

**37th Union World Conference on Lung Health: Plenary:  
Extensively Drug-Resistant Tuberculosis (XDR-TB): How Did  
We Get Here and What Are We Doing About It?  
November 2, 2006**

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**MARIO RAVIGLIONE, Ph.D., M.P.H.:** Thank you very much and thank you for coming to this quite important session of this conference, probably the dominant session in the sense that media and everyone is focused today on this issue of XDR-TB. I just wrote an editorial that will appear in the bulletin *Infecting the International Journal of the Union*, and I was talking there about are we entering the post-antibiotic era with this type of situation. It may be an exaggeration, but in reality we are running fast towards development of resistance to more and more drugs. The importance of this session will be effectively [inaudible] outlining the history that is behind all of this starting with the notion, once again and we have to repeat that, that this happens where TB control is inadequate. This is not something that comes from the sky. It's man-made.

There has been a lot of rumor this year about this epidemic. Starting in March when the NDMWR, CDC and ourselves actually published the initial report about this that in fact in a way report notified the world about the existence of XDR-TB without the denominators or without much science behind it in a way, but certainly the existence of XDR-TB in at least 17 countries. We have the list of the 17 countries, of course. We know where this has appeared.

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There was later on in the summer the big news about the outbreaks in KwaZulu-Natal that has then steered a number of meetings that you will hear about, in Johannesburg, in Geneva and lately in Pretoria. So you will hear about the country responses, you will hear about the introduction, hopefully, of new diagnostics soon. You will hear of the issue related to drug access and the fact that in the end what we need is many more resources than we thought we would have needed this year to face TB, because this is unfortunately a costly mistake that of allowing XDR-TB to grow.

With that I immediately call on Sarita Shah from the Montefiore Medical Center in Bronx, New York, is an assistant professor in the Department of Medicine at the Albert Einstein College of Medicine, Yeshiva University, New York, to tell us right away what is XDR-TB, what are the current definitions, the plans for the future surveillance, and report. And, I apologize, I will have to go out for ten minutes from this room for a meeting related to this issue and I will get back in the next 15 or so. Thank you, you have the floor.

**SARITA SHAH, M.D., M.P.H.:** This talk was prepared in conjunction with Erica Wright from the Stop TB Department at WHO. Multidrug-Resistant Tuberculosis is defined as resistance to least isoniazid and rapamycin and emerged as a

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major public health issues in the 1990s. MDR-TB is caused by inadequate treatment of drugs susceptible to TB or [inaudible] primary infection with a drug-resistant strain. The treatment of MDR-TB requires use of second line anti-tuberculosis drugs. Therapy is more expensive, complex, lengthy and toxic than treatment of regular drug susceptible TB. Inadequate treatment of MDR-TB will, predictably, result in the emergence of TB strains with resistance to second line drugs. If a patient with MDR-TB develops resistance to multiple second line drugs it may be very difficult, if not impossible in some settings, to treat successfully.

In order to understand that definition and implications of XDR-TB some point to have a basic understanding of the treatment of MDR-TB. Second line drugs are divided into six classes, which are shown in the blue boxes on the slide. Examples of drugs in each of the classes are shown to the right of each box. In designing a treatment regimen for a patient with MDR-TB a minimum of four to six drugs should be used. The remaining first line drugs to which the organism is susceptible should be used whenever possible, as these are the most effective and have the least side effects. Then second line drugs are added, starting with one from the injectable class, a fluoroquinolones, and as many as needed from the last three classes to bring the

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total to four to six drugs to which the organism is known or likely to be susceptible. However, these last three drug classes are less potent and DST for these classes is less reliable than for the other drugs.

If a patient is resistant to multiple second line drugs, such as in this case with the shaded boxes, it is very difficult to design a treatment regimen with enough drugs with proven efficacy against MDR-TB. Earlier this year the CDC in collaboration with WHO and the Supranational Reference Laboratory Network published a report that documented and defined for the first time the emergence of tuberculosis strains with resistance to multiple second line drugs. Extensively Drug Resistant TB, or XDR-TB, was originally defined as MDR-TB with further resistance to at least three of the six classes of second line drugs. The results in the MMWR Global Survey that Mario mentioned used this definition in reporting of results. However, following the reports from KwaZulu-Natal, South Africa, which are characterized by very high mortality among a largely HIV co-infected population there was discussion about revising the original definition. The meeting of the Global XDR-TB task force in early October brought together laboratory specialists, clinicians and epidemiologists. The main factors that were considered in revising the definition were the poor reproducibility of drug

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susceptibility testing for some second line drugs; the differing clinical importance of some second line drugs compared to others, mainly that patients with resistance to aminoglycosides and fluoroquinolones and have poorer treatment outcomes; and the limited testing for all second line drugs in most country. For example, a laboratory may not be equipped to test for drugs that are not available for treatment of patients in that country. Based on these considerations, the revised task force definition of XDR-TB is the occurrence of TB in persons whose islets are resistant to at least isoniazid and rapamycin or MDR-TB, plus resistance to any fluoroquinolone and at least one injectable, second line drug, mainly amikacin, kanamycin, or capreomycin.

I will now present the findings from the Global Survey of Supranational Reference Laboratories reported in the MMDWR. One important thing to keep in mind is that the lack of standardized data collection globally for second line drugs and susceptibility testing is a major limitation in systematically assessing the global burden and prevalence of XDR-TB at this moment. Nevertheless, prompted by anecdotal reports of second line drug resistance we start to quantify the extent to which resistance to multiple second line drugs has begun to emerge globally. We conducted a retrospective

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survey of Supranational Reference Laboratories for M-tuberculous islets that have been tested for second line drug resistance for any reason during 2000 to 2004. The SRLs R network of micro bacteriology laboratories on six continents so this provided a global geographic distribution for this survey. However, these islets were a convenient sample of a referral population, which is more likely to include high risk patients. Thus, we also looked at population level from South Korea, the United States and Latvia. There were 14 of the 23 eligible Supranational Reference Laboratories that participated in this study and sent data on islets tested in their laboratory. This map shows the geographic distribution of the countries that are supported by the 14 participating SLRs. There were 49 countries marked here in red that had data included in this study. However, the data we received were sparse from Africa and were not available from India or China. We received data on 17,690 islets for this study. Of these 3,520, or 20 percent were MDR-TB. A total of 347, or 10 percent of MDR-TB islets were resistant to at least three second line drug classes and met the original MMWR definition for XDR-TB. Using the revised task force definition, a total of 234 cases would be classified as XDR-TB.

