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Pharma Tab

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Antimicrobials And Its Resistance

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What does antimicrobials and antibiotics mean?

The word antimicrobial was derived from the Greek words anti (against), mikros (little) and bios (life) and refers to all agents that act against microbial organisms. This is not synonymous with antibiotics, a similar term derived from the Greek word anti (against) and biotikos (concerning life).

The word "antibiotic" refers to substances produced by microorganisms that act against another microorganism. Thus, antibiotics do not include antimicrobial substances that are synthetic (sulfonamides and quinolones), or semisynthetic (methicillin and amoxicillin), or those which come from plants (quercetin and alkaloids) or animals (lysozyme).

In contrast, the term "antimicrobials" include all agents that act against all types of microorganisms – bacteria (antibacterial), viruses (antiviral), fungi (antifungal) and protozoa (antiprotozoal).

The main classes of antimicrobial agents are

1. Disinfectants ("nonselective antimicrobials" such as bleach), which kill a wide range of microbes on non-living surfaces to prevent the spread of illness.
2. Antiseptics (which are applied to living tissue and help reduce infection during surgery), and
3. Antibiotics (which destroy microorganisms within the body).The term "antibiotic" originally described only those formulations derived from living organisms but is now also applied to syntheticantimicrobials, such as the sulphonamides, or fluoroquinolones. The term also used to be restricted to antibacterials. Antibacterial agents can be further subdivided intobactericidal agents, which kill bacteria, and bacteriostatic agents, which slow down or stall bacterial growth.

Mechanism action of Antimicrobial Agents

Antimicrobial agents act selectively on vitalmicrobial functions with minimal effects or without affecting host functions.Different antimicrobial agents act in different ways, however the mechanism of actionof antimicrobial agents can be categorized further based on the structure of the bacteria or the function that is affected by the agents. These include generally the following:

- Inhibition of the cell wall synthesis
- Inhibition of ribosome function
- Inhibition of nucleic acid synthesis
- Inhibition of folate metabolism
- Inhibition of cell membrane function

Mechanisms of Antimicrobial Resistance

Resistance can be described in two ways:

a) Intrinsic or natural whereby microorganisms naturally do not possess target sites for the drugs and therefore the drug does not affect them or they naturally have low permeability to those agents because of the differences in the chemical nature of the drug and the microbial membrane structures especially for those that require entry into the microbial cell in order to affect their action or

b) Acquired resistance whereby a naturally susceptible microorganism acquires ways of not being affected by the drug.Acquired resistance mechanisms can occur through various ways.

Mechanisms for acquired resistance

- The presence of an enzyme that inactivates the antimicrobial agent
- The presence of an alternative enzyme for the enzyme that is inhibited by the antimicrobial agent
- A mutation in the antimicrobial agent's target, which reduces the binding of the antimicrobial agent
- Post-transcriptional or post-translational modification of the antimicrobial agent's target, which reduces binding of the antimicrobial agent
- Reduced uptake of the antimicrobial agent
- Active efflux of the antimicrobial agent
- Overproduction of the target of the antimicrobial agent
- Expression or suppression of a gene in vivo in contrast to the situation in vitro
- Previously unrecognized mechanisms

INSIDE :

