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39th Union World Conference on Lung Health
Newsmaker Interviews - MELVIN SPIGELMAN
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JILL BRADEN BALDERAS: Mel Spigelman with the Global Alliance for TB Drug Development, thanks for joining us today.

MELVIN SPIGELMAN, M.D.: Thank you.

JILL BRADEN BALDERAS: Right now you're the organization's director of research and development. In January, you'll become the president and CEO, congratulations.

MELVIN SPIGELMAN, M.D.: Thank you.

JILL BRADEN BALDERAS: Explain to me why there is a need for a drug development alliance focused on a specific disease like TB?

MELVIN SPIGELMAN, M.D.: Specifically, because the need was just not being filled by any other available source. So, the TB Alliance, which is what we shortened so that we don't have to say a mouthful every time, was formed in 2001 because of the rising TB epidemic that was going on worldwide, and because of the fact that there hadn't been a new drug developed for about 40 years. And that really was a fact of two – what was a result of really two causes. One, because at one point the world was lulled into thinking TB was no longer a problem, and clearly that was a mistake, but second of all, because of the typical mechanisms that were in place for developing new drugs, just weren't working, and the typical mechanisms are really dependent on having a commercial return for developing new therapies, and specifically new drugs, and that really doesn't exist in TB. So, we as a nonprofit, and with a goal of

developing new drugs and bringing them out there in an affordable means, especially to those people in those countries who need them most, were formed without any need for a profit motivation.

JILL BRADEN BALDERAS: So who pays for it?

MELVIN SPIGELMAN, M.D.: Basically, we derive our funding from donors such as the Bill and Melinda Gates Foundation, government sources such as USAID, Dified [misspelled? 00:0:44], the Irish, the Dutch government – I'm going to leave somebody out and – and they really allow us to have the funding that's necessary to do the research and development to bring the drugs to market, and therefore, there's no incentive and there's no need to sell them at any price other than what the real costs of just manufacture is. And what real cost of manufacture is invariably very cheap compared to what most medicines are actually sold for.

JILL BRADEN BALDERAS: Now, we hear a lot about drug resistant TB, and I want to get to that, but still, the vast majority of people have treatable TB, but the regimen is really difficult. Can you walk us through what that regimen is like, and how you all are working to improve it?

MELVIN SPIGELMAN, M.D.: Yeah. Let me walk you through both perhaps. Both the regimen for drug sensitive disease, which is the majority of cases, close to nine million cases, but then still the regimen that would exist for drug resistant disease, which is now still about half a million cases a year.

For drug sensitive disease, the typical regimen is six to nine months of four drugs of treatment. The four drugs are taken daily, in almost all countries of the world, for the first couple of months, and then either three to five days for the next either four months or six months after that. So you have six to nine months of pretty much daily therapy of multiple pills, and therein lies the problem because stopping that treatment early is one of the reasons that – or inappropriately taking the medication and not staying on the exact regimen, is one of the reasons that both the potential failure for the treatment, but also for the possibility of drug resistance arising.

Now, if a patient does develop drug resistant disease, now we're talking about treatment that can span 18 to 24 months, and oftentimes not even be successful, so that there is either the need for repeated treatment, or the patient goes on and dies. And then by drug resistant disease, that's now broken up into two categories. One is called MDR, the other is called extreme drug resistance, or XDR – MDR, which is resistance to two of the four drugs that are taken for drug sensitive disease, Isoniazid, Rifampin, that will require 18 to 24 months, and those drugs now are even usually more than 4 drugs. They have multiple side effects. Some of them are injectable, they're not pills, so people have to get injected, which is always much tougher both on the health care system, but also on the patient obviously, and then when we get to

extreme drug resistance, there's a situation where sometimes there are no drugs that are still effective, so there can either be no therapy or very poor therapy for the vast majority of the patients with extreme drug resistance, and there, oftentimes it's not even a question of how long to treat for, there can be no treatment.

JILL BRADEN BALDERAS: So, can you walk us through what are some of the drugs that you have in the pipeline for all of those levels of tuberculosis?

MELVIN SPIGELMAN, M.D.: Sure. For drug sensitive disease, the primary program that we're working on is another - it still would be a four drug combination. We're substituting a drug called Moxifloxacin, for either one or two of the presently used drugs, either for Isoniazid or Ethambutol. And what we're trying to aim for there is to cut that six to nine months down to four months so that we would in essence, save patients anywhere from two to five months of treatment, with the use of Moxifloxacin, and that's in what's called phase three stage of development, which means that it's the last stage of the clinical trial, so if successful, we would then aim to do what's called registering the drug to try to get it approved worldwide for tuberculosis, and then have it actually be used as the basis of a four month regimen.