Looking at the geographic distribution of the XDR-TB cases from this survey, the highest number and proportion

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among MDR-TB cases were seen in South Korea, Latvia, and the countries of the former Soviet Union. Again, this survey does not allow us to draw conclusions about the true global burden or prevalence of XDR-TB but does tell us that XDR-TB is present in all regions of the world. In order to determine estimates of burden and prevalence of XDR-TB, standardized surveillance and reporting of drug resistance is needed.

Looking at existing systems. Historically, drug resistance data were not reported in a standardized way, making it difficult to compare rates between countries and estimate global burden. In response, in 1994, the WHO, IUHLD Global Project on Anti-Tuberculosis Drug Resistance was begun. To date, the Global Project has collected data from nearly 90 countries and many sub-national settings within countries on first line drug resistance. Approximately half of the countries reporting are conducting continuous surveillance, or culture and first line DST as part of routine diagnosis of TB cases. The other half of these countries conduct periodic surveys in order to estimate drug resistance.

In addition, since 2005, WHO has requested annual reporting of the number DSTs and the number of lab conformed MDR-TB cases reported, but because of the unavailability of

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testing and treatment in most countries, the cases reported are small and generally not a good way of estimating the prevalence of drug resistance. As testing and treatment programs scale-up, this will be a more useful indicator in the future. Because so few countries are routinely offering first line DST, second line drug testing is even less accessible in most countries. They're challenging second line resistance among can and is starting to be evaluated in a standardized manner. Currently the Global Project recommends that all MDR-TB cases detected in surveys are confirmed at SLRs and further tested for resistance to selected second line drugs. Many countries conducting routine culture and first line DST in TB cases also test for second line drugs. Second line drug resistance among MDR-TB cases can be collected from many of these countries. It's important to note, however, that an international quality assurance system for second line DST is still under development. [Inaudible] in place it is difficult [inaudible] laboratory results especially for some second line drugs, which are known to have less reproducible results.

These existing surveillance systems that I've just described can be enhanced by focusing attention on risk groups by use of new rapid testing tools and by incorporating

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HIV testing. Currently, WHO is recommending first line and second line DST on known MDR or failure cases to better understand the profile of second line drug resistance in the highest risk groups. In many countries testing will be facilitated by a Supranational Reference Laboratory. This information can be used to establish the presence of XDR-TB in high risk populations and will provide guidance for developing treatment regimens. Use of rapid testing, referring to all kinds, is being explored for both diagnostic and screening purposes, but also to facilitate rapid baseline surveys of XDR-TB in selected populations. It is expected that such surveys carried out by an external reference laboratory will be particularly useful while laboratory networks are being scaled up.

There is no movement towards integrating HIV testing into routine drug resistance surveys and they are beginning to emerge as access to HIV testing increases. HIV testing should also be integrated into rapid surveys of risk groups and sentinel systems where possible. As treatment for HIV becomes more widely available, HIV testing will surely expand.

There are several important implications of the emergence of XDR-TB. First, adequate diagnosis and treatment of drug susceptible TB remains the most assured way of

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preventing TB drug resistance. For this reason, it is critical to scale up and improve the quality of TB and MDR-TB diagnosis and treatment programs. International standards for second line drug testing have not been established, but are urgently needed. In addition, as will be discussed shortly, the reproducibility of DST for some drugs is poor and better, more reliable methods are needed.

Lastly, we must remember that these are people. These are mothers, husbands, teachers and nurses who are afflicted with virtually untreatable TB. We must increase access to modern diagnostic tools and second line drugs for all patients with MDR and XDR-TB to have a fighting chance of being cured of their illness. The importance of developing new diagnostics and new drugs is now more important than ever. All TB patients of all ages have the right to receive the highest quality care.

Thank you.

[Applause]

**KEN CASTRO, M.D.:** Thank you. In the interest of time, I request that those of you with questions, jot them down, write them down. We will have some time for group questions and answers.

Our next presenter is Dr. Karin Weyer, who is a director of the Unit for Tuberculosis [gap in audio] Research

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in the South African Medical Research Council. Karen, the floor is yours.

**KAREN WEYER:** Thank you, Ken. Good afternoon, ladies and gentlemen. I have been asked to give you a very brief overview of challenges with second line drugs susceptibility testing, the need for scaling up laboratory networks and an overview of rapid diagnostics that are currently in the pipeline.

It's been said over and over that laboratory services really represents the weak link in the chain of TB control. This weakness is now accentuated within the context of XDR-TB. The issues are summarized and I want to focus your attention on point three that when we talk about M and XDR-TB we need [gap in audio] safety in the laboratory and safety of lab workers. The WHO estimates with our current laboratory capacity that of the just over 4,000 cases of MDR-TB existing annually, only about five percent are being detected because of the problems related to DST. Trying to scale up laboratories is complicated and this slide shows you what's happened in the National Health Laboratory Services in South Africa over time. It's the same laboratory over three decades.

The WHO's Global Plan shows that expansion of laboratory services would have to be almost exponential to

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reach the 2015 targets and needs to happen very rapidly.

Sarita mentioned the network of 25 Supranational Reference Labs in the regions where they are most needed, particularly within the context of M and XDR-TB.

Also important to keep in mind that scaling up laboratory services require much more than just transfer of modern technology. These three pictures come my from country so the fact that South Africa is fairly far advanced in terms of laboratory capacity doesn't mean that we don't have problems of infrastructure and transport. In trying to scale up laboratory systems it's also very important that these factors be taken into account. As Sarita pointed to the new WHO protocols for screening high risk patients, one needs to be sure that those specimens reach the laboratory quickly. Laboratory infrastructure needs to be developed. And I'm not only talking about the laboratories, per se, electrical power supply, water supply, everything else that goes with that and it needs to be a proper plan of maintenance. Staff need to be specifically trained on DST and culture techniques and we have a huge problem with retaining capable laboratory staff, especially in developing countries. It goes without saying that we need appropriate quality assurance and quality control programs. We also need a system of rapid transfer of information once the results are available. It doesn't make

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such sense trying to accelerate the diagnosis of patients if we can't also provide adequate treatment for these cases.

Turning to some of the challenges that we face with second line drug susceptibility testing, if we take one step back and look at conventional first line drug susceptibility testing methods we have methods in solid medium where we define resistance based on a critical proportion of growth of a culture when exposed to drugs in that medium and there are different methods as outline B. New technology might use a liquid medium where we test for the presence of growth in the presence of a particular drug. These are largely automated systems. For the first [inaudible] the methodology's role, standardized role described and it doesn't really matter which method is used, the results are highly reliable and consistent and the predictive values of the first line susceptibility testing procedures have been well-described, although it's important to note that these values vary depending on the prevalence of resistance.