Table 1. Mechanisms of Resistance against Different Antimicrobial Classes

Antimicrobial class	Mechanism of resistance	Specific means to achieve resistance	Examples
Beta-lactams Examples: penicillin, ampicillin, mezlocillin, peperacillin, cefazolin, cefotaxime, ceftazidime, aztreonam, imipenem	Enzymatic destruction	Destruction of beta-lactam rings by beta-lactamase enzymes. With the beta-lactam ring destroyed, the antibiotic will no longer have the ability to bind to PBP (Penicillin-binding protein), and interfere with cell wall synthesis.	Resistance of staphylococci to penicillin; Resistance of Enterobacteriaceae to penicllins, cephalosporins, and aztreonam
	Altered target	Changes in penicillin binding proteins. Mutational changes in original PBPs or acquisition of different PBPs will lead to inability of the antibiotic to bind to the PBP and inhibit cell wall synthesis	Resistance of staphylococci to methicillin and oxacillin
	Decreased uptake	Porin channel formation is decreased. Since this is where beta-lactams cross the outer membrane to reach the PBP of Gram-negative bacteria, a change in the number or character of these channels can reduce betalactam uptake..	Resistance of Enterobacteraerogenes, Klebsiellapneumoniae and Pseudomonas aeruginosa to imipenem
Glycopeptides Example: vancomycin	Altered target	Alteration in the molecular structure of cell wall precursor components decreases binding of vancomycin so that cell wall synthesis is able to continue.	Resistance of enterococci to vancomycin
Aminoglyosides Examples: gentamicin, tobramycin, amikacin, netilmicin, streptomycin, kanamycin	Decreased uptake	Change in number or characterof porin channels (through which aminoglycosides cross the outer membrane to reach the ribosomes of gram-negative bacteria) so that aminoglycoside uptake is diminished.	Resistance of a variety of Gram-negative bacteria to aminoglycosides
	Altered target	Modification of ribosomal proteins or of 16s rRNA. This reduces the ability of aminoglycoside to successfully bind and inhibit protein synthesis	Resistance of Mycobacteriumspp to streptomycin
Quinolones Examples: ciprofloxacin, levofloxacin, norfloxacin, lomefloxacin	Decreased uptake	Alterations in the outer membrane diminishes uptake of drug and/or activation of an "efflux" pump that removes quinolones before intracellular concentration is sufficient for inhibiting DNA metabolism.	Resistance of Gram negative and staphylococci (efflux mechanism only) to various quinolones
	Altered target	Changes in DNA gyrase subunits decrease the ability of quinolones to bind this enzyme and interfere with DNA processes	Gram negative and Gram positive resistance to various quinolones

Reference: *1. http://amrls.cvm.msu.edu/pharmacology/antimicrobials/antimicrobials-an-introduction*

2. Mechanisms of Resistance Against Different Antimicrobial Classes — Antimicrobial Resistance Learning Site For Veterinary Students.html

Drug Resistance Malaria

Dr.D.Krishna Kumar, *Professor & Head, Dept. of Pharmacy Practice*

Malaria infection is caused mainly by four species of intracellular protozoa parasite namely Plasmodium falciparum, Plasmodium vivax, Plasmodiumovale, and Plasmodium malariae. These parasites are unicellular and eukaryotic organism. Among the species of plasmodium, the deadliest one is *P.falciparum.*[1]

Malaria remains an important public health concern in India where transmission occurs regularly. Malaria is a complex disease that differs highly in epidemiology and clinical manifestation in different states of India and worldwide. This variability is due to the factors such as the species of malaria parasites, their sensitivity to antimalarial drugs, the multiplication, spread and efficiency of mosquitoes and other environmental conditions and the level of acquired immunity of the exposed human populations. There are different antimalarial agents used either single or in combination to treat malaria (Table 2.).[2]

The antimalarial drug resistance has been described for two among the four species of malaria parasite that naturally infect humans, P. falciparum and P. vivax, among this P. falciparum has developed resistance almost all antimalarial used currently, however the geographical distribution of resistance to any single antimalarial drug varies highly.

Definition of antimalarial drug resistance:

It has been defined as the "ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject". This definition was modified to specify that the drug in question must *"gain access to the parasite or the infected red blood cell for the duration of the time necessary for its normal action".*[3]

Mechanisms of antimalarial resistance

Resistance to antimalarial appears to occur through spontaneous mutations that present with reduced sensitivity to a given drug or class of drugs. For some drugs, only a single point mutation (SPM) is required to induce resistance, while for other agents multiple mutations are required. The developed mutations are not harmful to the survival or reproduction of the parasite, drugs destroys the susceptible parasites, however the resistant parasites survive. The single malaria parasite isolates have been found to be made up of heterogeneous (mixed) populations of parasites, they have varying degree of response characteristics to drugs, from highly resistant to drugs or completely sensitive.[2]

Detection of resistance[4]

Four methods are mainly used to study or measure antimalarial drug resistance

In vivo test: It consists of the individual receiving known doses of drug treatment for a group of symptomatic and parasitaemic infections and monitoring for parasitological or clinical response over time.

In vitro tests: This type of test avoids many of the confounding factors which influence in-vivo tests. The most frequently used in-vitro procedure is the micro-technique the parasites received from a finger-prick blood sample are mixed in microtitre plates to precise (diluted to concentrated) quantities of drug and observed for inhibition of maturation into schizonts.

Animal model studies: The influence of host immunity is minimized by using lab-raised animal and parasite combinations. However the host factors would still remain.