JILL BRADEN BALDERAS: Any projection on time?

MELVIN SPIGELMAN, M.D.: That study has just started.

Really it's a very big complicated study, 2,400 patients, and

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the projection is to finish the clinical part of the study around the end of 2010, perhaps in that ballpark, and then we would have to go through the process of filing for approval around the world.

The other drug that is the furthest advanced in the pipeline, which is called PA-824, which should be beneficial in drug sensitive disease, MDR, and even XDR. It's a completely novel, what's called, mechanism of action, so there should be no cross resistance with any of the treatments that are in existence today, and the goal with that drug would be, number one, to be able to treat really any patient, whether they have drug sensitive or drug resistant disease. The goal for drug sensitive disease would be to put it into a regimen that would shorten the treatment time, and for drug resistant disease, both to shorten the treatment time and also to increase the cure rate.

With the treatment for drug sensitive, if used appropriately, treatment can already be upwards of 95-percent. But that means adhering to the regimen throughout that whole period of time. So, realistically, under controlled conditions, we don't hope to increase the cure rate for drug sensitive disease, but to shorten the time. In the field, we're hopeful that it should also shorten, because realistically, in the field, normal treatment, the treatment adherence is not nearly as good as in a clinical trial.

JILL BRADEN BALDERAS: I talked with Mario Raviglione earlier today from WHO's Stop TB Department, and he cited a country where now 20-percent of TB cases are resistant, show some form of resistance. So this is clearly an increasing problem. When you hear those statistics, does it change how you look at your job, knowing what you do day to day, knowing that it just gets worse and worse?

MELVIN SPIGELMAN, M.D.: It doesn't change it, but it really emphasizes the urgency and the need for getting the work done, and mustering really, all the resources that could be mustered to speed the work and to make sure that it can be done as quickly and effectively as possible.

JILL BRADEN BALDERAS: Now, another issue is TB co infection, and that makes both disease more difficult to treat. So, what are you all working on to synthesize that treatment better and improve it?

MELVIN SPIGELMAN, M.D.: Yeah. The difficulty there is, some of the drugs that are used for TB are difficult to administer because of the interactions with the antiretroviral. In really pretty much every one of our research programs, we specifically look for drugs that will not have interactions with the antiretroviral drugs, and PA-824 is a good example where we feel – and also Moxifloxacin, the drugs that I mentioned before. Right now we have – all the evidence predicts that neither of those drugs will have any interaction with the antiretroviral drugs, so those drugs, for example,

should be able to be given with the antiretroviral, so that for patients with TB and HIV, both of the diseases can be treated simultaneously. So that's really one of the cornerstones of all our development in our research programs, as we look to make sure that the drug can be used simultaneously with the antiretroviral drugs, to treat both diseases at the same time. That the drug should have the capacity to shorten treatment, and also that they should be effective in resistant disease.

JILL BRADEN BALDERAS: Now, what you described sounds so complicated when it comes to a clinical trial, and testing all of that. What are some of the challenges that you face when you are working on clinical trials, and then a follow up, what do you do when working with patients, to make sure that they're respected, people who are actually living with these disease. Do you work with them also, as you're designing these clinical trials?

MELVIN SPIGELMAN, M.D.: Well, first of all, what makes it certainly more costly and longer is that each of these issues have to be dealt with in separate trials, so that a clinical trial that address the issue of what's called drug sensitive disease, to shorten therapy there, is a separate clinical trial than a clinical trial that looks at multidrug resistant patients. So each of the issues have to be addressed separately, which, in a way, adds to the, both complexity of the whole programs, and also the duration and the costs, etcetera.

So, but they still are very complicated trials. They're certainly doable, but it requires an enormous amount of work, effort, and resources to do these studies. In terms of what are some of the challenges, clearly there are quite a few. One of the challenges is simply the availability of trial sites that are capable of doing the type of sophisticated clinical research that's necessary for drug development. The fact that no new drugs have really been developed, until recently, for decades, means that sites that were able to do this work, simply weren't being fostered or weren't being helped to be able to do the work. So, one of the main initiatives that we have today, is in fact to identify sites and help those sites get a level of sophistication and capability, so in fact they can do the work of being a component of these type of clinical trials. So that's one of the major areas that we have focused on really around the world and have several programs to do that.