When we come to second line drug susceptibility testing the picture is somewhat different. We have reliable, reproducible methods only for the aminoglycoside polythiazide group of drugs and for the fluoroquinolones. For the aminoglycoside and polythiazide there are issues of cross-resistance between the individual drugs in those groups and

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these are conflict interactions. With fluoroquinolones the cross-resistance is complete so one can reliably chase for one fluoroquinolones and extrapolate resistance to the others. However, for the classes of drugs at the bottom we have no reliable drug susceptibility test.

Currently our constraint in trying to do second line drug susceptibility testing rests with the fact that we need [inaudible] to be able to determine the drug resistance profile and, therefore, the diagnosis is always late. It's complete and [inaudible] and part of the reasons relates to the fact that the drug powders that we use are really unstable in the drug susceptibility testing process. Another major constraint is that the concentration at which we define resistance is often very close or similar to the serum level obtained in the attained in the blood or to the drug MIC and as a result one gets inconsistency with different tests of the same organism.

Talked about the issue of cross-resistance and the fact that for the second line drug, the methodology has not been standardized. We have very little information to link a resistant result in the lab to the clinical progress of a patient. And, as Sarita has pointed out, very few laboratories do have the technical capacity.

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So what is that we need? Well, we need a drug susceptibility test that has these six characteristics. Unfortunately, there is not a test available on the market today that meets all of these. But there are some promising case and I'll just very briefly go through them. This slide depicts the absorption of new technology and as we expect it's largely quick absorption in the developed countries where financial and other resources are available. But there is a growing demand for expensive, more sophisticated tests to also become available in developing countries.

Some of the new culture based technologies in liquid culture is now the standard of care in developed countries. They, unfortunately still expensive, fairly sophisticated and only in two studies have they been some selective validation of some of the drugs in proper studies. There are some directives that are being done on sputum samples largely. The problem with these cases that have not yet been systematically evaluated. In especially low volume laboratories where there's a tendency to batch the specimens, there's an unfortunate delay in reporting the results of that rapid test.

[Inaudible] methods that we have available all show good performance characteristics, sensitivity approaching that of culture, but they are so very expensive and, in most

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instance, requires sophisticated technology. Although, the foundation for innovative new diagnostics are working with manufacturers to try to identify suitable platforms for use in developing countries. And the aim of find is to find ultimately a point of [inaudible] test. That is for affordable, but there's also the recognition that some of these sophisticated test would out of necessity only be used at centralized level.

This slide from [inaudible] shows the deliverables up until 2010. Within the context of XDR-TB I think it's very important that these timelines be shifted up. We can't wait another ten years.

Brief overview of some of the technologies that find we'll be investigating. The first is a first block assay which rapidly tests for rifampicin resistance in smear positive sputum specimens, results available in two days. This is the principals, the cultures are being treated with rifampicin. The cells are then infected with forges and once the forges are killed, the uptake of rifampicin can be measured. If the strain is susceptible TB [inaudible] are killed and, therefore, there would be an observation of forges. This is typically what one sees in the laboratory, resistance strain, no difference between the cultures treated with rifampicin and a susceptible strain clear difference.

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Second thing that has been extensively used in Latvia, is the inner liver test from immunogenetics, which is a molecular line probe assay. It tests for, it probes for five types of susceptible genotypes and four types of rifampicin resistant genotypes and it's potentially a point of K test, but unfortunately, so very expensive.

[Inaudible] recently evaluated the first block in the inner liver case in [inaudible] Peru, comparing as gold standards indirect DSTNLJ and the purpose of this slide is just to point out that the negative predictive values of all four of these tests are really promising, meaning that we can quickly screen out MDR-TB.

Another test that's recently been introduced is the Hines [misspelled?] genotype MTBDR, line probe essay, again strip test, which depicts or diagnoses in tuberculosis and then probes for the genes that select INH resistance as well as the gene for rifampicin resistance so one could have a rapid diagnosis of MDR very quickly.

Small study recently reported, evaluated this test directly on sputum specimens and in a few samples showed a high concordance between the different tests evaluated.

The gene expert system is another system that can potentially provide results within a few hours. Unfortunately, again, so expensive, so under development.

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Then the fourth test is a microscopic test where makes use of the principals that tuberculosis organisms grow rapidly in liquid culture and that they form characteristic cords that can be observed microscopically. This paper, again, shows very promising performance characteristics of that test. This is what it looks like under the microscope, typical cord formation, where there's resistance and [inaudible] susceptibility.

I think one final talk about new tools for diagnosis of XDR-TB without talking about the need to molecularly characterize these strains. We need to look at where outbreaks are occurring and which strains are responsible.

This is second to last slide. I'm just going to quickly go through the recommendations from the Global TB Taskforce in Geneva, where the need laboratory capacity strengthening was again highlighted as a prerequisite for maintaining an appropriate response to XDR-TB. There's an absolutely urgent need for lab capacity strengthening to be expanded, to be adequately funded, and to be accelerated. We very quickly need to look at the role of rapid rifampicin tests as surrogate markers for M and XDR-TB and how they would fit into diagnostic algorithms and the SRL network needs to be expanded if we have to provide the support to the surveys and surveillance programs that are coming.

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In terms of research needs there's an urgent need to standardize second line susceptibility testing to be sure that what we see in the laboratory actually corresponds with the patients clinical response. To look more closely at some of the second line drugs like fluoroquinolones in direct testing on sputum. We need, very quickly, large scale demonstration projects to evaluate the role of rifampicin tests. And to look at the inclusion of fluoroquinolones in some of the more novel case like the first block and the strip test. And to add to the previous speaker's call, we urgently need new diagnostics, especially for smear negative cases of M and XDR-TB, which is increasingly becoming prevalent in our HIV burden settings. Thank you. [Applause]

[Gap in audio]

**MARIO RAVIGLIONE, Ph.D., M.P.H.:** [Inaudible]. She is at the State Centre of TB & Lung Disease in Riga, Latvia, as well as a WHO Cooperating Center for the training on MDR-TB. Vaira, you have the floor.

**VAIRA LEIMANE, M.D.:** Thank you. Dear chairpersons, dear colleagues, I will present you management and treatment of XDR-TB in Latvia. Latvia is one of cebaltic states consistently ranked among countries with highest rates of MRD-TB worldwide and implemented both country wide in 1996. MDR-TB management started in '97. Latvia has very rapid

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increase in tuberculosis incidents and MDR-TB incidents. We speak in 1998 and later [inaudible]. Our numbers of resistant cases decrease 2.2 times over six years. Among old cases or treatment cases, MDR-TB decreased four times during six years. The resistant numbers among TB HIV patients increased total number as well as MDR-TB/HIV cases. However, it's not big numbers it's increasing.

