

# Use of Preventive Therapy for At-Home Exposure to Drug-Resistant TB, Pakistan

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

[Sarah Gregory] Hello, I'm Sarah Gregory, and today I'm talking with Dr. Aryn Malik. He's an epidemiologist and postdoctoral associate at Yale University. We'll be discussing the use of preventive therapy for at-home exposure to drug-resistant TB.

Welcome, Dr. Malik.

[Aryn Malik] Hi Sarah, it is a pleasure to be here. Thank you for inviting me.

[Sarah Gregory] Let's start with a basic. What is TB and how is it different from other lung infections and diseases?

[Aryn Malik] TB is a bacterial infection caused by a bacteria called *Mycobacterium tuberculosis*. This bacterium usually attacks the lungs, but it...it's capable of attacking any other part of the body. However, not everyone who becomes infected with TB gets the disease. Some people develop what is known as latent TB infection, which can be understood as that the bacteria are sleeping within the body (they are dormant) and...but still viable and can be activated later in life.

[Sarah Gregory] We have heard over the years of lots of people dying from...from it in the 19th century. Famous people like the author Chekov died of it. Is it still a big problem? And how many people die from it annually?

[Aryn Malik] So, TB is still a huge problem globally with approximately 10 million new cases and about 1.4 million people dying of it annually, which translates to about 4,000 deaths per day.

[Sarah Gregory] The number of deaths have declined. You do hear of it killing people less often. What made things somewhat better?

[Aryn Malik] Yes. The number of deaths and the number of cases have come down. So, what happened was that in the 1940s the first antibiotic (streptomycin) was discovered, which was effective against the bacteria. And over the next few years, more antibiotics were discovered which led to a cure for TB. This led to an overall improvement in TB care. However, the decline in the TB cases and deaths preceded the discovery of the antibiotics. At the turn of the 19th century, there was improvement in sanitation and housing standards with good ventilation, and with that TB started decreasing. It also became a notifiable disease in the early 1900s, which also helped.

[Sarah Gregory] So what happened later? Why is there now this drug-resistant TB?

[Aryn Malik] So, as the antibiotic use to cure TB increased, the bacterium started to adapt as well and became resistant to different antibiotics in use through the process of natural selection. This was identified early on and there was...there was a movement towards multidrug therapy to cure TB. However, use of inadequate treatment or patients not completing treatment for any number of reasons in place, including governmental or program policies, led to the development of drug-resistant TB, which now accounts for over 450,000 cases annually worldwide.

[Sarah Gregory] So is there any treatment for these multidrug-resistant TB cases and how effective is that treatment?

[Amin Malik] So, treatment is available for multidrug-resistant TB, or MDR TB as it is known. But it is considerably longer and more toxic than the standard treatment. It used to be for 20 months or longer. However, with the development of newer drugs and regimens, this time period has decreased to 9–12 months now. Treatment is generally effective in just over 50% of the time (close to 56%), but the use of newer agents can improve this considerably.

[Sarah Gregory] Are there any vaccines for TB on the horizon? I mean, since TB has been around for so long, why isn't there a vaccine already?

[Amin Malik] There is a TB vaccine called BCG. It was developed in the...in the 1920s and is used commonly in the developing world (it is not used in the U.S.). It is partially effective in children, but its effectiveness in adults is quite variable. There has been a recent candidate vaccine developed by a big pharmaceutical company that has shown considerable promise, with close to 50% effectiveness in adults. The reason that there hasn't been a better vaccine is that the disease process for TB is not well-understood and it is hard to replicate this process in an animal model, which is used as a baseline to develop vaccines. We do not know what the correlates of protection really are for TB. Also, there hasn't been a lot of funding for research and development in TB. It is estimated that the annual budget deficit for research and development for TB is in excess of one billion dollars globally, and pharmaceutical companies do not deem TB vaccines to be a particularly...a profitable venture. So all of this has led to a TB vaccine not being...a better TB vaccine not being around.

[Sarah Gregory] Your article is specifically about giving TB therapy prophylactically at home. Why is this important?

[Amin Malik] So, TB is a disease that spreads from person to person. It is estimated that a person with TB can pass it on to 10 to 15 people. Household members of a TB patient are particularly at high risk of contracting the disease. Hence, it is important to provide preventive treatment to them so they'll...they do not go on to develop the disease itself.

[Sarah Gregory] So what does this at-home treatment involve?

[Amin Malik] So, TB preventive treatment involves screening and testing household members of the TB patient to make sure they do not have the TB disease before offering them medication that they have to take for some time to prevent future development of the disease. In this particular case, for drug-resistant TB they have to take two medicines daily for six months. There are different and shorter regimens available for drug-susceptible TB as well.

