrobial stewardship after we initiated it in a project form. Almost all hospitals now had AMSP document and AMSP committees. They were meeting regularly as well. AMR data analysis was being done by 100 percent of the hospitals. Hospital antibiotic policy was created by all the hospitals who participated in this program.

The point prevalence of cultures which was being done only by 10 percent hospitals earlier was now being done by 100 percent hospitals. Antimicrobial agent usage data analysis was being done by all the hospitals. More than 70 percent hospitals include formulary restrictions. And also 2 hospitals created the permanent post of a clinical pharmacist following the implementation of this program. The challenges faced in implementation was the time which was available because the PI for all these projects were clinicians or intensivists.

So, time that they have to give to this kind of a project monitoring is very limited because they have lot of clinical and administrative responsibilities. Then sustaining the funding after the completion of the project was a challenge. Manpower was difficult to get specially in the government funded hospitals. The support from peers sometimes was not there and the data capturing modules were cited as one of the key challenges by most of the hospitals.

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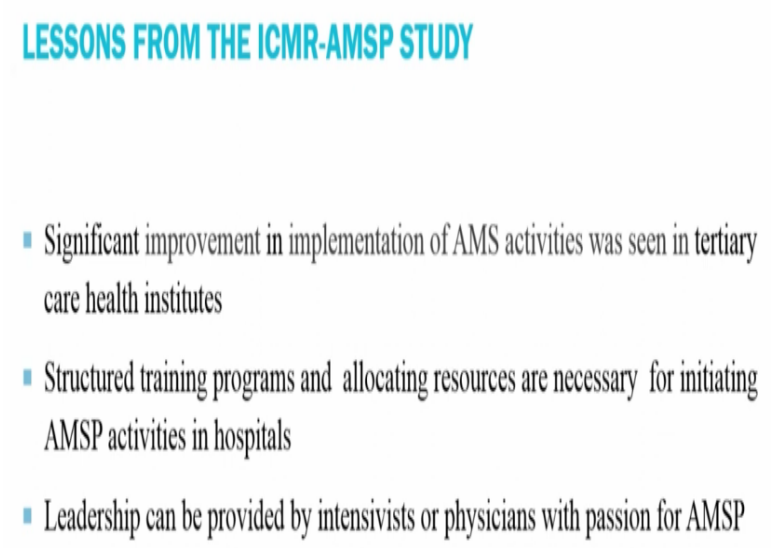

So what we learnt from doing the small study, although it was interrupted by COVID, was that there was significant improvement in implementation of AMS in tertiary care institutes. The structured training programs and allocating resources are necessary for initiating AMSP activities in these hospitals. Most of the hospitals do not have ID physicians. So, in absence of ID physicians, the leadership can be provided by intensivists or physicians who have passion for AMSP.

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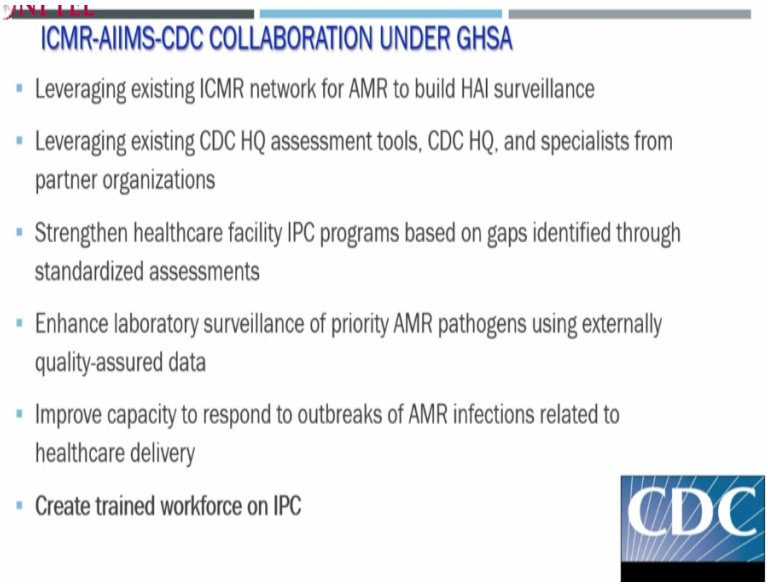

For infection control, we have a collaboration with CDC under which we are trying to create a trained workforce on infection prevention and control in these hospitals so that the IPC rates are

less. There are less rates of Klebsies or catheter associated UTIs thus requiring less antimicrobial prescriptions.