Molecular techniques: Molecular techniques are use polymerase chain reaction (PCR) to identify the presence of point or multiple genetic mutations encoding biological resistance to antimalarial drugs.[5] The frequency of occurrence of specific genetic polymorphism within a sample of parasites received from patients came from a given area could provide an indication of the frequency of drug resistance in that particular area and confirms to information derived from in vitro methods.[5]

Preventing drug resistance:

The prevention of antimalarial drug resistance mainly focus on reducing overall drug usage or exposure through more selective use of drugs; the second point is improving the way of drugs used by improving prescribing, follow-up practices, and patient compliance. Further using drugs or drug combinations which are minimize or eliminate resistance or that do not facilitate development or spread of resistant parasites.

References:

1. Chugh M, Scheurer C, Sax S, Bilsland E, van Schalkwyk D. A, Wicht K. J, et al. Identification and Deconvolution of Cross-Resistance Signals from Antimalarial Compounds Using Multidrug-Resistant Plasmodium falciparum Strains. Antimicrobial Agents and Chemotherapy. 2015; 59 (2):1110-1118.
2. Sinha S, Medhi B, Sehgal R. Challenges of drug-resistant malaria. Parasite. 2014;21:61.
3. Bruce-Chwatt LJ. Chemotherapy of malaria, Geneva, World Health Organization, 1986.
4. Global report on Antimalarial Drug efficacy and Drug Resistance: World Health Organization. 2000–2010.
5. Sharma J, Dutta P, Khan SA, Soni M, Dey D, Mahanta J. Genetic polymorphisms associated with sulphadoxine-pyrimethamine drug resistance among Plasmodium falciparum field isolates in malaria endemic areas of Assam. J Postgrad Med. 2015;61(1): 9-14.

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Influenza Antiviral Drug Resistance

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Antiviral resistance means that a virus has changed in such a way that the antiviral drug is less effective in treating or preventing illnesses with that virus. Influenza viruses can become resistant to influenza antiviral drugs. In the United States, there are three FDA-approved neuraminidase inhibitor antiviral drugs recommended by CDC this season: oseltamivir (brand name Tamiflu®), zanamivir (Relenza®), and peramivir (Rapivab®). In the United States, most of the recently circulating influenza viruses have been susceptible to the neuraminidase inhibitor antiviral medications.

Testing of Antiviral Resistance

Virus samples are tested to determine if they are resistant to any of the FDA-approved flu antiviral drugs. Antiviral resistance testing involves several laboratory tests, including a specific functional assay, the neuraminidase inhibition (NI) assay, and molecular techniques (sequencing and pyrosequencing) to look for genetic changes that are associated with antiviral resistance.

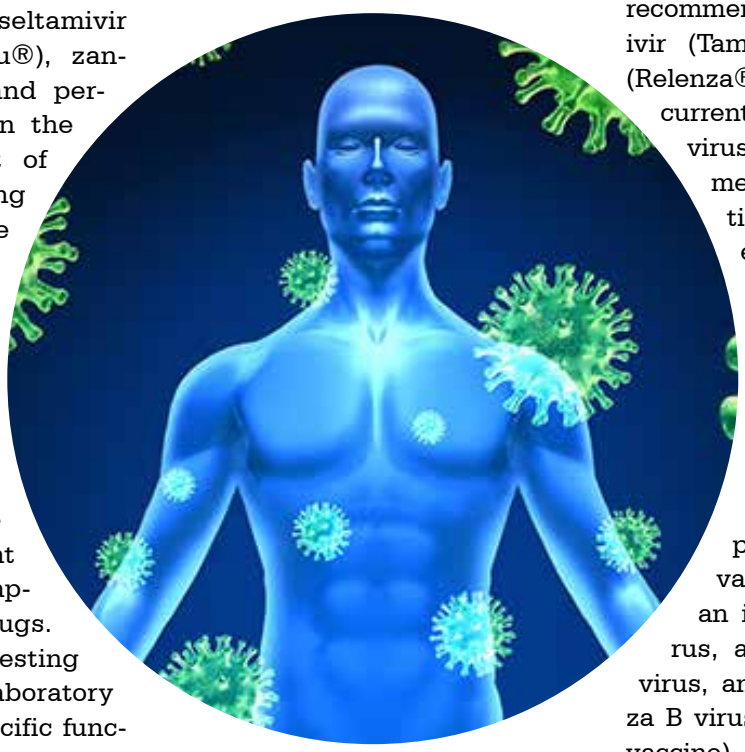
Oseltamivir Resistance

Oseltamivir (trade name Tamiflu®) is an antiviral drug that is used to treat flu illness. "Oseltamivir resistance" refers to a flu virus that is resistant against the drug Oseltamivir.