[Sarah Gregory] You studied people in Karachi, Pakistan. Why there? Is it particularly a problem there and if so, why?

[Amin Malik] Pakistan ranks fifth globally for new TB cases each year and has approximately 25,000 new MDR TB cases per year as well. Of these, approximately only 15% of the cases are registered and treated annually in the country. Karachi is the largest city in Pakistan with a population of...in excess of 20 million, and it reports approximately 400 drug-resistant TB cases each year. Karachi has three sites that manage drug-resistant TB patients, and this study was conducted at one of these sites.

[Sarah Gregory] What's the global importance of studying a population in one area, such as Karachi?

[Amin Malik] So, Karachi is typical of a large megacity in low- and middle-income countries and has a high prevalence of TB. Our study was embedded in an existing TB treatment program in this city, and hence our findings can be generalizable to other such large cities across the globe, especially in areas where there exists a TB treatment program.

[Sarah Gregory] Tell us about the Zero TB initiative you mention in your study.

[Amin Malik] So, TB is a preventable and a curable disease but still it kills a lot of people annually. To effectively control this disease, there is a need for a comprehensive approach which focuses on three main areas like search for new patients for TB, treat the patients that are identified, and prevent TB development in contacts. The purpose of the Zero TB initiative is to create islands of elimination that will contribute towards lowering rates of TB disease globally. The initiative is committed to utilizing evidence-based comprehensive framework that focuses on these three areas to increase case detection...detection and reduce TB disease and deaths. It also includes provision of TB preventive treatment to household contacts.

[Sarah Gregory] Why don't you take a moment now and give us the highlights of your study?

[Amin Malik] So this study provides preventive treatment using fluoroquinolone-based two-drug regimen to household contacts of drug-resistant TB patients and then assessed the efficacy or effectiveness of the treatment after two years. We found that the preventive treatment was effective in preventing development of TB disease in these household contacts.

[Sarah Gregory] What methods did you use to carry the study out?

[Amin Malik] So, this is what is commonly known as a prospective cohort study where we provided TB treatment to these household contacts and then prospectively followed them up for a period of two years to see whether they will develop TB or not. For a control group, we used data from other cohorts globally to estimate what the TB development rate should have been in our cohort of household contacts had they not been given preventive treatment.

[Sarah Gregory] What did you find in your study?

[Amin Malik] We found that only two of the 172 household contacts that we provided preventive treatment to developed TB disease. And the treatment was 65% effective in preventing TB disease development over two years.

[Sarah Gregory] What do you consider to be the most important aspect of your study?

[Amin Malik] So, this is one of the largest study to estimate the effectiveness of TB preventive treatment for drug-resistant TB with excellent follow-up over two years. Our results were also really robust to range of different assumptions about disease development rates in our cohort. In absence of clinical trial data...there are clinical trials that are being conducted for...to assess the effectiveness of this, but they will not be reporting results for another few years. So in absence of such data, this study provides a robust estimate of the effectiveness.

[Sarah Gregory] Your article is one of two chosen monthly to be a CME activity by the *Emerging Infectious Diseases* journal. Would you explain what that means and why do you think it was chosen?

[Amy Malik] CME, or Continuing Medical Education, consists of educational activities which serve to maintain, develop, or increase the knowledge, skills, and professional performance and relationships that a physician uses to provide services to their patients or public. I believe this study provides an important information for physicians to update their knowledge regarding preventive treatment for drug-resistant TB. And the methodology used to determine the effectiveness, making use of historical data, are probably some of the reasons why this is one of the two articles that EID selected for CME credit.

[Sarah Gregory] How is your study different from other studies done on MDR TB?

[Amy Malik] So, there are a few studies that estimate the effectiveness of preventive treatment for drug-resistant TB. The largest study (which actually had a comparison arm) was done by the CDC team in the Federated States of Micronesia. This study provided preventive treatment (this study meaning my study) provided preventive treatment to a bigger number of patients and we tested the effectiveness using a range of different assumptions about disease development rates in our cohort.

[Sarah Gregory] What were the biggest challenges to doing this study?

[Amy Malik] The biggest challenge in this study was nonavailability of a comparison arm. This study was embedded in an existing TB control program where we provided TB preventive treatment to all high-risk contacts. Hence, there wasn't a comparison arm available. To counter this, I searched the literature to find rates of TB disease development from other cohorts that could suitably apply here. As there wasn't a perfect match with any on study, I took rates from multiple different studies and applied them to my cohort to look at the effectiveness under different assumptions of disease development rates.

