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**38th World Union Conference on Lung Health
Stop TB Symposium: XDR-TB and TB/HIV: A Threat or
Opportunity for TB Control: Part 2
November 8, 2007**

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RICK O'BRIEN, M.D.: -priority for tuberculosis control at least from the vantage of WHO as strengthening laboratory services and increasing laboratory capacity, particularly culture and drug susceptibility testing to meet the challenges that MDR and XTR TB and TB/HIV pose. And so the last three presentations before lunch this morning deal with laboratory issues.

The first presentation is to talk about new global policy developments and laboratory issues will be from Karin Weyer, Ph.D. who is still currently with the South African Medical Research Council but at the conclusion of this meeting, will be joining the Stop TB Department in Geneva to head up a new laboratory unit. So, Karin? And please if we could have conversations stop so Karin can give her presentation. Thank you.

KARIN WEYER, PH.D.: Thank you, Rick. Good morning, ladies and gentlemen. As Rick has indicated, we are pressed for time, so I'm going to try to be very brief. We will have a short discussion session at the end of the three presentations, so we can pick up on issues then.

I think looking at health systems, it's well-recognized that the laboratory services are probably at this point the weakest link in already challenged health systems. It's also very clear from many countries that patients face significant

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economic barriers in accessing TB diagnostic services in many settings. And as a result, the time to diagnosis is often prolonged and delayed.

As you heard this morning from Mario and we'll hear repeatedly during this symposium is that the effective response to the two major challenges to TB control, which is TB/HIV and MDR-TB, the most crucial barrier at the moment is appropriate diagnostic services.

So I would like to share with you in this presentation two new developments: the one related to new policies for case finding and case definitions. Veronique Vincent, a colleague of mine at WHO, will share with you the new policy developments on the use of liquid culture. And then I will say a few words about the new Global Laboratory Initiative.

In the laboratory meeting this afternoon, we will be presenting new policy guidance that is still under development on second line drug susceptibility testing, so I will not talk about that today, but you're all invited to the session in the afternoon.

The new WHO recommendation for case finding was recently endorsed by the Strategic and Technical Advisory Group to WHO with wide support also by key agencies and Stop TB partners. And essentially what this boils down to is that the recommendation for case finding now is to reduce the number of sputum investigations from three to two in settings where the

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microscopy network is functioning and where there is evidence of an external quality assurance program. This is a pragmatic change in policy largely aimed to try to relieve the workload and the human resource constraints that we are facing in many settings.

The second policy change, which is related to the case finding strategy is the definition of a new smear-positive TB case, which currently calls for two smears to be positive or one smear being supported by radiological evidence or culture evidence, now has been changed to one smear positive found would constitute a case and would require that patient to be on treatment.

The background to these two policy recommendations can be found on the WHO website, and it explains the rationale, but I just want to summarize the evidence, which is in the background, and the process that's been gone through to reach this point.

In September of 2005 an expert group was convened to look at the available evidence related to the two smears as well as a single positive smear for case definition. That was followed by a systematic review of more than 30 studies that were considered to be eligible. It was published. You see the references at the bottom, which clearly show that the incremental yield of the third specimen is around 3-percent and that within a properly quality-assured microscopy network, 86-

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percent of smear positive cases, the most infectious cases, can be picked up by the first smear and then other 12-percent by having a second smear.

In looking at the revised case definition, it is currently estimated that up to 17-percent of additional cases would now enter treatment algorithms because of the change in the case definition.

Obviously, there are certain criteria for implementing these two new policy changes at country level, and the first requirement is a well-established microscopy network supported by a fully-functional external quality assurance program.

However, as I've said, the policy changes— and if you'll read the documentation— are flexible enough to allow country-specific adoption, so we're not advocating a change for all countries by the end of this symposium. It's understood that it has to be a systematic process, that one needs to build the evidence for the quality assurance component.

But I also want to make the point that both these new policy changes are already contained in the international standards for tuberculosis K, so we have a responsibility now, I think, to also promote these new policies by users of the international standards.

The expected impact on service delivery. Obviously, we can see a 30-percent reduction in the laboratory workload, which I think has relevance for settings with high burden of TB

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and human resource constraints in particular, and an associated reduction in laboratory costs. But the recommendation, the strong recommendation, is that any money saved needs to be reinvested in making sure that the quality of microscopy is improved.

If we do that, the expected outcome is a decreased delay in the time to diagnosis and decreased transmission and a decreased number of patients being lost somehow early on already in the diagnostic pathway.