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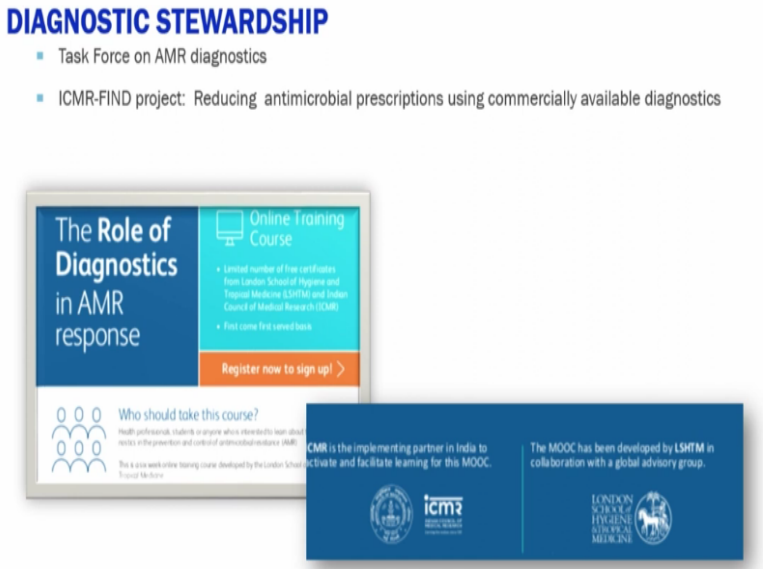

Now we are also working to strengthen Diagnostic stewardship. We have a taskforce on AMR diagnostics in which we are trying to identify any innovative products which have been developed within the country and which can be introduced in the system, which can improve the reporting of infections, their AMST patterns as well as creating target product profiles doing the cost effectiveness studies of using diagnostics so that this data is available from India.

With FIND, we are working on a project which is looking at reducing antimicrobial prescriptions using commercially available diagnostics. In collaboration with London School of Hygiene and Tropical Medicine, we also created an online training course on the role of diagnostics in AMR response and this course goes live every year in the antimicrobial awareness week and many Indian microbiologists and physicians have benefited and participated in this course.

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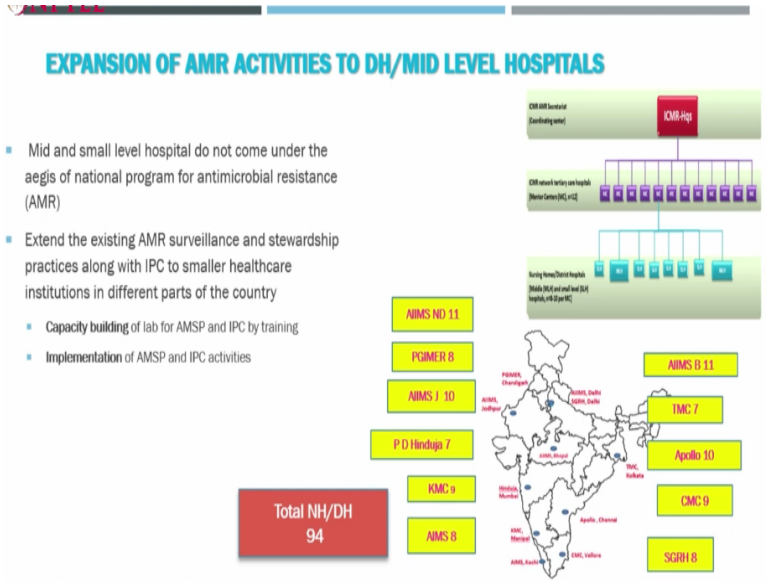

Now, having done a lot of work in the tertiary care hospitals, we are expanding this initiative to the mid level hospitals, which includes the district hospitals and nursing homes. Now, this initiative is so important because most of the time the tertiary care hospitals receive the patients who have had previous hospitalizations and had surgeries and had treatments from the secondary level hospitals. There is no awareness on antimicrobial stewardship or IPC. So, we are working with almost 90 to 94 nursing homes and district hospitals as a part of this activity.

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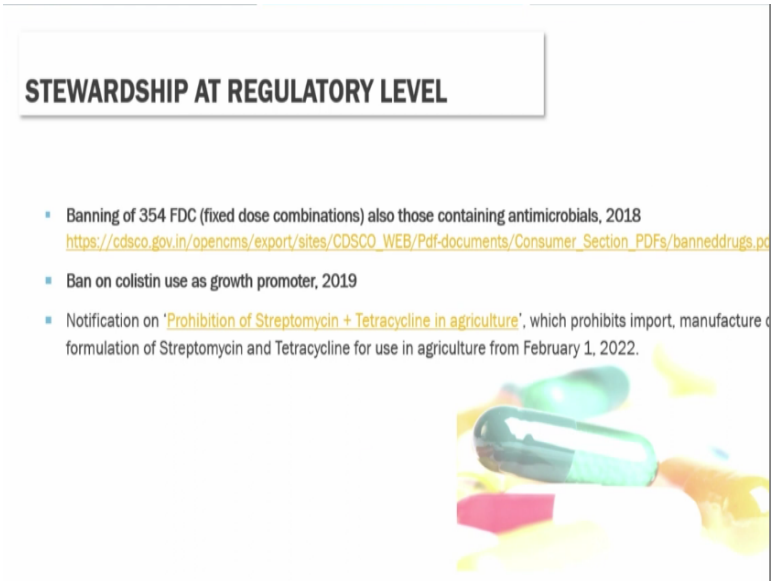

Government has also taken cognizance of the fact that there needs to be a regulatory oversight on availability of antimicrobials. On the advice of ICMR, government banned 68 fixed drug

combinations in 2018. There was a ban on colistin for use as growth promoter in 2019 and recently there was a notification on prohibition of streptomycin and tetracycline in agriculture because this particular combination negatively impacts our TB control program, so this regulatory stewardship is obviously very important.