[Sarah Gregory] How would you like to see the results of your study used going forward?

[Amy Malik] Now that we have established the effectiveness of preventive treatment for drug-resistant TB exposure in household contacts in this study and feasibility of its provision under program conditions in a previous study from the same cohort, I would like the national programs globally to implement this to better control drug-resistant TB epidemic.

[Sarah Gregory] And what further studies would you like to see done?

[Amy Malik] So, there are many barriers to TB preventive treatment, including acceptance of treatment (a lot of contacts tell us that they do not feel sick and they...and therefore they do not need medication) and the long duration of the treatment itself (the preventive treatment that's for over...for about 6 months). So, future studies should focus on looking at shorter regimens for preventive treatment and strategies to further improve acceptance in household contacts.

[Sarah Gregory] Is the public health system in Pakistan doing anything in particular to protect people from getting TB in the first place?

[Amy Malik] So, national and provincial TB programs in Pakistan with other nongovernmental partners are implementing a number of strategies to diagnose, treat, and prevent TB disease. They have adapted the Zero TB approach that I talked about earlier for provision of a comprehensive care package. There is a focus on case detection using innovative approaches such as mobile x-ray vans which go into the community and screen community members to diagnose TB, and provision of preventive treatment using newer regimens like the 12-weekly

isoniazid and rifapentine (also known as 3HP) for drug-susceptible TB that is widely used in high-income countries.

[Sarah Gregory] And on a personal level, how can we best protect ourselves from getting TB?

[Amin Malik] So, TB education is necessary for people with TB and for the general public. So, we can educate ourselves as to how the TB disease spreads and what are some of the precautions that we need to take. People with TB need to know how to take their TB drugs properly. They also need to know how to make sure they do not pass TB to other people, like practicing good cough etiquette. The public needs to know basic information about TB for a number of reasons, including reducing stigma that is associated with TB in some countries.

For protecting household contacts, houses should be adequately ventilated, anyone who coughs should be educated on cough etiquette and respiratory hygiene, and should follow such practice at all times. Use of masks to protect transmission in hospital or other congregate settings (like prison) can also help reduce TB transmission.

[Sarah Gregory] So that raises another interesting question. Apparently several diseases and infections in 2020 were at kind of an all-time low because of COVID—people wearing masks and social distancing, and lockdowns and stuff. I know that flu was very, very minimal and just basic colds and that kind of thing. Do you have any idea if this has helped with TB transmission?

[Amin Malik] So on the contrary, TB services were really hard-hit by COVID-19 because of the disruption of daily lives. So people could not come in to take their medication (collect their medication), people could not come into be diagnosed with TB. So the case detection rates and treatment success rates have gone down globally. There is a fear that the pandemic might undo 5–10 years of work that has gone on in trying to improve TB care worldwide. TB is transmitted at home a lot of times and people don't usually wear masks at home, even during this pandemic. So, I'm not sure how much effect of the use of masks would have been in preventing this. But disruption of TB services would definitely lead to an increase in TB cases in the coming years.

[Sarah Gregory] Ah, that's a shame. So sort of the opposite of what's happening with some other infections.

Tell us about your work and what you enjoy most about it.

[Amin Malik] So, I am an infectious disease epidemiologist. And as one, I enjoy researching and applying my knowledge to develop interventions to protect the most vulnerable populations from illness. Currently in addition to TB, my work is also focused on understanding and tracking the epidemiology of SARS-CoV-2, specifically in the U.S., to inform timely policy decisions and vaccine priorities.

[Sarah Gregory] Are you doing anything in particular to relieve the stress of this pandemic? Hobbies, yoga, that sort of thing?

[Amin Malik] I've mostly been working from home during the pandemic. During this time, I have been going to the gym, playing some snooker with my wife and friends, cooking, and reading to relieve some of the stress that the pandemic has caused.

[Sarah Gregory] Well thank you so much for taking the time to talk with me today, Dr. Malik.

[Aryn Malik] It was a pleasure to be on this podcast. I hope this will help spread the message that preventive treatment for drug-resistant TB is quite effective and feasible and should be implemented. Thank you, Sarah, for inviting me to be here today.

[Sarah Gregory] And thanks for joining me out there. You can read the March 2021 article, Effectiveness of Preventive Therapy for Persons Exposed at Home to Drug-Resistant Tuberculosis, Karachi, Pakistan, online at [cdc.gov/eid](https://www.cdc.gov/eid).

I'm Sarah Gregory for *Emerging Infectious Diseases*.

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