Laboratory diagnostic methods used for drug susceptibility testing basically is [inaudible] infant methods by absolute concentration, but we use very widely [inaudible] system according priorities to use this test. Perhaps priority is patient with high risk of MDR-TB. The second priorities are sputum [inaudible] cases for better detection of MDR-TB and the infection control purposes. Inner liver test is used for high risk MDR-TB patients for more readily a detection of multidrug resistance and start proper med treatment.

We use drug susceptibility test for all second line drugs we use for treatment for MDR-TB patients. Don't use [inaudible] because we don't have this test.

Objectives of our studies is that the nation of proportion of extensively resistance patients according to methods of resistance. A number of XDR-TB patients according WHO definition and the previous definition and patients

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categories over said time. The determination of treatment outcome by potential extensive resistance and the determination HIV set of prevalence, the rates by potential of extensive resistance. We used for this analysis registration cohort for 2000-2005 and treatment cohorts for 2000-2003. All these data is entered in MRD-TB database and the underlies of these data from this database and the treatment outcome for this three years.

Definitions. MDR-TB it's resistance at least [inaudible] XDR-TB we used revised WHO definition task force definition accepted now. MDR-TB resistance plus fluoroquinolones and one of injectable. Previous definition published in March, MDR-TB resistance plus three second line drugs out of six classes. Proportion of extensively drug resistance according these two XDR-TB definitions you can see on this table the first definition is increasing over the years starting from 11 percent in 2000 and increasing up to 30 percent in 2005, but if you look on the new definition accepted by task force, it's lower number of cases and the starting from 2.5 percent and increasing to 7 percent.

If we look in each patient groups it's mostly distributed this excessive drug resistance you can see the occupations who previously was treated with second line is more rapid increase in this number of patients and most

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distributed in this group. But among the new patients never treated it's also increasing among patients who was treated only with first line drugs before.

Resistance happens to individual drugs among these 820 patients we have resistance in [inaudible] but as you can see the resistance to first line drugs is very high [inaudible], 70 percent [inaudible], streptomycin, 97 percent, kanamycin, as well, is close to 50 percent, capreomycin, 39, ofloxacin, 9 percent, [inaudible] 30 percent, as well, low risk cyclocline, 2 percent.

These [inaudible] characteristics for all patients who were treated for MDR-TB, using these year 2000 cohort, which was published in Lancet we had 204 patient with 107 DST treatment regimen. It means that the management of these patients was extensive resistance to second line drugs is very difficult and many of drugs used for this treatment seeks in most common used drugs was ofloxacin and [inaudible]. Treatment outcomes by drug resistance patterns shows us that MDR-TB had treatment outcome pure plus completion 67 percent and rates decreasing according to definitions. But, all definition MDR-TB plus three say second line drugs achieve cure rate for 58 percent, but for new definitions it's decreased very much. It's cure rate

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only for 28 percent of patients and for [inaudible] increased to 55 percent of patients.

HIV rates among drug MDR-TB patients groups so that overall MDR-TB patients group there's a three percent, we don't have high rates of HIV among MDR-TB patients up till now. But, for these subgroups, the percent of these patients increasing. The highest is among patients which fits the new definition.

In conclusion, MDR-TB is decreasing in Latvia, but still not increasing primary of the MDR-TB. XDR-TB is increasing steadily among all MDR-TB categories, but particularly in patients who have a history of previous treatment with second line drugs. Cure rates decreased significantly when potential drug resistance includes injectable, aminoglycosides and fluoroquinolones, but it should be studied more and find out how many drugs these patients have resistance. HIV may be a factor in worse treatment outcomes in drug resistant patients and this laboratory test to second line drugs sometimes makes the management of MDR-TB patients difficult. The challenges in controlling drug resistant tuberculosis in Latvia perhaps is in improving treatment outcomes for drug sensitive case and not alone develop new cases of MRD-TB. Rapid drug resistant detection, appropriate treatment, rapid diagnostic tools for

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all the infectious cases, expand use of conduct investigation, decrease treatment introduction and [inaudible] improving patient compliance and, if necessary, use compulsory treatment for this patient, infection control measures should be strengthening and separation of patients with risk for extensive drug resistance should be sold more strongly in health care setting, in prisons, isolation for patients on palliative care, which you can't reach cure, it's a difficult issue and can be sold and new drugs and treatment regimen, it's necessary for these patients for extensive drug resistance, which can't achieve cure. Thank you very much for your attention. [Applause.]

**KEN CASTRO, M.D.:** Thank you, Vaira. I'll remind the audience that we will have questions and answers at the end of the presentations.

I invite Dr. Paul Nunn, who is the coordinator of the WHO team in Stop TB Department concerned with TB and HIV as well as tuberculosis drug resistance, to join us and present on the global emergency response. Paul, the floor is yours.

**PAUL NUNN:** All right. Well, let me start by thanking Ken and the organizers for inviting me to give this talk. So I'm going to focus on the global level and the emergency aspect of the response to XDR-TB. I speak on behalf of a lot of people involved in this process.

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I will discuss what's taken place up till now; what we have we already done; what the framework is under which we are planning the work forward; and what actions, more specifically are planned. On the actions to date - I hesitate because this isn't the last version of the presentation, but never mind. It's one of these PowerPoint moments. Many of you will be aware of the meeting in Atlanta in May, which took place under the Partners [inaudible] and was also the working group meeting of the MDR working group, at which we first heard about the problems in Tagliaferri. The WHO's strategic and technical advisory group took up the issue in June and made it very clear that they were expecting a swift response to the problem being addressed. The Tagliaferri information was presented at the IES Conference in Toronto and picked up by a few major newspapers. Then we moved quite quickly, the South African Medical Research Council and the Center for Disease Control with WHO to have an expert consultation in Johannesburg on September 7<sup>th</sup> and 8<sup>th</sup>. In preparation for that meeting WHO issued a note to the media expressing concern about the situation and the response to that note to the media I'll discuss in a moment.

The following Friday, September the 15<sup>th</sup>, we got the go ahead to form a response team after discussions with the teams involved in WHO in the SARS and avian flu and Ebola

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work. The following Monday, September the 18<sup>th</sup>, the response team was formed. Within a few days, quite quickly although not quickly enough for some, we had basic information on the website, both Stop TB and WHO, we had frequently asked questions prepared, we had a paper for the Weekly Epidemiological Record ready and we were already embarking on fundraising, of which more later.