The next steps at the level of WHO is to guide and support countries to modify the relevant TB control programs, the recording and reporting tools, the training materials, to coordinate the necessary technical assistance to help countries upgrade their microscopy networks, very importantly to monitor the impact of these policy changes at country and regional and global level. Katherine presented this morning where we are with targets, and we can anticipate a change, for example, in case detection coverage by implementing the new policy changes.

And coming back to laboratories, we also need to model the impact of these changes on the projected costs and the needs to scaling of laboratory services, which brings me to the second part of the presentation, and that is the realization that we need to move from not being able to provide lab services to not being able to do without lab services.

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The slide at the bottom is the projected number of MDR-TB patients that would require treatment by 2015, 1.6 million that Mario showed this morning. But we have to realize that to be able to treat those cases, we have to find them, and currently, the estimate is that around 5-percent of existing MDR cases are being detected because of the lack of laboratory services.

In May the World Health Assembly called for universal access to culture and drug susceptibility testing as the standard of care in TB. But if there is a recognition by every single partner in TB control, that laboratory capacity currently is a global crisis and that to scale up and to expand really requires a paradigm shift in thinking about providing guidance. How do we manage quality, and how do we share information?

It's also clear that we need to move up the visibility of laboratories, and one way of doing that is through a global integrated laboratory network called GLI, and I want you to remember GLI in the future, which has recently been endorsed by the Stop TB coordinating board two weeks ago in Berlin.

This slide illustrates the dramatic scale up in laboratory, culture and drug susceptibility capacity that we are facing moving from 2008 to 2015. Not going to go into the details. Currently, we are refining some of these estimates,

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but you can see, it's a dramatic scale up, both in terms of capacity, also in terms of funding that would be required.

The components of the GLI, first of all, would be to coordinate, guide global policy guidance on especially second line drug susceptibility testing and culture; to be the voice for lab services through advocacy and resource mobilization; to assist countries with developing the necessary capacity to scale up the laboratory services; to be very sure that there is an interface with other laboratory systems so that we are not working in isolation; to take care of the necessary quality assurance; to promote the involvement of technical agencies and technical partners; and to be able to rapidly communicate new policies, new changes, new information on laboratory standards.

This slide summarizes the conceptual framework of the GLI with the coordinating office that will be based in Geneva at WHO, which would provide the Secretariat to the initiative. But then, as you can see, very much a partnership, global stakeholders consisting of the various constituencies, the network of supranational reference labs, the network of national reference labs in countries and all the associated services. And on to the outside of the slide you see some of the essential core activities that the GLI will be undertaking, and I'm not going to go into detail.

To make the point again that we see this very much as an integrated health systems way of approaching the diagnostic

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need, cutting across different diseases, cutting across issues like infrastructure, human resource development, but also at the same time, being very clear about what kind of laboratory service is required at what level, and this is meant by a tiered laboratory service.

Over the last year, the laboratory working group has been very active. The supranational reference lab network has now involved into general laboratory capacity building. The technical guidance, the policy-making component has been moved from being previously an expert opinion driven activity now to a structured consensus-building process involving all the partners supported by technical work groups, which are called together as required.

We are in the final stages of developing, finalizing a business plan for the GLI, and this afternoon we will be presenting the newest, latest policy guidance on second line drug susceptibility testing, which will be followed very soon, hopefully before the end of the year, with detailed technical manuals on the laboratory component of doing second line DST.

There has been a reorganization at the WHO in Geneva, integration of the TB laboratory activities, and as the Secretariat to the GLI, we are revising the work plan, and we are reorganizing certain key components, cross-cutting components at the level of WHO.

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There was also a core group formed in the beginning of this year under the guidance of John Ritterhoff [misspelled?], who is the Chair of the GLI, and as you can see, this is a broad-based partnership with key agencies involved, representatives from national TV programs, from patient communities. And it's anticipated that in the future, the core group will be expanded based on specific needs that may be identified.

Last slide, next steps, the priorities for the GLI is to come up with clear estimates for the numbers of laboratories needed under the various scenarios of epidemiology of MDR-TB and TB/HIV, for example, and to cost this properly. The second priority is to really be flexible in the business plan and be ready to absorb new technologies. As we heard this morning, we probably will have a new diagnostic long before we have a new drug, and we need to be ready to provide the lab capacity strengthening and model the impact that new technologies will have on the needs for laboratories.