Clearly, having community both involvement, acceptance, in any clinical trial, is crucial. It's crucial certainly both for the respect and dignity of the patients, but it's also crucial for the success of the trial, to make sure that the community really understands the significance of the trial, understands why it's really in the community's best interest to have the trial be performed, as well as in the global best interests of patients around the world. We have programs such as community boards that we try to initiate. So, to educate

and to allow the community activists and community members, to really play apart, and to understand the clinical trial, why we're doing it, and what our goals are. Because for most people in these communities, this is a totally foreign concept of actually doing clinical trials, and realistically and understandably, there are oftentimes worry about am I a guinea pig, what are you testing on me, etcetera, and those are very real questions and very real concerns on the part of patients that we have a responsibility to make sure that we're dealing with appropriately.

JILL BRADEN BALDERAS: Now, you mentioned from the get go, taking out the profit element and the need for a profit, so that frees you all up to do this drug development, but the drugs will still have to get to patients, and many of these people are in low-income countries. How do you plan on getting these drugs to them?

MELVIN SPIGELMAN, M.D.: Well, there's a few elements to that. The first element is simply the price. What we have in each of our programs is a guarantee, a contractual obligation from our partners, that no entity involved in this will be making a profit in those countries. So we at least now are down to what is the true cost of making the medicine and there's no profit involved. Other than depending on who manufactures it, there could be a slight markup simply for true manufacturing costs, but that pales in comparison to the sort of profit margins that exist in a typical drug program.

So, then we only have the issue is the true cost, the real cost of manufacture, will it be affordable? And that's a key element in all of our development programs, so we both strive to bring the cost down to a reasonable amount, but we also will look at programs and say is the cost even to the true cost? Will it be too high, and therefore is this a program that we should continue?

Obviously, there still are funding mechanisms out there, that if one has a really good drug, but it may be somewhat expensive to produce, to really produce, that one can still go to donor agencies around the world to even supplement and to subsidize the true cost. So, for the Global Fund, etcetera, so that those are the elements that are used in terms of the question of affordability.

Then there's the issue really of access and adoption, and that is what do we do to make sure that the decision makers in different parts of the world really have enough information so that they're in a position to make the decisions locally for whether they will recommend actually bring the new treatments on board. So that's another whole initiative, coupled with WHO in terms of the whole area that WHO has to be involved in qualifying the drugs, because for many countries that's a sine qua non for the drugs being adopted, so that's a whole other area of working with local national treatment programs and though leaders to make sure they're on board during the process so that at the time when the drug would be ready, they're

prepared to truly make their decisions and bring it on board as quickly as possible.

The other element of making sure the health care system is in position to really utilize the drugs, and that's another hurdle that's tough, clearly just bringing on board treatments that will require shorter periods of time to take, in and of themselves will help the health care systems. So that's certainly, and we've heard this from so many of the countries, that if they only have to supervise treatment for four months, instead of six or nine months, right away, that decreases the burden on the health care system.

JILL BRADEN BALDERAS: And that actually segways into my last question, which is what do you see – the theme of this conference is improving health care responses. So what do you see as the TB Alliance's role in improving health care responses?

MELVIN SPIGELMAN, M.D.: Well, first of all, the drugs that we work on are such that when they're out there, they will allow the systems to be more efficient and effective because they'll require less care and less resources from the health care systems. So, from that perspective, part and parcel of shortening the treatment, simplifying the treatment, is a direct beneficial effect on the health care system to make that better able to manage the numerous patients, the volumes of patients, that are out there with TB in the high-burden countries.

Clearly, we also like to serve the advocacy role of bringing to everybody's attention that the health care systems also need to be butcherst [misspelled? 00:18:20]. That it's not just a question of new drugs. Both new drugs and improved health care systems are both crucial, and they both have to go in lockstep, together with each other. They feed on each other to the extent that if you can get resources to improve the health care system, that'll make the adoption of new drugs better. If we get new drugs, that'll make the resources necessary for the health care systems less. So these are really two sides of the same coin and they clearly have to work together, and we work part and parcel with the advocates and the people responsible directly for the health care systems.

JILL BRADEN BALDERAS: Mel Spigelman with the TB Alliance, we do appreciate your time today.

MELVIN SPIGELMAN, M.D.: Thank you. Appreciate your work in bringing this to everybody's attention.

JILL BRADEN BALDERAS: Thank you.

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