By October 9<sup>th</sup> and 10<sup>th</sup> we had a meeting prepared of the first meeting of Global XDR Task Force. The day after we had the revised definition that you've just heard about on the website and a meeting report prepared for the Weekly Epidemiological Record, but some of you will have seen, I think it was last week, the new definitions already in the Weekly Epidemiological Record. The South African Department of Health asked us and WHO to take part in a consultation with the SEDIT countries, of which seven were able to make it on October 17<sup>th</sup> and 18<sup>th</sup>.

This is some headlines taken from the rather unprecedented media response in preparation for the September meeting. And you will, if you just cast your eye over some of these headlines, note the problem in getting out accurate messages. Now I'd like to present the framework under which the global level response is being organized. The first and most important priority I think is the immediate

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strengthening of the essentials of TB and HIV prevention, care and control in countries. I'll go into all of these in a bit more detail in a moment.

Secondly, strengthening the management of M and XDR-TB and, particularly, this is both case management and programmatic management and introduction of new rapid diagnostic tests. There must an intensified effort to build laboratory capacity in addition to existing efforts. Infection control is paramount together with protection of health care workers, especially in high HIV settings. Surveillance and monitoring of M and XDR-TB is essential if we're to understand how far and to what extent we have a problem, but it needs to be incorporated into more long-term surveillance methodology as quickly as possible. We need clear advocacy, good communications and mobilization of societies. Research and development of new tools needs to be accelerated and, in order to pay for all this, we need urgent resource mobilization.

So in order to take the [inaudible] i.e., basic TB control, as well as the more [inaudible] resistance related issues in this second area here, which I will come to in a moment. South Africa and La Sutu have officially requested WHO assistance and there are discussions ongoing with many of the other Southern African countries. And, in particular,

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South Africa has requested assistance with some resource issues, with the cross border migration or XDR cases, particularly in the mines returning home, possibly to foreign countries for the holiday period. There needs to be a significant increase in both international and national TB staff addressing the basics as well as the drug resistance issues and an urgent increase in training courses for drug resistance management. We held the first training course in the African region in October in Dara Sa Lam, but we are moving very quickly to organize a second course. There will be immediate revision of the Global Plan to Stop TB to reflect the need to incorporate XDR-TB, increase the budget, and increase the speed of scale up, amongst other things. That work has already begun.

The management of MDR-TB and XDR-TB both case managements and program management clearly needs to be strengthened. There are being addenda produced to the guidelines for the programmatic management of drug resistant TB that came out in May in order to reflect the issues of XDR and make it very clear that XDR is included in those guidelines.

The algorithm for identification and management of suspects is being revised and will shortly be disseminated

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and WHO and CDC staff are both very much involved in these two issues.

Access to rapid tests for both rifampicin and INH resistance needs to be achieved and, as you've heard, there will be a meeting conducted by Find and the South African Medical Research Council on November 16<sup>th</sup> to address this in the Southern African region. And enlargement of the Green Light Committee is already underway in order to expand access to second line drugs. I think it's important to mention here that the global fund has already agreed to undertake procedures which will facilitate access to second line drugs for countries and to support the Green Light Committee's work and UNITAID, the French pursuit with partners approach to use airline tax funding for AIDS, TB and Malaria have agreed to support the provision of procurement of second line drugs, as well as the acceleration of the prequalification of manufacturers of second line drugs. They've made an agreement with the WHO Central Drugs Program to do this just recently. So this is a major step forward I think. WHO is undertaking to disseminate legal and ethical global guidelines that address the compulsory issues surrounding medical treatment and isolation.

Karin has discussed has intensified laboratory capacity building in some details so I will emphasize just a

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couple of things here. The need for a national budgeted plan for accelerated laboratory capacity. You'll notice in this table here that if you just look at the high burden countries in Africa, excluding South Africa, population of nearly 400 million, there are just 13 laboratories capable of doing culture, and 11 of these can do drug susceptibility testing. South Africa, with a population of 47 million exceeds this capacity on its own. If you look at the non-high burden countries, the number of laboratories capable of carrying out reliable culture I think can be counted on the fingers of one hand. So we have a problem with laboratory capacity. Yet, ultimately, our goal needs to be, I think, access to timely, quality assured, TB lab services, including rapid acid fast culture and DST for all patients, which is a difficult goal in this context.

Infection control, the infection control guidelines prepared in 1999 are being updated thanks to CDC and Paul Jensen, particularly. We've recently prepared an addendum to those guidelines to address the issues of infection control in high HIV settings. These are ready and they are being prepared for publication electronically and in hard copy. And rapid implementation of these infection control measures needs to be put into place immediately in health care settings and other risk areas, including prisons.

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A working group on infection control is being established within the Stop TB Partnership and members of my team have organized a first meeting of people interested in joining this working group, which will take place this afternoon at, I think, 4:00, but somebody will correct me if I'm wrong in the discussion period. I think this group needs to address, particularly, an urgent implementation plan of the infection control guidelines at country level.

In surveillance there's a lot of things that could be said, but to simplify it I think we need rapid simple tests to determine the geographical distribution and the size of XDR-TB. We have a generic protocol ready, which will also link this XDR work with HIV, which is fundamentally important. At least some of these surveys I hope will look at the genetic strains and at least some of them also will be linked to the rapid rifampicin testing. But, I think we need also to look at the detailed epidemiology of a number of cases to determine more precisely how these cases arise. The South African government has agreed that this shall be done in South Africa.

Advocacy, communication, social mobilization is fundamental. A task force has been established and they are addressing the priorities the strategy and the funding for increasing capacity and strengthening communications at all

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levels. They will address the development and dissemination of messages on XDR-TB following the guidelines if you like discussed at the Global Task Force meeting and they are planning media events, both globally and nationally to get out the messages.

On new tools, WHO and the research working groups are organizing a meeting on the research implications of XDR-TB in early-2007, probably in Cape Town and the Minister of Health is being invited.

Now, all this costs money. These numbers may be a little bit too small to see. But they focus on the financial requirements from now until the end of 2007 in the Southern African countries. We calculate somewhat crudely the country costs as being around about \$18 million USD, with \$35 million going to all the activities that we have already presented. About \$40 million for the cost of second line anti-TB drugs to some 6,000 M and XDR-TB patients and \$5 million for rapid diagnostic tests. The international agencies require about \$50 million to support this and provide the technical assistance required. Now, this is effectively the summary of a more detailed plan that we have ready and that will be disseminated to potential donors next week.