Several key activities have been identified, and we are now prioritizing the priorities, so to speak, largely centered around three things: really finalizing standards for equipment, for quality assurance, all the technical standards. Biosafety is another one. Assisting with building management capacity at global level to be able to rapidly respond to the challenges and to help countries set up accelerated systems for

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lab capacity strengthening also involving the private sector, which I believe is a large untapped source of laboratory capacity that we need to bring into the picture.

The business plan will be followed with a global stakeholder/funder meeting that is planned for early April next year where we would like to get all the stakeholders in lab capacity strengthening together, do some mapping of what is happening where, and then tidy up and finalize the resource mobilization plan so that we are able to go to funders with a firm estimate of what this is going to cost. Thank you, Rick.

[Applause]

RICK O'BRIEN, M.D.: Thank you very much, Karin, for this very nice overview of major policy changes on diagnosis as well as this exciting new initiative that we hope will engage all of you over the coming year. As Karin indicated, we'll proceed with the presentations and then have a joint discussion at the end. The next talk will be given by Dr. Veronique Vincent from the WHO Stop TB Department to present the new WHO policy guidance on liquid culture drug susceptibility testing and rapid species identification that was issued just last month formally by WHO. Veronique?

VERONIQUE VINCENT: Thank you, Rick. Though I'd like to focus your attention for the next few minutes on the rather technical issues related to lab activity and especially lab diagnosis using liquid culture.

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At present, the vast majority of patients are diagnosed using microscopy, that being the same technique used by Robert Carter in 1882 when he discovered the TB bacillus. Having said that, I do not mean that microscopy should be discontinued. It's an essential component of lab network, and it's interesting to note that the new WHO recommendation for 2007 to address microscopy and liquid culture.

And microscopy is certainly the most rapid test, cheap and portable, which can be in very peripheral settings. However, it's not sensitive, and this slide I summarize its sensitivity. To be rather consistent, microscopy requires to 5,000 to 10,000 bacilli per amount whereas culture, either on solid or liquids, the sensitivity level is 1-percent to 100 AFB per amount.

But being much more sensitive, culture is also much more slow, and the time for diagnosis differs according to whether the smear is positive or negative. But while liquid have the advantage to almost half the time for diagnosis, and the time for DST results is certainly the most benefit is regarding this time to DST results, which using a solid medium, seven weeks are required, and this can go down to two weeks in smear positives using the liquid culture. And this is the reason why we would like to expand the use of liquid culture because of this increase of sensitivity over microscopy and certainly reduction of delays over solid culture.

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So the WHO recommends the use of liquid cultures and the rapid species identification. These two techniques have to go along in association to really have the benefit of better, of shorter delays using liquid cultures. And this liquid culture is used to direct the needs for culture and DST, and this is, of course, especially true regarding challenges posed by MDR-TB because we need cultures to determine the drug susceptibility pattern and for challenges posed by HIV because microscopy fails in most HIV patients.

And this implementation of liquid culture should be integrated in a country-specific comprehensive plan for lab capacity strengthening. That means needs should be assessed and integrated in a strategy plan before considering the adoption of liquid culture.

And in fact when we consider the implementation and how should this be done in countries best in three main bullets. One addresses the need for a budgeted package with different components which have to be all present to have the benefit of this technology.

We'd like also to phase out all this, but the background documents, which has been used for the proposal of the purpose presentation of this new recommendation is available on the website, and this background document mainly relies on studies led by find in endemic countries.

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Liquid culture is not a new technique. It has its part of, it's been developed many years ago, so the rogermetric [misspelled?] method was the reference method for liquid. And now what's really changed is that we have automated. That means machines able to handle a lot of samples by the same time, and this automate uses non-radioactive liquid medium, and those tests also contributes to for an easier implementation because whatever waste disposal of radioactive compounds was a problem and, certainly, a costly problem.

In the package we considered, safety is a component. Maintenance of infrastructure and equipment in laboratories. Does the equipment have to be adequate, well maintained, and this is also, of course, regarding safety issues when we consider effects on biological safety cabinet. If it's not well-maintained, it's more hazardous and protective.

Staff has to be well trained. This is also a key issues because these techniques are not easy to perform, to carry out. People have to be well experienced. One of the prerequisites we recommend is that people already master solid culture because using solid culture is a bit easier to have indicator, for example, contamination rate, anyway, all the proficiency of the system before, and certainly, this is also important before adopting liquid medium.

