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TUBERCULOSIS: A NEW VISION FOR THE 21ST CENTURY

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Abstract Tuberculosis is a global problem that we can't afford to keep ignoring. In 2006, tuberculosis killed 1.7 million people—almost twice as many people as malaria—and it is the leading cause of death among people living with HIV/AIDS. This is all the more tragic because these deaths are preventable. For a long time the world thought that we had defeated tuberculosis, but just because tuberculosis doesn't make headlines doesn't mean it has gone away. The fact is that tuberculosis is getting worse, as complacency and lack of adequate tools and funding fuel the disease and the spread of drug resistance. Drug resistant tuberculosis is the wake-up call, it is an airborne epidemic of increasingly untreatable disease. Drug resistant tuberculosis develops when tuberculosis patients take low-quality drugs, do not finish their full course of treatment, or pass drug resistant tuberculosis from one person to another. In 2007, there were approximately 500,000 cases of drug resistant tuberculosis globally. MDR-TB is resistant to the two most commonly used first-line TB drugs, and requires long, complex and expensive treatment. XDR-TB is resistant to first- and second-line drugs, severely limiting treatment options. While progress is being made, much more is needed. Basic tuberculosis control is one of the most cost-effective interventions in global health. Appropriate treatment can save a life and stop the spread of disease for US\$14. It is essential that countries implement the World Health Organization's (WHO) internationally recommended Stop TB strategy, which includes DOTS. But due to outdated tools and methods, DOTS alone is not enough. The remarkable fact is that global control of tuberculosis, a disease that kills someone every 20 seconds, depends upon a 125-year-old test, an 85-year-old vaccine and drugs that take six months to cure and haven't changed in four decades. To successfully treat tuberculosis and prevent resistance, we need to use current tools better and accelerate the development of new tools for the future. Simple improvements in tuberculosis control, such as expanding the use of under-utilized technologies, can have enormous impact. Fixed-dose combinations have existed for over 25 years, and could help ensure that more patients complete treatment; yet globally, only 15 percent of patients are using them. We also need new drugs, vaccines and diagnostics, as well as innovations in tuberculosis control and case management. Better diagnostics are already available, and new drugs and vaccines are coming. But more commitment and resources are needed. Better prevention and control of tuberculosis is the surest way to stop drug resistance. To ensure that drug resistance does not pose a wider threat, we need to employ a number of equally important approaches. These include improved basic tuberculosis control, increased use of under-utilized technologies such as fixed-dose combinations, and new technologies and health systems innovations. At the same time, we should expand access to M/XDR-TB treatment and diagnostics for those who already have drug resistant tuberculosis. Some of the most innovative solutions can come from the private sector and through partnerships. An untapped market of two billion people carries the tuberculosis bacterium. Since tuberculosis requires a comprehensive approach, companies should also explore opportunities to work together and pool complementary technologies to ensure new tools are used most effectively. Japan is poised to play a leading role in the discovery, development and delivery of tuberculosis solutions in the 21st century.

I really appreciate the opportunity to come back to Japan, a country that I feel a deep affinity with, both because of the tuberculosis situation here, but also the significant contributions that this country has made to addressing those problems — not just here in your own country but around the world. So it's with great pleasure that I give this talk at the Japanese Society for Tuberculosis.

Tuberculosis has dominated my entire professional life, from the earliest days when I was a clinician in San Francisco, treating cases at the San Francisco TB Clinic, to the middle years when I was a researcher at Stanford University in California, to my current capacity as the leader of the tuberculosis activities for the Bill & Melinda Gates Foundation. But ironically, in medical school I never learned about tuberculosis. The myth at the time was that tuberculosis had been conquered, and many students during that time in the United States went through school with little or no understanding of tuberculosis. But the myth that tuberculosis was a disease of antiquity was shattered for me when I was doing my training at San Francisco General Hospital, and found myself treating increasing numbers of immigrants and HIV-infected men who had tuberculosis. The full consequences of this misconception that tuberculosis had been vanquished, and the decades of neglect that it spawned, became even more apparent to me when I worked in Tanzania. There I was exposed to the real world, where HIV and tuberculosis collude to overwhelm under-resourced health systems armed only with antiquated and inadequate tools. In such settings, tuberculosis is most lethal: killing 1.7 million people last year — almost twice as many people as malaria. And tuberculosis, as you know, is the leading cause of death worldwide amongst people living with HIV/AIDS.