At the most recent consultation in South Africa in Pretoria, these countries that were present in this list here

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have also agreed to provide national level plans with costing by, I think it was, the 10<sup>th</sup> of November. So we hope that they will appear. If not, we will provide the technical assistance to get them pretty soon thereafter. There needs to be briefing of the development partners and agencies, i.e., potential donors, on the topic of the plan. A network has already begun and that's why your Chairman skipped out and came back a moment ago.

The Global Fund is open to reprogramming of existing grants to incorporate XDR activities and, of course, they're very interested in receiving applications in round seven, which we hope will take place next year. The PEPFAR Country Operational Plans for 2007 are virtually a done deal, but there are in a number of countries still possibilities of incorporating XDR-TB activities and therefore that opportunity where it exists should be seized. And USAID have said that the TB cap system can be used to support XDR-TB, but this, of course, requires that countries request that it be done.

So, the next steps with respect to global coordination. There will be meetings between WHO and the South African Department of Health around about November 15, 16 and I will be going down to have further discussions with the Department and that occurs around the time of the

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workshop on rapid testing in Pretoria, also. South Africa has agreed to bring up the issue of XDR-TB at the Southern African Development Community Health Minister's Meeting, which I think is on November 17<sup>th</sup> in Namibia. The coordinating board of the Stop TB partnership will address XDR-TB in [inaudible] in four weeks time or so and will consider, amongst other things, the importance of strengthening links between all the working groups and the MDR-TB working group in order to develop the response that we've been talking about in XDR-TB and, in particular, revising the Global Plan. We would anticipate that country level implementation should be underway in the worst affected Southern African countries by December of this year.

Now it's impossible to present in detail, an emergency response in 15 minutes. So here's some issues that I must mention or they will otherwise be forgotten. In terms of getting support for activities in countries need to request that support. Secondly, partnerships are essential. Partnerships with other groups, the HIV community, the community themselves affected by TB and HIV. TB/HIV link is absolutely essential if we're to decrease the mortality in the HIV infected, but I think here we still need better to define the products that are going to be created as a result of TB and HIV collaboration. The people working on human

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resources for health must be involved in this process, it's crucial. And the economic analysis of the impact of TB and TB control being prepared for the African Ministerial Conference, which keeps being postponed, needs now to incorporate issues of XDR-TB.

So this presentation is focused on the Southern African context, but of course there are already MDR efforts underway in China, India and Russia and we need urgently to incorporate the XDR component into those efforts. So, I will finish by quoting the Lancet that "if we fail to act now to contain the threat posed by XDR-TB it will have devastating consequences for patients with TB, particularly those co-infected with HIV/AIDS." So I sincerely hope that the plan that I've laid out will rapidly be funded and, for those of you who may be responsible, we need \$5 million USD by the end of this year in order to keep existing efforts rolling. Thank you very much. [Applause.]

**MARIO RAVIGLIONE, Ph.D., M.P.H.:** Thank you very much, Paul. Since we are in an emergency mode, let's proceed and very rapidly. I introduce now Mrs. Elizabeth Huff, who is the Chief Operations of the newly established interim secretariat for UNITAID, that is based, at the moment at WHO Geneva. Elizabeth, you have the floor.

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**ELIZABETH HOFF:** Thank you. Thank you very much.

I'd like to thank the organizers for inviting UNITAID here to this conference. I'm very pleased to inform you that we are now moving ahead to support multidrug resistance TB. I would just like to bring you back to inform you what UNITAID is. It is actually an international drug purchase facility, which is popularly called UNITAID. There are five funding countries. It was actually the Minister of Foreign Affairs in France, Dr. Douste-Blazy who took the initiative to establish this and he was quickly joined by Chile, Brazil, Norway and United Kingdom. The idea is that this is going to provide sustainable and predictable financing. France introduced the airline tax and we have seen from the media that more than 96 percent of the French population is now supporting this solidarity fund. Norway has introduced a tax on the omission on CO2 and the other countries are also providing funding, which is predictable and sustainable through long-term budgetary contributions.

It is moving ahead after the G-8 Summit in St. Petersburg this year, 19 countries actually expressed an interest in joining UNITAID. UNITAID has declared that they are going to support treatment for TB, Malaria and HIV. This they are going to do by actually reducing the prices on

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quality drugs and accelerating the pace at which they will become available to the people who need them.

There are three quite clear approaches that will be followed. They will work through partnerships and the partners have been identified. For HIV they are working closely with UNAID with the Clinton Initiative and also for the TB it's the Global Drug Facility and the Green Light Committee in WHO. For Malaria, ACT, UNICEF and the Global Fund.

As I said, that's for UNITAID's mission. It is quite clearly that lowering prices for drugs and diagnostics is a key issue. When the proposals have come in from the partners it hasn't been sufficient just to say that we can provide treatments to the people and a number of treatment. That also had to describe the process that they will go through in order to lower the prices of the drugs and the diagnostics. And this will be done through strong negotiations through pool procurements. There will be a cost plus methodology and increased demand as you know and increased volume and there will be increased competition. And all countries should have access to favorable prices that have been obtained by UNITAID. Clearly we are targeting the poor countries. So, 85 percent of the funding should be going to low-income countries.

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For TB the support will be for MDR programs in 2006, \$7.9 million USD, which will be made available in the beginning of December and for 2007 there will be \$38.2 million available. This might even increase for 2007. We are also supporting a pediatric TB by making available appropriate strength TB drugs. For this year it will be \$0.9 million, which will be increased to around \$5 million next year.

We worked closely with all of our partners in setting up these programs. UNITAID will not implement, it will just be a very lean secretariat, established at WHO, which will be working with partners. We will work very closely to try to identify the funding gaps for drugs and diagnostics and hope to come very strongly at the arena at the end of 2006 and to also be working more closely with you in 2007. Thank you very much. [Applause.]

**MARIO RAVIGLIONE, Ph.D., M.P.H.:** Thank you very much. This is most welcome news. And now let's have those that are suffering the real burden of XDR, MDR and TB, and Patients and the Community representatives. So we want to hear their perspective. I have hear three colleagues and people that will be talking starting with Case Gordon, director and founder of the World Care Council, coordinator also of the Patient Charter, that I'm sure he will be talking

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about. I already see there and an acting board member of  
UNITAID.

Later there will be Mrs. Carol Nuranda [misspelled?],  
President of World Care Council, based in Lusaka, Zambia, TB  
Village Activist and also an alternate board member of  
UNITAID, with Case Gordon and, finally Mr. Maxime Lunga  
Nsumbu, who is the President of the Club des Amis Damien, a  
patient TB advocacy organization based in Kinshasa in the  
Republic of Congo for MDR occupation and member of World Care  
Council. Thank you very much, Case.