And because we speak about commercially-available products, that means that is a very strong ties with

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manufacturers, and they should be also very cautiously considered. And transportation logistics, rapid communication of results, well, it's one part just to have still the benefit of shorter delays.

And transportation logistics, customs problems, et cetera, are also be part of the customer plan, which represents all the guarantees and commitments of the manufacturer. And one of the main commitment of the manufacturer is to provide all these products, all the products necessary for the technology, at an affordable price and over time. In other words that people that have these technologies can really use them without any budget problems.

All the customer plan also have to address very carefully all the issues related to training to servicing to maintenance. And considering the implementation, it should be a phased implementation with national reference laboratory as first priority. We speak about autobase [misspelled?] as I just say. That means with high workload and only its focus for national reference laboratories depending on every country, on the size of the country, of region, et cetera. But this centralization then should be phased according to country needs and capacity, and people at the national reference laboratory then could serve as trainers for the prototype of implementation.

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So serve ballot for the recommendation regarding implementation of liquid technology is regarding biosafety. Biosafely is really an issue when it comes to the general use of culture and DST especially large amounts of bacilli are being handled, so this biosafety issue should be reflected in country plans for liquid culture implementation.

I would like to stress in conclusion that these tools I'll not alternate for molecular tools. I heard many, many comments on the use of molecular tools. We still have no recommendation, but hopefully, next year this should be available. Anyway, molecular tests are screen tests to diagnosis MDR. They do not go provide further details on the drug-resistant pattern of a strain of a culture. They're also very good tests to rule in MDR but not to rule out.

And anyway at present we have this recommendation on liquid culture. That doesn't mean that it's not to be performed in association then with molecular tests in the very near future according to recommendations.

I would like also to say that these tools are not perfect, but they are the ones that we have in our hands today, and we cannot suggest a status quo because we have only to consider the patients today who deserve proper management. And this recommendation can really contribute to improve and shortening delays in diagnosis and DST results. And we know that there's a rapid progress in the allotment of new

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diagnostic tools, but these tools are not ready today, and this is the reason why this liquid culture has a place, I think, in all lab. Thank you very much for your attention. [Applause]

RICK O'BRIEN, M.D.: Thank you, Veronique. I just have to comment that it seems like the environment has changed radically. It was only a year or two ago that people were saying don't put too much emphasis on culture. We need to maintain smear microscopy and assure quality-assured microscopy network, which remains true, but it was saying no, no, no culture. And now we're saying yes, culture is needed, but it's too soon to say the molecular tests would render culture obsolete. So I mean just to hear that now is a real change.

VERONIQUE VINCENT: No, no. I wanted to be very clear on that, you know? It's not culture is not to replace microscopy, and it's also we have to consider the future that molecular tools according also to find studies can be usefully used, but at present we don't have this recommendation. That's it.

RICK O'BRIEN, M.D.: We're going to move our last presentation now and then have questions at the end. As Karin Weyer implied, the global estimates for culture and DST capacity are truly staggering, implying in some estimates the need to establish up to 2,000 new culture- and DST-capable laboratories by 2015, a staggering, staggering challenge. But to describe one small glimmer of hope, then the recent

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experience in Lesotho in collaboration with FIND and Partners in Health Dr. Keke.

KEKELETSO KAO: Thank you. I'm pleased to present the efforts made in Lesotho in addressing the issues of MDR and XDR by establishing a quality-assured culture in DST facility within a short period of six months. And we have also been able to streamline, to have a streamlined, quality-assured smear microscopy and the following is going to be basically a progress report and our achievements to date.

Lesotho is a small, mostly mountainous, landlocked country that's completely surrounded by South Africa. It is divided into ten districts and has a population of approximately 2.2 million people. Last year we had a recorded 603 TB cases per 100,000, and this was one of the highest TB incidence rates in the world.

Sputum smear microscopy is used for both diagnosis and the monitoring of treatment. We have 17 microscopy centers, and all of these are linked to hospitals, and seven of these are run by the Christian Health Association of Lesotho. The central TB laboratory is located in the capital Maseru, and this lab functions as both a microscopy center and a TB referral point. Previously, there was lack of an organized quality assurance program and no network of laboratories.

This slide basically highlights the distribution of our microscopy centers and the population that they serve. You

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also see that our population is mostly concentrated in three districts, and these are in the lowlands. And these are catered for by seven microscopy centers.