And yet today I stand before you, optimistic; more optimistic than I have ever been about the future of tuberculosis, because we are witnessing a sea change in the way the world responds to tuberculosis. After years of neglect, more people from more backgrounds and more sectors are getting involved in tuberculosis, and most importantly there is an increasing recognition that innovation is the key to continued progress. The global tuberculosis community, which has been long known for its ability to execute, is increasingly engaged in large-scale innovations to discover what needs to be done differently and better in the future. And it is this transition amongst the tuberculosis community from execution to large-scale innovation that I believe will characterize tuberculosis in the coming decades. I'm not suggesting that a field that is so firmly and appropriately rooted in data-driven, evidence-based execution should become reckless and scale-up ideas and technologies that are not demonstrated, but I am suggesting that if we don't bring a new sense of urgency to experimenting with innovative tools and systems that we will lose the fight against tuberculosis. And don't get me wrong; I firmly believe that basic tuberculosis control remains one of the most important

and cost-effective interventions in global health. Appropriate treatment can save a life and stop the spread of disease, for US\$14. It remains essential that countries around the world implement the WHO's internationally recommended Stop TB strategy, because this strategy has made huge progress, and we have made great strides in the control of tuberculosis in the past decade. In the past 11 years, DOTS has been delivered to 26 million tuberculosis patients. And there is a global plan to continue and expand these efforts, which if executed will save 14 million lives. Programs supported by the Global Fund to fight AIDS, TB & Malaria (GFATM), for example have already detected and treated some 4.6 million cases of TB worldwide, allowing these people to return to productive and healthy lives. According to the WHO, tuberculosis incidence rates have declined steadily since the year 2003, and this is a phenomenal achievement. But while progress is being made, much more is needed. For a long time the world thought that we had defeated TB, but just because TB make the headlines doesn't mean that it has gone away. The fact is that in many places tuberculosis is actually getting worse. Complacency, a lack of resources and inadequate tools are all fuelling the disease and the spread of drug resistance. In fact, while tuberculosis incidence rates have been decreasing, the actual number of cases of tuberculosis in the world — the only statistic that really matters — is increasing. The number of incident cases has now risen to nearly 10 million new cases last year, and this rise is fuelled by HIV. Twelve million people living with HIV are infected with the tuberculosis germ, and about 750,000 of them become ill every year, roughly half of them dying. These deaths are all the more tragic because they are preventable. I find it a particularly cruel irony in the modern global health arena that we are increasingly able to deliver relatively expensive drugs that keep HIV at bay, only to have patients die from the want of US\$14 worth of antibiotics that could cure their tuberculosis.

Particularly in the context of HIV, DOTS alone is not enough. One of the major limitations of our current tuberculosis strategy is that we are executing it using outdated and inadequate tools and methods. It is a remarkable fact that should be known to many more people; it's a secret we keep in the tuberculosis world that we have to share with others — we are fighting a disease that kills someone every 20 seconds with a 125-year-old test that even in the best of hands misses half the cases. We are using a vaccine that is essentially ineffective in adolescence and old age — the times when people are most prone to develop the disease. And we are using drugs that must be given for six months that have basically not changed for 45 years. Who among us would even consider driving a 45-year old car?

Now that we are 15 years into implementing DOTS, the results are clear. DOTS, when executed well, has a dramatic and prompt impact on the prevalence and the mortality of

tuberculosis in communities. But the disturbing realization is that the impact on tuberculosis incidence is far less than the 5% per year reduction, which we were led to believe would result, based on data from the rich world in the 1940s and '50s. And when you stop and think about what DOTS is, this observation is not surprising but expected, because everything about DOTS is, as we say in the United States, closing the barn door after the horses are out. DOTS is focused on treating sick patients and not interrupting transmission. While prompt diagnosis and treatment is a stated goal of DOTS, given the inadequate tools, all too often what happens is that the patients show up in your clinics after they have already infected their family, co-workers and social acquaintances, who could be infected. And thus, those patients will go on to progress the disease and incidence isn't decreasing. While the outcome of those patients who do show up at clinics is dramatically improved, we are not getting at the crux of the matter. One of the most important focuses of the experiments and innovation that I think needs to occur, has to be about how we interrupt transmission.

Drug resistance is the wakeup call, with the very real possibility of an untreatable airborne epidemic. And while acute epidemics such as H1N1 flu and SARS garner considerable attention, the slow and inevitable epidemic of drug-resistant tuberculosis has been ignored for far too long. Drug-resistant tuberculosis develops when tuberculosis patients take low-quality drugs, do not finish their full course of therapy, or pass drug-resistant tuberculosis from one person to another. In 2007 there were approximately half a million new cases of drug-resistant TB tuberculosis globally. MDR-TB is resistant to the two most commonly used first line antibiotics, and requires long and complex and expensive therapies. XDR-TB, as you well know, is resistant to first and second line drugs, severely limiting the treatment options.