Causes of Oseltamivir resistance

Flu viruses are constantly changing and circulating flu viruses typically involve the structures of the viruses' two primary surface proteins: neuraminidase (NA) and hemagglutinin (HA). (See image below for a visualization of a flu virus and it's HA and NA surface proteins.)

Oseltamivir is known as a "neuraminidase inhibitor" because this antiviral drug binds to a flu virus' neuraminidase



and inhibits the activity of this protein. By inhibiting NA activity, oseltamivir prevents flu viruses from reproducing and spreading from infected cells to other healthy cells. However, as the NA proteins of flu viruses change, oseltamivir can lose its ability to bind to and inhibit the function of these viruses' NA proteins. This results in oseltamivir resistance. A particular genetic change known as the "H275Y" mutation is known to confer oseltamivir resistance in 2009 H1N1 flu viruses. (The H275Y mutation is a substitution of histidine for tyrosine at position 275 in the NA.) This substitution prevents oseltamivir from inhibiting NA activity, which results in the drug not working as well and flu viruses still being able to infect healthy cells.

Recommended antiviral drugs for use during the 2014-2015

Antiviral medications currently recommended include oseltamivir (Tamiflu®) and zanamivir (Relenza®). The vast majority of currently circulating influenza viruses is sensitive to these medications. Rare exceptions have been detected.

Protection against antiviral resistant flu viruses

Getting a yearly seasonal flu vaccination is the first and most important step in preventing the flu. The vaccine protects against an influenza A (H1N1) virus, an influenza A (H3N2) virus, and one or two influenza B viruses (depending on the vaccine). CDC recommends that everyone 6 months of age and older get vaccinated each year. If you are in a group at high risk of serious flu-related complications and become ill with flu symptoms, call your doctor right away, you may benefit from early treatment. If you are not at high risk, if possible, stay home from work, school and errands when you are sick. This will help prevent you from spreading your illness to others.

Reference: http://www.cdc.gov/flu/about/qa/antiviralresistance.htm

Drug Resistant Tuberculosis

K. Karthickeyan, *Assistant Professor, Department of Pharmacy Practice*

Tuberculosis (TB) is a disease caused by bacteria that are spread from person to person through the air. TB usually affects the lungs, but it can also affect other parts of the body, such as the brain, the kidneys, or the spine. In most cases, TB is treatable and curable; however, people with TB can die if they do not get proper treatment. Sometimes TB bacteria become resistant to the drugs used to treat TB. This means that the drug can no longer kill the bacteria.

Drug-resistant TB can occur when the drugs used to treat TB are misused or mismanaged. Examples include:

- When people do not complete the full course of treatment;
- When health care providers prescribe the wrong treatment, the wrong dose, or wrong length of time for taking the drugs;
- When the supply of drugs is not always available; or
- When the drugs are of poor quality.

Drug-resistant TB is more common in people who:

- Do not take their TB drugs regularly
- Do not take all of their TB drugs
- Develop TB disease again, after being treated for TB disease in the past
- Come from areas of the world where drug-resistant TB is common
- Have spent time with someone known to have drug-resistant TB disease

Drug-resistant TB is spread the same way that drug susceptible TB is spread. TB is spread through the air from one person to another when a person with TB disease of the lungs or throat coughs, sneezes, speaks, or sings. People nearby may breathe in these bacteria and become infected.

Multidrug-Resistant TB (MDR TB)

Multidrug-resistant TB (MDR TB) is caused by an organism that is resistant to atleast isoniazid and rifampin.

Extensively Drug-resistant TB (XDR TB)

It is a rare type of MDR TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).

Because XDR TB is resistant to the most potent TB drugs, patients are left with treatment options that are much less effective.

XDR TB is of special concern for people with HIV infection or other conditions that can weaken the immune system. These people are more likely to develop TB disease once they are infected, and also have a higher risk of death once they develop TB.

