Conversation between Peter Cegielski, MD, MPH, Division of TB Elimination U.S. Centers for Disease Control and Prevention & GiveWell (Elie Hassenfeld and Wendy Knight), November 2, 2011

How bad is a TB treatment default?

[We use] a conceptual model to understand and explain the development of drug resistance.

[There are a] very small fraction of individual bacterial cells that have mutations in their DNA that confer resistance to specific anti-TB drugs. These mutations occur spontaneously at a well-defined frequency. For example, mutations that confer resistance to the drug isoniazid (INH) occur in about one out of 100 million cell divisions (10^{-8}) [These are] bacterial cells that will continue to grow; so in any naturally occurring large population of TB bacilli, there will be a small number that are naturally resistant to each of the anti-TB drugs.

Inside a person, especially with cavitary lung disease, [because] the bacterial population reaches 10^9 bacteria – a billion – within that there will be 1,000 or so that are naturally resistant to isoniazid (INH), maybe 100 that are naturally resistance to rifampicin (RMP) just because DNA replication is not perfect.

If a person takes anti-TB drugs and doesn't take them to the end of treatment to eradicate all the [bacteria] in their lungs, then the drug (or drugs) will kill the organisms that are susceptible but [not] the resistant ones. The resistance ones will continue proliferating. Eventually, the large majority of susceptible bacteria will be killed, but the resistant ones will continue to replicate until they become the dominant population of bacteria. When someone doesn't complete their treatment, you've killed the susceptible bacteria but not the resistant ones. So if you don't take [the antibiotics] to the end, then the bacteria that are left in your body are much more likely to be drug- resistant.

What is the rate at which a patient who defaults becomes an MDR case?

There is information on that. [Once] the bacteria have been exposed [to treatment], the risk of harboring drug-resistant bacteria is ten-fold higher than what it would be in someone who has not been treated before. It differs in different countries, but a typical situation might be that about 3% of new patients may have MDR TB, while among previously treated patients the prevalence is 10%-20%.

The WHO has five volumes of drug resistance surveys. They are called the WHO/IUATLD Global Project on Anti-TB Drug Resistance Surveillance. That will give you data on over 100 countries that have participated in the surveys. For patients who havebeen treated previously there are three categories of re-treatment, TAR (Treatment After Relapse), TAF (Treatment After Failure), and TAD (Treatment

After Default). The most recent volume of the WHO/IUATLD report would break it out by retreatment categories.

How bad is MDR? If they don't get the right drugs, how many people die?

Cure rates worldwide are around the 60%-65% range. The remaing 35%-40% consists of mortality, treatment failure, and default. Mortality rates are 10%-20% during treatment. Mortality rates are worse than some types of cancer.

Does the timing of a default/ the amount of drugs taken before default matter?

Yes it matters. For drug susceptible [TB] the intensive phase is typically around 2-3 months and the continuation phase around 4-6 months, a total of 6-9 months. For MDR-TB the treatment regimen is typically about 2 years in total.

At the beginning of treatment there are a lot more bacteria in your body than near the end of treatment, so there is a higher body burden of organisms if you default during the beginning of treatment. The earlier you default and the more often you default the higher the risk of MDR-TB.

Does this imply that someone who doesn't take the drug is the least likely to get MDR-TB?

The bacteria have to be exposed to the drug(s) in order to select for the resistant population. Bacteria that have never been exposed to the drugs are not likely to be drug-resistant, because, like we said before, only about 10^{-6} to 10^{-8} will be naturally drug resistant. So, you need the drug to kill the bacteria selectively. You need to take the drug(s) for at least about a month. The WHO says that if you take treatment for less than a month it doesn't count as having taken treatment at all.

MDR is defined as resistance to two specific drugs, isoniazid and rifampin, the two most important drugs, but there are other TB drugs too. With drug susceptible TB, if you take the full regimen under regular TB treatment protocols you kill off all of the bacteria because while some are resistant to one drug, they are not resistant to the other drugs.

If you have a population where 10^{-6} are resistant to isoniazid (INH) and one in 10^{-8} are resistant to rifampicin (RMP), then the chances that they are resistant to both is the product of those two probabilities: 10^{-14}.

The longer you go on ineffective or partially effective treatment, the more you will kill the susceptible bacteria, while the resistant bacteria will continue to grow. M. tuberculosis doubles about every 24 hours. [If you] start with one on day one, they will double on day two, will double again by day 3, etc.

Do you have any thoughts on the type of intervention we are looking at, which provides ongoing counseling in order to lower default rates along with active case finding? Do you have any knowledge regarding the type of care a developing world patient, especially those living in slums, would receive without such an intervention? If they were to go to a private provider?

The primary international strategy for TB is DOTS (directly observed treatment), which includes treatment where a health care provider watches the person take the treatment and also goes to their home or workplace in order to follow up when they miss a dose. That is the "tried and true" means of making sure people take their medicine.

For people not to take their medicine as a doctor prescribed is normal human behavior. After taking treatment for a few months a patient may start feeling well and not go back to finish treatment. Or the medicine might have side effects that make the patient feel bad, so they might stop taking it, especially as their TB symptoms subside. Since TB is communicable, the public health service position is that it takes responsibility that TB treatment is fully delivered. To facilitate this you can offer incentives, etc. Private practitioners don't have the field staff who track patients who miss an appointment, whereas the public health system has personnel that can track each individual and go looking for them.

Would you say the main driver of new MDR cases is MDR-TB transmission or MDR as a function of default?

It differs by geographic context. Globally, I'd say it's about 50/50, but that is just a guess. In places where TB patients are routinely hospitalized, primary MDR TB is probably more. In places where they are treated entirely outpatient, it's probably less.

Our impression, based on the recent increased interest in MDR-TB, is that inadequate or partial treatment may be happening more. Does that sound right? And why would that be? The model you describe seems like it should be constant over time.

As TB drugs were developed, TB treatment has become standardized for drug-susceptible TB but not for drug-resistant TB.

1) One of the two drugs rifampicin (RMP) was discovered in the 60's and began being used in the 70's. It was very expensive until the 90's, when it came off of patent. The more a drug is used the more resistance to it you will get.

2) Treatment of TB wasn't strictly standardized until after rifampicin (RMP) was introduced and tested. There weren't really any clear, universal guidelines or recommendations on how to manage a TB program until the early 90's when the WHO stated promoting the DOTS strategy that was developed by the Union and

KNCV in the 1970s and 1980s. DOTS included keeping track of how many people are treated, diagnosed, cured, died, etc. It was ad hoc before that. Now most countries in the world are DOTs countries.

Once you have a standardized system of reporting and recording the information, you start to look for [resistance]. We started looking for it in the late 80's and early 90's because there were a lot of outbreaks of MDR TB with high mortality rates in the 80's and 90's. The WHO and the Union started doing the drug resistance surveys I mentioned previously because of all the outbreaks.

Do you know of any modeling of the impact that improvements to the system would have on the rates of MDR?

Look for anything by Christopher Dye or Sally Blower by doing a pub med search. There is also Ted Cohen.

Would you say the only real solution is more drugs?

I personally don't think that will solve the problem because they are introduced one at a time and they develop resistance unless there is an entire new regimen (i.e. 3-4 new drugs at a time). New drugs will benefit individuals, but will just keep pushing back the phenomenon of resistance.

In my opinion, the solution is prevention. What I mean by that is making sure TB patients are treated properly the first time; treating through to completion or cure. That prevents transmission to others. With MDR TB cases, detecting them promptly and treating them effectively is essential so so it is not spread.