**CASE GORDON:** Thank you Ken, thank you Mario, for  
allowing us here. I'm actually here not to talk about my  
experience and my recent upgrade from being an MDR survivor  
to now an XDR survivor. [Laughter] I'm also not here to  
talk about the Patient's Charter, it's rights and  
responsibilities, nor to address the human rights question  
about MDR and XDR. I am here actually to applaud over the  
last few months a movement from the people up here and many  
of you to begin to gear up, to begin to address an issue that  
I have been well aware of for about five years has been  
hidden in the shadows. Many of my peers dying, slowly,  
horribly and nobody really wanting to talk about it. Over  
the last five, six months, since Atlanta actually, it has  
given me a breath of fresh air. But, this is only the

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beginning. We need to scale up, gear up, move up, a lot faster and address all the questions as have been outlined already. We'll come back to that.

But, anyway, one of the things I'm also here to speak about shortly and I'll then pass the mike to my friends, is that our need as the community to not only get involved, but to lead and to drive the resource mobilization that is needed. Resource financial, but also social mobilization. Right now over the last few months we keep hearing about XDR and MDR. Quite a few of my colleagues and peers and friends, were afraid. They don't know what this. They don't know what they should do. Should they bother continuing to take their treatment if it serves no purpose. We need to mobilize our communities with you the professionals and the experts to basically pull out a lot of resources to address as is being outlined by Paul and others.

One of our first action sin this mobilization will be in support of UNITAID. I got involved with UNITAID about a year ago because I thought it was a lovely idea. You folks get on airplanes, we get drugs. Good idea, innovation. From that the communities have been working to figure out how we can use UNITAID and how we can push UNITAID to get bigger and bigger, more money. The more you fly, the more drugs for us. Not just drugs, we're now talking with UNITAID about,

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oh, we need diagnostics. We will ultimately need new drugs. What can we do about it? There's a limited number of countries involved at present in UNITAID. We intend to push a lot more countries, not just the donor nations. Every country in the world has a class of people who get on planes. We would appreciate their assistance that when they get on a plane some of their money ends up buying drugs and driving down the prices of what drugs there are already. Now, I will pass the mike to a few people who live in communities that are living in fear today. The more we talk about XDR, the more their afraid. This is Carol. [Applause.]

**CAROL NURANDA [misspelled?]:** Good afternoon everybody. From several sessions that we have been a part of since we were here, including this one, we have heard over and over again the gravity of MDR-TB and now they emergence of XDR-TB in South Africa and other parts of the world. We people living with the disease are happy that there is this session today that has been organized to begin to address this problem.

At present, very few people have access to second line drugs or to the good MDR treatment, generally. One without with other serves no purpose. We have no idea how many people in the world today die of MDR-TB or XDR-TB. This is an enormous problem that certain the whole global efforts

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for stopping TB. We need together to advocate for second line drugs now and new drugs at long-term. We also need laboratories that can do drugs and [inaudible] testing to know if one is resistant to the drugs. In the South only South Africa has that kind of laboratory. We have heard about the new initiative namely, UNITAID. We the community of people living with the disease have also developed an innovative campaign. Under the banner, "You Fly, We Live". My colleague Maxime will expand more on this system of resource mobilization. Thank you. Maxime. [Applause.]

**KEN CASTRO, M.D.:** Excuse us, we thought there was going to be bilingual translation from French into English, but apparently it's not working. I know there is a doctor in the house. Is there somebody who can translate in the house, who can quickly? Elizabeth?

**MAXIME LUNGA NSUMBU:** For a serious problem, a serious solution. Imagine the number of people with drug resistant tuberculosis not diagnosed, not treated across the world. My country, the DRC, drug resistance is only known about only in Cachucha. So what happens to multiresistant patients in the rest of the country? In 1998 primary resistance had a prevalence of 2.1 and secondary resistance over 20 percent. And what about today? It's extremely important that everybody involved with tuberculosis control

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supports this initiative. Let me share with you some thoughts. When I'm facing a patient with tuberculosis and I have TB myself, initially such a patient is told well this is a curable and treatable disease and later he has to be told that, well now you're going to spend money to buy additional drugs for MDR and that persons believes then this is no longer a treatable disease. So, with all of our energy we will support this initiative. So, therefore, I'm extremely pleased to be able to assist the launch of this initiative "You Fly, I Live" at this the 37<sup>th</sup> Meeting of the International Union at the Special Session of MDR and XDR. We just want to say when you take a plane we have life. So, please we plead with you, ask your countries to join this initiative supported by five countries. Let the airline tax be applicable everywhere. The TB patients everywhere may have access to diagnostics and treatment. You fly, I live and thank you. [Applause.]

**KEN CASTRO, M.D.:** Thank you Maxime. The last presentation or last set of remarks come from Dr. Devin DeCock, who in addition to being an impromptu interpreter, happens to be the Director of the WHO HIV/AIDS Department and he will talk from the perspective of the HIV Program.

**DR. KEVIN DECOCK:** Thank you Ken and thank you my colleagues, friends. I just want to make some very general

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comments from the perspective of the public health community from the HIV perspective. Firstly, I want to congratulate the TB community, which has changed so much over the past ten years since I first attended this meeting. I'm struck by the successful advocacy that's going on. On the other hand I also find some concern in the fact that this is driven, as we've witnessed our friends who've spoken, by the issues of multidrug resistance or XDR. It's driven by HIV infection. And yet the majority of those two million or so who die annually of tuberculosis actually have susceptible TB. It's susceptible TB that's at the very problem of these issues that we're talking, of HIV associated TB and XDR.

I'm impressed also at the emphasis that's being put again at this meeting on the need for new tools. The comment that actually we're using technologies, some of which is developed in the late 19<sup>th</sup> century, and yet that mantra, I remember first hearing in the late-1980s. I think it was actually Dr. Jim Mason, the then Director of the Center for Disease Control, who actually said it at that time when the United States was experiencing it's resurgence of TB. Just to emphasize that this is true, but my goodness, we have to accelerate that work, that pressure and those initiatives.