To successfully treat tuberculosis, and to prevent resistance, we need to first and foremost use our current tools better. Simple improvements in tuberculosis control, such as expanding the use of under-utilized technologies can have an enormous impact. Fixed dose combinations have existed for more than 25 years, and could ensure that more patients complete their therapy. And yet, globally, only 15 percent of patients are using them. As is typical for the tuberculosis world, we get hung up in detailed discussions about whether fixed dose combinations really improve compliance, really prevent drug resistance, and we lose track of the fact that decreasing pill burden is reason enough. If you were faced with the option of taking 13 or 4 pills a day, which would you do, and why wouldn't you do it for your patients? But to successfully treat tuberculosis and prevent resistance, we also need new drugs, new vaccines and better diagnostics, as well as innovations in tuberculosis control and case management. From my personal perspective, one of the most exciting developments in the last seven or eight years has been a dramatic change in the

pipeline of new technologies. Seven years ago there was virtually no pipeline for drugs, diagnostics and vaccines; there were scattered efforts, much of them in academic institutions — passionate people, but not people who had the know-how to develop them into quality products. And those people who were making products had no understanding of the global health architecture, and how those products would get out to those who need them the most. Today all that has changed: we have a dozen diagnostic tests in the pipeline, including some such as liquid cultures and the line probe assay, which are now endorsed by the WHO for use in poor countries. So there is simply no excuse for having to wait weeks for drug susceptibility results when that data can be available in hours. Fortunately, there are many new diagnostic tests coming along that will be easier to use and greatly expand the number of situations in which clinicians can get out of the fog of diagnostic uncertainty, know what they are facing and do the right thing.

In vaccines, there are six vaccines that are in human trials as we speak. By the end of this year there will be three vaccines — maybe four vaccines — in phase II clinical trials. That means that within four years we will have some preliminary indications whether these vaccines are working or not. And perhaps most exciting to me personally is the availability of now nine molecules that are in clinical trials, many of which have new mechanisms of action and could be used to treat both drug-susceptible and drug-resistant tuberculosis.

The Bill & Melinda Gates Foundation is committed to the development of new tools, but we cannot do it alone. The Gates Foundation has invested more than US\$750 million in tuberculosis, 75 percent of that towards new tool development. This has played a small but important role in developing this promising pipeline, but the foundation's resources are limited. And while this seems like an enormous amount of money, it is in fact but a drop in the bucket of the global needs. It is increasingly important that governments like yours, and the private sector, which is so robust in this country, continue to support the development and the delivery of new tuberculosis tools. But these product development programs, exciting as they are, are built on a very thin veneer of science. And when you scratch the surface of that, you will find a fund of ignorance that challenges our very success. For example, while we have exciting tools that can be used at the level of a microscopy center for diagnosing tuberculosis, coming down the pipeline, there's little progress in a point of care diagnostic. We simply do not know what biomarkers to look for and we have no platforms that can be deployed at the level of the patient. We are a very long way away from a test that can sit in the equivalent of the mother's medicine chest, so that patients are empowered to diagnose themselves. That is a scientific challenge.

In drugs, only in the last three months have we found a

really new target for tuberculosis drugs. We have so little understanding of the biology of this organism that much of the drug development we are doing is the same kind of shooting in the dark that Selman Waxman himself pursued 50 years ago. Vaccines are an interesting problem because we don't have correlative protection, and without a correlative protection there is only one way to find out if a vaccine works, and that is to do a US\$100-million clinical trial. That means for each of those six vaccines that I'm talking about, we will not know if they work until we have spent more than half a billion dollars on empiric trials, where you give 30,000 people half the vaccine and half not. In the fields that have good vaccines, the critical step was a biomarker of protection. Take hepatitis C for example; there were really only one or two clinical trials done of a hepatitis C vaccine, and those trials showed that if you had a certain antibody titer, you were protected. And since then, more than 20 vaccines have been licensed through quick, little studies that measure antibody levels. We don't have that in tuberculosis, and that's a scientific challenge.