Antituberculosis drugs and the gene(s) involved in their resistance

Drug	Gene(s) involved in drug resistance
Isoniazid	inhA
	katG
	ahpC
	oxyR
Rifampicin	rpoB
Pyrazinamide	pncA
Streptomycin	rpsL
	rrs
	strA
Ethambutol	emb A,B and C
Fluoro-quinolones	gyr A and B

Spontaneous chromosomally borne mutations occurring in M. tuberculosis at a predictable rate is thought to confer resistance to antituberculosis drugs. A characteristic feature of these mutations is that they are unlinked. Thus, resistance to a drug is usually not associated with resistance to an unrelated drug. A tuberculosis cavity usually contains 107 to 109 bacilli. If mutations causing resistance to isoniazid occur in about 1 in 106 replications of bacteria, and the mutations causing resistance to rifampicin occur in about 1 in108 replications, the probability of spontaneous mutations causing resistance to both isoniazid and rifampicin would be 106 x 108 = 1 in 1014. Given that this number of bacilli cannot be found even in patients with extensive cavitatory pulmonary tuberculosis, the chance of spontaneous dual resistance to rifampicin and isoniazid developing is practically remote. Thus, the fact that mutations are unlinked forms the scientific basis of antituberculosis chemotherapy. The primary mechanism of multiple drug resistance in tuberculosis is due to perturbations in the individual drug target genes. Previously reported mutations reveals that several novel mutations were also observed in the rpoB (rifampicin), katG and the ribosomal binding site of inhA (isoniazid), gyrA and gyrB (ofloxacin), and rpsL and rrs (streptomycin).

Preventing Drug-Resistant TB

The most important way to prevent the spread of drug-resistant TB is to take all TB drugs exactly as prescribed by the health care provider. No doses should be missed and treatment should not be stopped early. People receiving treatment for TB disease should tell their health care provider if they are having trouble of taking the drugs.

Health care providers can help prevent drug-resistant TB by quickly diagnosing cases, following recommended treatment guidelines, monitoring patients' response to treatment, and making sure therapy is completed.

Another way to prevent getting drug-resistant TB is to avoid exposure to known drug-resistant TB patients in closed or crowded places such as hospitals, prisons, or homeless shelters. People who work in hospitals or health-care settings where TB patients are likely to be seen should consult infection control or occupational health experts.

Drug Resistance In Chemotherapy

Bharathi Priya, Assistant Professor, Dept. of Pharmacy Practice

Patients receiving chemotherapy can develop resistance to previously effective drugs to the point that the drugs are no longer effective. Resistance – also called tachyphylaxis – occurs when a cancer cell develops the ability to keep the chemotherapy drug from entering it, or at least reduce the amount that can enter to a level that does not cause damage.

Cancer cells accomplish this phenomenon by emitting a substance called p-glycoprotein, which can remove the chemotherapy drug from the cancer cell even after it has entered. This process can occur over time, with the cancer cells emitting more p-glycoprotein with each exposure to chemotherapy until resistance is established. However, p-glycoprotein is emitted by normal cells of the colon, kidney, pancreas, and liver, so cancers derived from these organs may be resistant to chemotherapy even before it begins. The point in treatment at which resistance occurs is largely dependent on the type of cancer being treated, and can be at any time from the very beginning throughout the treatment schedule.

Chemotherapy drugs that are most often associated with resistance are paclitaxel, docetaxel, vinorelbine, vincristine, vinblastine, doxorubicin, daunorubicin, epirubicin, etoposide, teniposide, topotecan, dactinomycin, and mitomycin C. These drugs are used to treat a wide variety of cancers from those producing solid tumors to those like lymphoma. These drugs also come from several different families of chemotherapy drugs, so the phenomenon of drug resistance is not confined to one family of cancer drugs or one type of cancer.

In order to combat resistance, chemotherapy drugs are often given in combination in the hopes that the cancer will fail to resist at least one of the drugs in the combination. Once a cancer has developed resistance to one type of drug, it is more likely to develop resistance to other drugs, making treatment more difficult. This is why it is so important to determine the best possible drug combination and to use it first when the probability of resistance is lowest. Another interesting method on the horizon – though it is not yet used widely – is administering the chemotherapy drug on a long regimen of low doses.