Together with having one of the highest TB incidence rates in the world, Lesotho also has one of the highest HIV infection rates at 23-percent. And the incidence of TB among HIV-positive individuals is estimated at approximately 80-percent.

In 2006 at the request of WHO the Foundation for Innovative New Diagnostics conducted an assessment of the central TB lab in Maseru, and the main objective of this assessment was to evaluate the lab's capacity to conduct TB culture and DST.

Following that assessment, the following recommendations were made: That the lab needed to be renovated and upgraded. The workflow had to be streamlined. Five more technicians had to be recruited to work full time within the TB lab, as at that time only two technicians were working full time in the lab. Equipment that had already been procured using funds from global FIND had to be installed into the lab, and this was because the equipment was sitting outside the lab because it was found to be too big to fit through door. We had a single door entry.

We had to carry out countrywide training and establish an EQA for sputum microscopy, and we had to establish quality-

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assured culture and DST, and once that had been done, we would then establish liquid culture and DST and also introduce rapid identification methods and then later implement rapid molecular methods to diagnosing the TB.

Our objectives in the first year were to develop manuals and modules and to train the technicians on smear microscopy, to establish a quality-assured smear microscopy lab and to renovate the central lab for culture and DST, to streamline solids culture and DST and to introduce liquid culture in DST method and to also carry out fast [inaudible] tests using capilliar [misspelled?] TB.

To assist in the upgrading of the central lab, FIND appointed a consultant for onsite evaluation and technical expertise. FIND also provided method culture and DST system, capilliar [misspelled?] TB, and they will also be providing the supplies needed for the liquid culture for a period of two years.

And Partners in Health together with the Ministry provided all the logistics and financial support, and the WHO appointed an officer to monitor MDR-TB related activities in Lesotho.

The central lab in Maseru had originally been built as a microscopy center, and over the years, minimum culture activities had been introduced, and to renovate what was previously the office of the microbiologist who is in charge of

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the lab was converted into a sample receipt and microscopy room. What was the main area of the lab previously used for staining and minimum culture works was converted into a media room, culture room with negative air pressure. And that was also, the storage room was also converted into being part of the culture lab. And what was previously our microscopy room was converted into the sterilization room.

This is the hospital, Three Fellow [misspelled?] Hospital in Lesotho. And we can see there the doorway the equipment wouldn't fit. We have since put in a double door entryway. These are basically pictures that show the renovation process of converting our microscopy lab into a lab that meets the minimum biosafety requirements for culture and DST. An anteroom was put in. The office was converted into a microscopy room. Lab partitioning was put in to create a media prep room and sterilization room. An onsite autoclave was also put in and negative pressure.

And then all the hardware, the incubators, refrigerators, autoclaves were also installed, and we've also ordered X-ray equipment. All the renovations on the building were supported by Partners in Health, and they are also supporting salaries for three additional lab technicians. USC is supporting a salary for an additional lab technician, and FIND is supporting the liquid culture system. And FIND has also provided onsite technical assistance. And our lab

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currently meets the minimum biosafety requirements for TB culture.

We've since started conducting quality-assured smear microscopy and solid culture. To improve the quality assurance program within the labs, training was conducted at the central level for all the technicians and initially introduced a 15-percent rechecking, random, blinded rechecking of the slides, but this was found to be too much work and lot quality assurance sampling was introduced. Control slides are used for set and stain incidence, both since August, and we do both negative and positive control.

And training for the culture in DST was done in August. The equipment was installed and validated, and SOPs were prepared. Antenna controls for the medium and culture in DST were introduced, and we enrolled into an external culture program that is run by the supranational that brought you in Pretoria.

To standardize our TB culture on solid medium, 213 samples were processed in August and September, and of these when you look at the quality indicators, our smear positives and culture positives at 97-percent. And our smear negatives that are culture positives 31-percent and the contamination rate is below 1-percent.

With the random blinded rechecking that was done in August, 300 smears were rechecks, and with these we found that

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the percentage of false positives was 1.4-percent. The percentage of false negatives was 0.7, and the discordance between the laboratory technician and the controller was 1 to 0.6. In August over 2,650 sample smears were processed. In September we decided to go with the lot quality assurance sampling method, and only 26 slides were rechecked.

In conclusion, we have been able to upgrade our lab within a short period of five months and have adequate proficiency in carrying out culture and DST on liquid media was demonstrated as per internationally acceptable standards, guidelines for EQA network of smear microscopy. Training manuals and modules for technicians have been developed. Standard operating procedures for culture and DST as well as for smear microscopy were introduced. Four additional lab technicians were recruited. Proficiency testing is currently being done. And the Baxter [misspelled?] liquid culture system was installed, and standardization of the culture and DST in process and other repeat diagnostics will follow.