Furthermore, these control programs are actually built on a thin veneer of data. The tuberculosis community does a remarkable job of collecting and interpreting and acting on the data that come out of our tuberculosis programs, but that data is grossly inadequate for the tuberculosis epidemic that we are facing now, and for the innovation that we need to bring to the field. I will talk only about drug-resistant tuberculosis here, but I think the same can be said for all forms of tuberculosis. As I pointed out in a recent Lancet editorial that accompanied this year's WHO data about drug-resistant tuberculosis, we actually don't know much about the epidemiology of drug resistance. I think we are all convinced that it's a problem; I think we are all scared that it's getting worse; but if you really look at the data, you will see that we have so few data points that it is impossible to draw rigorous conclusions. And the reason that we have so few data points and such a sparse data set upon which to make decisions is because once again we are using antiquated and inadequate technology. When you use a 125-year-old culture technique to determine if there is drug resistance in a population, a large country has to set up a prospective cluster-randomized trial, then build BSL-3 facilities in each of those areas, then isolate the bacteria, then subculture them on antibiotics. We are talking about millions of dollars and four or five years of work, and you will end up sampling far less than 1 percent of the cases in that country. Because our data sets are so sparse, we actually don't know how big the drug resistant problem is; we don't know where it is most problematic; we don't know if it's getting better or worse in most settings; and most disturbing, we do not know if what we are doing is helping or hurting. And it doesn't have to be this way. I've been talking with some of you about the fact that an AFB smear contains about 100 genomes, and to a clever engineer that is plenty of material upon which sequence can be derived. And if rather than throwing out all of the AFB smears in a country, they could be brought to a central facility

where, in a high throughput fashion of robotics and microfluidics, you could scrape those slides, sequence the drug-resistant referring genes, you could rapidly turn the trash of the tuberculosis program into a treasure of data that would allow you to monitor the resistance gene frequencies in natural populations. And while there may be some problems with that approach given that we don't know whether the resistance-conferred mutations account for 100% or 60% of the resistance in some areas, suffice it to say that if your *rpoB* mutation rate is increasing year after year, you've got a problem. And if that *rpoB* mutation is known to account for half the tuberculosis Rifampin resistance, multiply it by two and you'll actually know the absolute magnitude of that. So how are we as a community going to wrap our minds around this opportunity to go from antiquated surveillance to state-of-the-art surveillance, which ultimately would bring in a very interesting and enormous set of data and theory about gene frequencies in populations and what drives them, and essentially turn tuberculosis drug surveillance into a unified theory with bacterial population genetics?

In order to do any of the things that I'm talking about, more commitment and more resources are clearly needed. And all of us, whether we are clinicians or scientists or public health officials need to make sure that we are spending part of our day doing the advocacy that it will take to get the resources that we need to transform tuberculosis control in the way that I know we can. But nonetheless, we do know enough to get started. We know that better prevention of tuberculosis is the surest way to stop drug resistance. To ensure that drug resistance does not pose a wider threat, we need to employ a variety of equally important approaches. These include improved basic tuberculosis control, the increased use of underutilized technologies such as fixed dose combinations, and new technologies and better healthcare systems. At the same time we need to be sure not to get caught up in this ridiculous argument about prevention versus control. We need to focus on prevention and not neglect control—expanding access to MDR- and XDR-TB treatment to those who are already infected. It was extremely gratifying for me to see that South Africa and China really pushed drug-resistant TB prevention and control onto the World Health Assembly agenda, so that is now the official mandate of the global tuberculosis community.

Some of the most innovative solutions will not come from Geneva or Seattle, Washington or even Sapporo, Japan, but they can come from the private sector and through partnerships. In addition to traditional donor and endemic countries, leading companies in the global north and the emerging economies in the global south should see tuberculosis as an opportunity. We need to reach out and embrace the engagement of the private sector in a way that we have never done before. Companies need to understand that an untapped market of two billion people carries the tuberculosis bacterium. A drug that may not

have much market for treating active disease could ultimately turn into the drug that would have an enormous market in the rich world for the shorter-course treatment of latent infection. In addition, because tuberculosis requires a comprehensive approach, companies need to explore opportunities to work together and pool complementary technologies to ensure that these tools are used most effectively. I was most excited in mid-June in Seattle at the Pacific Health Summit to see a group of high-level industry executives coming together to talk about how they can combine novel tuberculosis molecules early in the development process. For example, the standard way of developing—indeed the cardinal rule of developing—drugs is you never take two experimental drugs and put them together. And yet in tuberculosis if we don't violate that rule it will take us eight years to get these novel drugs licensed, and another eight years to figure out how to use them together. We don't need a TB drug; we need a TB regimen. So these companies are actually sitting together now—high-level CEO-level discussions between groups such as the Global Alliance for TB Drug Development, Tibotec, Bayer, Sanofi-Aventis—to talk about how they can combine their molecules early and cut eight years off the process. The ultimate vision that if we can take two or three new molecules that have a new mechanism action that mycobacteria have never seen before, and put those into a combination, and put those into first-line therapy, the very concept of MDR-TB will become a historical oddity. If you had these molecules in fixed-dose combinations this would be, in my mind, transformational.