I think the TB community has done a great deal to change and accommodate to the needs of HIV and yet

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unfortunately I think we still remain two communities divided by two common infections. I think the TB community still has to reach out more to the HIV community. But I also want to comment and to acknowledge I think the TB community has changed more than the HIV community has and that actually the balance, more effort needs to come from the HIV side. From the HIV perspective we have to remember that in high burden countries and high burden settings TB intervention is actually going to have to be delivered through HIV services and TB needs to be at the center of AIDS care in high burden developing countries. That requires effort from the HIV community, but it's also going to require understanding and support and some generosity from the TB community, including perhaps, letting go sometimes of a little bit of the control. Clearly one of the most significant historical events in AIDS has been the introduction of anti-retroviral treatments and it's scale up, which is a double-edged sword for TB. Because on the one hand it can increase life in TB patients. It's probably, I often say, that the introduction of ARVs may be as important for tuberculosis in high HIV settings as the introduction anti-tuberculous drugs themselves, in terms of saving patients lives. It can reduce the incidents of TB by restoring immunity, but it also paradoxically can increase complexity and vulnerability by keeping HIV infected patients

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alive, obviously a good thing, but alive with continued vulnerability to tuberculosis. So it's certainly, our lives have become much more complex.

We also need your help to deal with stigma and discriminations. I think the TB community has many, many years of experience with stigmatizing disease, but somehow gets on and deals with it. I think we on the HIV side and can learn from that. I think we need your help as we deal with a very important issue, that of scaling up HIV testing, provider initiated HIV testing and counseling in health care settings. The TB community has a very important role to play.

In this the three by five era I think some things have changed fundamentally. Obviously, one thing that's changed also is that access to drugs for multidrug resistant and XDR-TB is something we just have to, in the same way that we did with ARVs, we are just going to have to say this is a right, this is something that has to be achievable everywhere.

So, finally, to finish my quick comments, just a few thoughts on the lessons of XDR, the implications of XDR for the HIV community and the struggle against HIV/AIDS. Firstly, I think one of the really worrying things is that what brought this to attention in South Africa was first the

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HIV that all of the patients are heavily affected and with high mortality drew attention to it, but also the fact that it was South Africa that had the ability to drug resistance testing. If this had happened somewhere else we might never have known. I think because the development of drug resistance in XDR is really a phenomenon of mandolin revolution and second line therapy is hardly used anywhere else in Africa. The true extent of this problem may not be that widespread in Africa, but what I think is possibly widespread, or will become so, is MDR, with XDR then just the sort of tip of the iceberg. MDR, because those drugs are used elsewhere and patients will live longer as ARVs are scaled up. So as we have these discussions on XDR I think we need to be prepared for a much, much broader need and attention to be paid to the problem of MDR-TB, of which XDR after all is just an extension.

It brings into the issue the same, as did the whole three by five program, the whole issue of health systems and human resources. Health systems, meaning the whole gamut, human resources, infrastructure, lab capacity, procurement systems, supply chains, management, et cetera. I think we're sort of drawing a line in the sand here saying, finally, we have to deal with the issue of labs. We cannot make progress on this issue of drug resistant TB without labs. The

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situation in Africa is actually amazingly dire. Outside of South Africa, in many, many countries in the public sector it is not even possible to make a bacteriological diagnosis salmonella typhi let alone sophisticated drug resistance testing for tuberculosis. So a reinvestment in the laboratory capacity that is eroded in Africa in front of our eyes over the past 15 to 20 years, is I think an absolute priority and should be a priority for donors. This whole issue obviously raises the problem of tuberculosis transmission in congregate settings in hospitals and we are congregating patients for ARV services in hospitals where infection control has been neglected over the years. It will not be restricted, this problem of TB transmission to hospitals, but it goes on in prisons and other congregate settings as well. The issue of human resources is the subject of WHO's World Health Report in the last year. Obviously, it's tragic that in the South African experience there were health care workers who died. Providing a safe working environment is going to have to be a priority because we cannot tolerate the impression to emerge that caring for AIDS patients or caring for TB patients is dangerous and is something that people won't want to do. That is something that we just cannot allow to emerge.

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Finally, is any of this new? Not really. What we're witnessing really is the events of New York City in the late-1980s and early-'90s playing out in a Southern African context. It reinforces again the tragedies that can emerge when basic public health infrastructure is allowed to erode and when lessons of surveillance and infection control and so on are not taken care of.

So, thank you for the opportunity to speak from the HIV perspective and I hope that these two communities, TB and HIV, will unite around this extremely serious issue. Thank you.

**KEN CASTRO, M.D.:** Thank you Kevin. [Applause.] Appreciate it. I need to acknowledge that in spite of our best laid out plans, we are on time, but have run out of time for questions, which I am mortified about, personally. I know that there's another session in here at 2:00 p.m., but I'll be bold and allow a couple of questions as long as they're short and the answers are equally short. Members of the press, please refrain. Know that there will be a press conference in room 235 Mezzanine, which is 2.5 level, here in the conference center. If I can see a microphone or persons at the microphone. With this glare I can be barely see.

**KEVIN CONNELLY:** Kevin Connelly, New Jersey, U.S.  
Let me try to make a weak attempt to represent a human

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resource that we've not heard from. That is the clinician facing a patient with MDR or, worse, XDR. I think this is a desperate situation and on an individual basis, the clinicians are going to have to tell these patients that if they have HIV they're likely to die, if they don't it will be a protracted course with very toxic medicines. What I'd like to see a call for is for clinical trials on what the optimal way to treat MDR-TB, cause obviously XDR-TB is resulted from inadequate treatment of MDR-TB, just as MDR-TB is a result of inadequate treatment of drug susceptible. So, we not only need new tools, new drugs, but one thing that's been omitted is that surgical resection has improved outcomes in the U.S. and I think it should be considered for desperate situations in other areas. South Africa has a lot of talented people and I'm sure something could be mobilized, but people will need to be trained. But, as you know, in Denver, outcomes improved dramatically with surgical resection of cavities in selected patients.

**KEN CASTRO, M.D.:** Thank you very much. I appreciate that comment. The last comment is going to come Dr. Perlman from the Russian Federation.

**DR. PERLMAN:** My name is Perlman, I am from Moscow. I want to several words about...

**KEN CASTRO, M.D.:** Short several words, please.

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**DR. PERLMAN:** Yes. Several worlds about the classification of resistance. In my opinion the classification must be clear and short. No resistance, this is great zero. MDR-TB, this is grade one. XDR-TB, this is grade two. The resistance to all drugs, this is grade three. The paper, this is very short and simple. After the diagnosis we must write R0, R1, R2 or R3. This is my proposal. The last, in the treatment of the MDR and XDR-TB there are very important tool all matters, [inaudible]. This is [inaudible] therapy and surgery. Thank you.

**KEN CASTRO, M.D.:** Thank you Dr. Perlman.  
[Applause.] You have hereby been recruited to be part of the technical group revising definitions. Thank you all for being here.

[END RECORDING]