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Government has fixed standards for the tolerance limits of antibiotics in seafood, however, the one in the poultry is still not done because there is an extensive use of antimicrobials in poultry as well. Then the central pollution control board is also trying to create standards for direct discharge of antibiotic emission by pharma sector and they are trying to develop standards for antibiotic residues in effluents.

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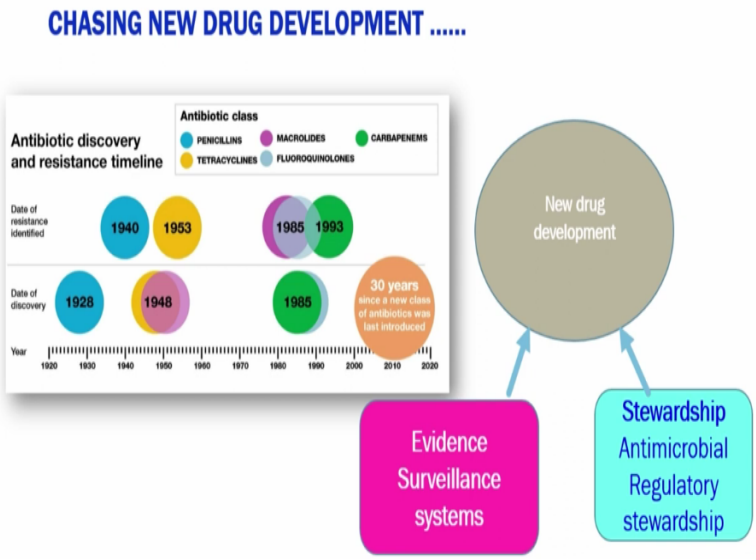

So, we need new drugs for the patients and for 30 years there has not been a new product which has been introduced in the market. We also have large burden of gram-negative infections and we would really need new treatment molecules for treating these patients who have extensively drug resistant pathogens. But the truth is that it makes more sense to use responsibly and judiciously what we have today.

And that is why we need a strong antimicrobial stewardship program because a bird in hand is better than two in the bush. Development of antimicrobials is a very resource intensive exercise. You can invest billions of dollars in new drug development and you may find that within 2 years that drug has developed, the pathogens have developed resistance to that drug. So, while we look for new drugs, new drug molecules, we must strengthen the antimicrobial stewardship program within our country so that we judiciously use what we have today.

We have seen in typhoid that when the drugs like amoxicillin, co-trimoxazole, chloramphenicol was not used for 20 years, we have seen that they have again become sensitive to those drugs. So, it clearly conveys that extensive drug use is one of the key drivers of antimicrobial pressure which leads to development of drug resistant pathogens and using judiciously the antimicrobials in what we have today is our best chance to survive the pandemic of antimicrobial resistance.

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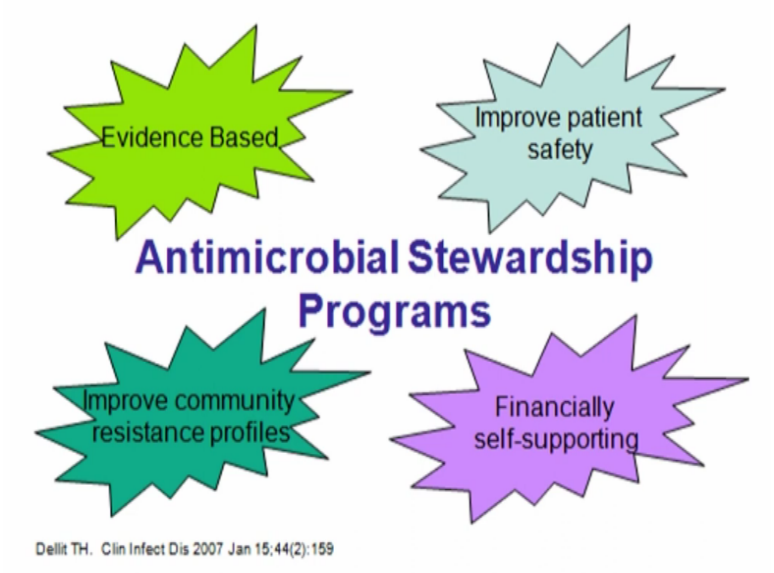

Antimicrobial stewardship does sound like a very intense program which is both resource intensive, it requires training, but the countries who implemented the evidence based AMSP program they improved the patient safety profile, they improved community resistance profiles and in the long run they found that it made financial success as well.

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So, we need to take the threat of antimicrobial resistance seriously today, otherwise we will miss on 18 targets out of the 9 Sustainable development goals that we want to achieve as a country as well as globally. Thank you.