Another transformational trend that we're going to see in the coming decade is that the high-burden emerging economies are actually leading the new tuberculosis efforts. Increasingly, emerging economies with high tuberculosis and drug resistance burdens are generating new ideas and new tuberculosis commitments. In March at the Stop TB Partnership Forum in Rio de Janeiro, Brazil, President Lula's administration announced plans to get off the list of high-burden countries, and an ambition to help Lusophone Africa. In short, for Brazil to do for tuberculosis what it did for HIV. This is an amazing commitment from a country that in many ways redefined the standard for HIV treatment for the poor in the 1990s. In April, the Chinese Ministry of Health, in partnership with the WHO and the Gates Foundation, convened a meeting of health and science ministries from the 27 countries most affected by drug-resistant tuberculosis. This meeting was opened by the Vice-Premier of China, the Director General of the WHO and Bill Gates. At the meeting, Bill Gates said that what TB needs is urgency and innovation, and that now is the time that those can come together—that is the rallying cry for the next decade. As I mentioned, China and South Africa succeeded in putting MDR-TB onto the World Health Assembly agenda when everyone else was concerned about the economic crisis and the H1N1 flu epidemic. And India's burgeoning generic drug industry is already a leading producer of current tuberculosis

treatments, while South Africa is increasingly vocal on tuberculosis and is home to many of the critically important clinical research trials.

I think that this new leadership could represent a new paradigm for global health, where emerging economies themselves catalyze a global response. In the established paradigms such as malaria and HIV, rich countries come up with solutions and fund these for the poor world. Now, China, India and Brazil and other emerging economies that have nearly 40% of the world's tuberculosis and more than half the world's MDR-TB are beginning to solve their own problems. And, as we move into the age of the G20 over the G8, tuberculosis provides another example of emerging economy leadership that complements and expands on the work of traditional donor countries. In the context of continued support from traditional donors like Japan, this could represent significant new resources in the global fight. These high-burden emerging economies could accelerate the access to existing tuberculosis tools as well as the development of new and more effective technologies. As the emerging economies work to solve their own tuberculosis problems it will have global impact. Pharmaceutical and biotechnology companies in the emerging economies could use tuberculosis to apply their competitive advantage in a new way. Rather than competing in the extremely competitive worlds of cancer and CNS drugs, these companies could play in the much shallower end of the pool of tuberculosis. At the same time, China, India, Brazil and others have a strong interest in engaging and supporting less developed countries. Through partnerships and twinning programs with countries such as Japan, these countries could share innovative tuberculosis tools and practices with other countries—particularly in Africa.

Let me conclude by saying that I feel we really are, as a community, at a critical juncture. The good news is that we have done a phenomenal job of scaling up DOTS; we have a credible global plan for the next decade; we garnished unprecedented resources; and we have pipelines that are fuller than any we've seen in the tuberculosis world. However, the threat of MDR and the threat of HIV are real threats that could undo all of the progress that we have made to date. Our biggest challenges are to go from a sense of complacency to a sense of urgency, and from a focus on execution to an interest in innovation. Several years ago I spent a day in Cape Town, South Africa with Bill and Melinda Gates. They were there on vacation and they wanted to take a day to understand what it was like to have tuberculosis. I sat with them in Kayelitsha, a slum outside Cape Town in a home that was roughly five times the square footage of my car, in which 10 people lived—four of whom had tuberculosis. Bill and Melinda sat with them for 40 minutes and talked to them about how they experienced the disease and what it was like to have tuberculosis and live in such desperate conditions. At the end of the day it wasn't clear what to do about their dismal living condition, but it was

obvious how to treat their tuberculosis. We then went to a clinic where they collect 1,500 sputum samples each month, and treat 2,100 tuberculosis patients each year. This was an incredible testament to the commitment of healthcare providers and what they can do—and what they are doing—with the antiquated tools that they have. At the end of the day, both

Bill and Melinda were caught up in the vision of what the providers could do if these care-givers had the tools that they really needed, and the systems to deliver them. I challenge you in the coming days to repeatedly ask yourselves; do you have the appropriate level of urgency and the appropriate focus on innovation. Thank you very much and enjoy your conference.