List of drugs approved in India by CDSCO in 2015

Sl. No	Name of the Drug	Indication
1.	Lixisenatide pre-filled solution for injection 10μg/20 μg	For the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in patients who are not controlled on existing therapy: In combination with the following oral antibiotics: -Metformin, a sulphonyl urea, or a combination of these agents. In combination with a basal insulin: alone, in combination with metformin, or in combination with sulphonyl urea.
2.	Bedaquiline Tablet. 100 mg	In adults (≥ 18 years), as part of combination therapy of pulmonary tuberculosis due to multi-drug resistant Mycobacterium tuberculosis when an effective treatment regimen cannot otherwise be provided".
3.	Sofosbuvir Tablet 400 mg	"In combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults".

Source: http://cdsco.nic.in/forms/list.aspx?lid=2034&Id=11

KANMANI of IV Pharm D received 3rd prize in the National level PPT competition on Entrepreneurship by Women Pharmacists conducted by POWER (Pharmacists' Organization for Women Empowerment and Research) at Sri Ramachandra University on the occasion of International Women's day on 8th March, 2015.

Table 2. Drugs available for treatment of malaria[2]

Drugs	Use
Combination therapy	
Mefloquine+ Artesunate	Treatment of non-severe falciparum infections with chloroquine resistant.
Sulfadoxine/Pyrimethamine+ Artesunate	
Lumefantrine+ Artesunate	
Single agent therapy	
Chloroquine (CQ)	Treatment of non-falciparum infections and P. falciparum infections as chemoprophylaxis where chloroquine remains effective.
Amodiaquine (AQ)	Treatment of non-severe falciparum infections thought to be chloroquine resistant
Sulfadoxine or Pyrimethamine Sulfalene or Pyrimethamine	
Mefloquine (MQ)	Chemoprophylaxis in areas with chloroquine resistance.
Halofantrine	Treatment of suspected multidrug resistance falciparum
Quinine	Treatment of severe malaria, multidrug resistance falciparum and 1st trimester of pregnancy
Tetracycline/Doxycycline	Prophylaxis, used in combination with quinine for quinine resistance malaria or to reduce the duration of quinine and its side effects
Clindamycin	For patients unable to take tetracycline
Atovaquone/Proguanil	Treatment of multidrug resistance P.falciparum
Artemisinin compounds Artesunate,Artemisinin, Artemether	
Primaquine	Treatment of P.vivax infections (reduce likelihood of relapse), Gametocytocidal agent.

PATIENT SAFETY AWARENESS PROGRAM ON 26.03.2015

IN FORTIS MALAR HOSPITAL, CHENNAI

An awareness program on Patient safety among the Healthcare professionals was conducted in Fortis Malar Hospital organized by Mr. Shankar and Mr. Syjo, Clinical Pharmacologists on 26.03.2015. Pharm.D students of fifth year actively participated and presented a skit program to the Doctors, Nursing staff and other Health care providers which was well appreciated. Pharm.D students participated in the poster competition with the theme UNITED UNDER PATIENT SAFETY and won the second prize with a cash award Rs.1000/-.

WORLD TB DAY CELEBRATION

24th March marks World Tuberculosis Day. India is known as the TB capital of the world and needs new commitments and action in the fight against tuberculosis – one of the world's top infectious killers. The Pharm.D students conducted an awareness camp for the general public and patients of Voluntary Health Services, Adyar on 23rd and 24th, March 2015.

Students took out a rally on the OMR and distributed informative pamphlets on TB. The patients at VHS were counseled on the symptoms, causes, prevention and treatment of TB. A special guest lecture for students was organized on 'Initiatives in TB Research' by Dr. K.Priya, Scientist, Department of Clinical Research, VHS. Mrs. Cyntia from Corporation of Chennai also spoke on the topic 'DOTS therapy-the heart to stop TB strategy'

World TB day was commemorated on 19.03.2015 at Public Health Centre (PHC), Tuberculosis Unit, Raghavan Colony, Saidapet West. The Pharm D IV year students actively participated in the program by performing a skit and giving a speech about tuberculosis and its causes, and about DOTS therapy. The students received appreciation prizes from the chief guests Dr.Rajeshwari from General Peripheral Hospital (GPH), KK Nagar and Dr.Chandrasekar from PHC, Nalankuppam.

Senior tuberculosis supervisor Mrs.K.Vennila and her team of health visitors and lab technicians elaborately outlined about tuberculosis and DOTS therapy. Patients who were cured by DOTS gave positive feedback and stressed on the importance of the treatment.

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