Our future plans are to establish a liquid culture system for DST by November, December this year, to complete the proficiency testing in collaboration with the supranational lab in Pretoria, to carry out trainings for the rest of the lab technicians in the country and to introduce EQA using random blinded rechecking at regional level, to be a trial site for rapid identification kits, the rapid identification kits

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capilliar [misspelled?] TB and to establish additional microscopy centers. These would be located within the health centers. And to carry out the countrywide threat resistance survey as the last one was done in 1995 and to also have additional manpower as the plans to construct a new referral TB lab and to also establish EQA for sputum microscopy and TB culture in three regional labs. Thank you. [Applause]

RICK O'BRIEN, M.D.: Thank you very much, Keke, for a presentation of what is obviously a very positive project and outcome and what we hope can serve as a model for the expansion of culture and DST capacity that will now be expanded significantly.

Can I invite all three of the previous speakers to join me here for a short period for questions and comments? And, please, if you do come to the microphone. Yes?

TOOL STIN: Yes, my name is Tool Stin [misspelled?]. I'm from Botswana, so I would particularly like to congratulate Lesotho with all the progress they made, but I've got a question. It's mainly for the second speaker I think. Now, you made quite a convincing case for starting to use liquid media, but I just wondered could you say a little bit about the cost implications? Now, if you are using solid media, approximately how much would your costs increase if you want to switch to liquid media? Thanks.

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VERONIQUE VINCENT: Rick will answer you because can you hear me?

RICK O'BRIEN, M.D.: If I can, I'll answer the question. As Veronique indicated, this guidance was developed on large part based on the experience of FIND and what we've referred to as demonstration projects looking at the commercial BD system for case finding and TB-HIV as well as enhanced and more rapid detection of MDR-TB and dots plus [misspelled?] settings, and these were done in eight settings in the developing world. And a number of people who have participated are with us.

For that BD significantly discounted Midget equipment and con-symbols [misspelled?], culture to drug susceptibility tests systems, and in response to WHO's issue and some guidance, FIND and BD just this past Monday, announced a new pricing structure for the Midget system that will be available to 39 high-burden, low-income countries for the foreseeable future that provides for midget culture for, in most cases we would guess, under \$3.00 per test.

We did some detailed costing exercises in a couple of our demonstration projects in the Philippines and in Samara, Russia, and found that for case finding, the cost for liquid culture at the prices that were available to us which will continue now and even further reduced, was very comparable to

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that of solid culture, within a few percentage points difference, not significant over it.

So I think the costing will become less of an issue. I think the challenges are, as laid out in the guidance which is very cautionary because as Veronique indicated, it's not so easy. Contamination rates are much higher and highly, there's a degree of training that's required that exceeds that of solid culture, too, but we did find that it was feasible. Yes?

MUMBA MWIME: My name is Mumba Mwime [misspelled?] from the National Defense Lab in Musaka [misspelled?]. I'd like to know if there's any policy changes in regard to the number of specimens to be submitted at follow-up visits.

KARIN WEYER, PH.D.: Thank you for that question. Yes, the policy has changed to obviously the same definition for defining a failure case, and the follow-up investigations are still the same as in the current who guidelines, which means one smear at two months, one smear at the end of treatment.

RICK O'BRIEN, M.D.: In the back? Yes?

RUTH MCNALON: Ruth McNalon [misspelled?], School of Hygiene. I think it's fantastic news that the labs are being rolled out and expanded on. I'm lab background, so I'm very biased, so it's tremendous that this is finally happening. But I have one concern about rolling out liquid culture in high HIV areas. We haven't yet seen what impact it actually has on the patients. To wait, I guess, a month by the time you've got

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your sample to the lab, they do the tests, you get the results back, it's got to be round about a month?

So you're going to delay treatment for that patient for a month in an area where there's a lot of extrapulmonary disease. You're not treating for extrapulmonary disease. Is it going to have an impact on your conditions, are they already going to have started treatments or are they going to delay treatments?

I haven't seen any studies reported yet on impacts of the liquid cultures on patients in high HIV areas. Are they about to be published?

RICK O'BRIEN, M.D.: Well, one of the intents of the demonstration projects was to collect information, patient and clinical information, to assess impact. These weren't available for presentation at WHO in Stack [misspelled?] this year, but it is our intention to collect these data and make them available next year. And I fully agree with you, but I would also say that we're also quite supportive of further assessments of the new WHO algorithm for the diagnosis of smear negative tuberculosis in settings where HIV is prevalent and where it's possible to be supported by culture.

But I think we will be learning a bit over the next couple years, both through the algorithm and expanded use of culture, how best to use these systems. Here and then in the back?

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JOSEPH WILLIAM: Thank you very much. I'm Joseph William of CDC Kenya [misspelled?]. I have two comments. One is with respect to the place for fluorescein microscopy in a revised definition of a case of TB. I know that fluorescein microscopy's more certainty than regular microscopy, and there are a number of settings currently investing this. Just a comment on the need or the place of fluorescein microscopy.

The other issue is there is rightly increasing interest in putting as many HIV-positive TB patients, particularly children. This has been a difficult area. Many, many settings, you say, you talk about the diagnosis of TB in children, and many, many people would kind of like to dismiss these. At the same time, there is heightened increased interest in increasing opportunity for children, particularly those who are HIV positive, putting them into treatment or into ART, and it is hoped that their primary diagnosis of TB is an important step in channeling them to ARBs. Is there any particular progress or interest in tightening the objectivity in the diagnosis of TB in children?

RICK O'BRIEN, M.D.: Let me just make a brief comment about fluorescent microscopy. Later this week FIND will be announcing a major initiative in the development and implementation of a very low-cost, high-quality LED microscope that we hope will be implemented widely over the next years. I think there are a lot of data indicating that this technique is

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quite good, increased case finding, reduces technician load and can make a real difference. You have a comment on pediatric TB?

KARIN WEYER, PH.D.: No, I wanted to pick up on the first point to be clear that the new policy changes are not explicit about a preference for zeta [misspelled?] or fluorescent microscopy in anticipation of some really exciting new developments around affordable fluorescent microscopy that will be coming.

RICK O'BRIEN, M.D.: As far as the diagnosis of tuberculosis in children remains difficult. It's on our priority list. There are no tests in the near horizon that we think would make a huge difference. We are looking at an interfering gamma-release assay for the diagnosis of pediatric TB as an aid in the diagnosis in collaboration with a number of partners. But in terms of something specific for TB diagnosis in children, not yet, but it's critical. In the back, please?

NONA SHUTI: Nona Shuti [misspelled?], South Africa. I have two questions for Keke in Lesotho. You gave us the TB incidence among HIV-positive patients as 80-percent. I wanted to know how you measured that because HIV is, of course, an illness over a long period.

And then also your quality assurance indicators false positives were 1.4-percent and false negatives 0.7. What are the normal values or what is expected? Thank you.

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KEKELETSO KAO: Okay, the HIV, the TB in HIV-positive people, that's an estimate that's done by WHO. We don't have any concrete data on that. And the other one was—sorry. Forgot the second part of the question?

KARIN WEYER, PH.D.: False positives, what is your criteria and what is the norm?

KEKELETSO KAO: Oh, okay. For false positives, it should be anything less than 5-percent is okay, and for false negatives, I think, was the second part of the question? It's also the same.

RICK O'BRIEN, M.D.: Okay. We'll take three more questions and comments before breaking for lunch for those that are currently standing. Jane?

JANE CARTER: Jane Carter from Moi University Empath Program in Eldoret, Kenya. I had a question about the Lesotho project. I was just very impressed. As one of the FIND demonstration projects, we've struggled with our contamination rates with the midget, and I thought I heard you to say that your contamination rate was under 1-percent and you got there within about six months? Do you have [interposing] of that?

KEKELETSO KAO: No, no. This was on solid medium, not on liquid.

JANE CARTER: Okay, thank you.

KEKELETSO KAO: We haven't started the liquid medium yet.

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JANE CARTER: Okay. I misunderstood that. Thank you.

KEKELETSO KAO: Yes.

RICK O'BRIEN, M.D.: Carol?

CAROL HAMILTON: Carol Hamilton, Duke University. I just had a question when you talked about— this is to Veronique—when you talked about the recommendation is for culture implementation first at the national reference laboratory. So I guess my question or my concern is it seems like the place it's most needed is really where the patients are at the local level so that we have more patient-specific real-time culture data available for making treatment diagnoses, as opposed to what I think of national reference laboratory priorities, which is kind of a more global look at things.

Maybe that's a wrong assumption, but I just was hoping you could maybe comment on why the priority would be at the reference lab as opposed to trying to get out at some areas at the local level first.

VERONIQUE VINCENT: Sure, it's advisable that samples be treated as close at the referral laboratory, but it would be very difficult to implement using cultures. You see, the reason why we insist so on the logistics in order not to create delays with the transportation of samples. And why to start with the national reference center? Is it because we speak about automate so in fact it's to have a rather centralized

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system at the beginning, and there's several reasons for that. Because of the automate of the workload, then to be able to handle many samples to have the best experienced people, especially and we can see it's illustrated in the Lesotho because it starts with solid medium. It must have done that well to start them before implementing liquid.

And this has to be phased because of this constraint, because of the difficulty of the technology, and then people at the NRL could be trainers for the Photostat of decentralization, but that you're right that the literal goal would be to achieve such a decentralized system.

MALE SPEAKER: Thank you very much. My question is related to extrapulmonary tuberculosis. What's the place of liquid culture in identifying microbacterial in pleural, in cardio and central and the central spinal fluid?

VERONIQUE VINCENT: I'm sorry. I didn't understand quite well your question.

MALE SPEAKER: What's the place of liquid culture in identifying microbacteria in pericardio, pleural, pectoral and central spinal fluid media?

VERONIQUE VINCENT: The technique is rather sensitive. It's even more sensitive than solid, so you can anticipate better results for this extrapulmonary specimens.

MALE SPEAKER: What results have you got so far to show?

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VERONIQUE VINCENT: I'm sorry?

MALE SPEAKER: In regard to specificity and diagnostic accuracy.

VERONIQUE VINCENT: There's a lot of literature dedicated to this issue. You see, this is not new technology. It has been used for years and especially in low and endemic countries, so you can really, you have huge literature about all this results.

RICK O'BRIEN, M.D.: Okay, we will take two more questions, and then we'll break for lunch. Yes, sir.

JOSEPH: Thank you so much for your good presentations. My name is Joseph from CRL Kenya. My question comes when we talk about liquid media implementation, and I'm getting concerned because I'm the user, but so far I have not dealt with that result to give us a questionnaire to feel, how do you feel about the Midget 960 or the LG system?

Because like we are doing something. We are trying to evaluate the kit, and we found some discrepancy on the isonassay [misspelled?] on the high level and the low level. When you are trying to compare, the LG was giving even low levels. But when it comes to Midget system, it does not give low levels of isonassay. So I believe when you are coming up before you implement something, I think it's good consult the user to give us what we feel about it because I think we are having a bit of problems. Thank you.

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RICK O'BRIEN, M.D.: Okay, regarding the discrepancies which can be found between the LG system and the liquid system for drug susceptibility testing, in fact we revised this. We have this exercise because of the second line drug, but we also provide a rather simple table to be used for the different concentrations according to the different methodologies because you're right. There were some changes because historically LG was the first method. Then came the back test method, I mean the rogermetric [misspelled?] liquid medium method and then the cold liquid ones. And the comparison was always made with the LG and some adaptation because of the changes of medium, but I think now the differences or difficulty is over.

RICK O'BRIEN, M.D.: Yes?

ZAFICIA AYIAD, M.D.: I am Dr. Zaficia Ayiad [misspelled?] from Provincial Reference Laboratory Pakistan. First, I would like to appreciate the presentations given by you. My question is that you are suggesting to establish solid culture and liquid culture one by one. So what would be the utility of the solid culture once the liquid culture would be established fully?

VERONIQUE VINCENT: Thank you very much for the question because that's what many persons ask me, so in fact, yes, it's important to have solid master the technique, I mean the culture technique. And then you can steer them to the use of solid, not exactly as a culture per se, but at the backup

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for isolation. I mean the difference when you use, when you completely develop a system from scratch with the medium preparation, it's a heavy task to be performed.

Once liquid is implemented, then you can continue the use of solid just for as a backup culture, not really part of the culture itself but maybe for identification or just in case the contamination rates would spoil the liquid.

ZAFICIA AYIAD, M.D.: Thank you.

RICK O'BRIEN, M.D.: Well, in conclusion I'd like to thank all this morning's speakers and all of you for attending and being attentive. Bon appétit and we will return at 2:00 to resume. Thank you. [Applause]

[Interposing]

VERONIQUE VINCENT: Thank you very much.

RICK O'BRIEN, M.D.: Thank you.

[END RECORDING]