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TUBERCULOSIS: THE GLOBAL TIMEBOMB

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The Burden of Tuberculosis, reveals 1.7 million deaths (28/100,000)—98% of these deaths in the developing world, almost 230,000 deaths due to TB/HIV, 8.8 million new cases (140/100,000) including 674,000 TB/HIV cases, 80% of the cases are in 22 high-burden countries, 15.4 million prevalent cases (245/100,000) and multi-drug resistance (MDR-TB) present in 102 of 109 countries surveyed from 1994–2003. If one looks at TB Historical Permutation one finds that during the 17th–18th centuries, TB took 1 in 5 adult lives. During 1850–1950 one billion people died of TB. During the current decade 2000–2010 there will be 300 million new infections; 90 million new cases; 30 million deaths; more people died from TB last year than any year in history.[1)]

TB could be eliminated because we understand it. We know it's cause, transmission, treatment and prevention. TB isn't eliminated because nobody seems to care and that wouldn't be tolerated for any other disease. What people seem to care about are: SARS which killed 813 total, Angola Marburg Hemorrhagic Fever—356 (current epidemic), Ebola (1990's outbreak total)—244, Avian Influenza—54, Anthrax—5, Mad Cow Disease—1 (Cow), and Smallpox—0. Compare this to TB—2–3,000,000 deaths (annually) and hardly anybody notices.

The question remaining: Why TB Remains a Global Killer? Why does TB still infect one third of the world's population and remain a global health threat despite the fact that highly cost-effective drugs and strategies are available to eradicate it? In order to answer this question, one could divide the world into industrialized nations and developing nations. In industrialized countries there is a lack of public concern and awareness of the potential threat of the disease and a subsequent reduction in government funding for TB initiatives—the perception is that "this is a disease of developing countries and thus is a low interest to areas such as the US, Europe and Japan." There is also little media attention to both the international and the national problems associated with TB as well as lack of physician education regarding the diagnosis and proper management of the disease—again, this is an "old disease" whose diagnosis and treatment may/may not be taught in today's medical schools and failure on the part of physicians to follow internationally standardized multiple-drug regimens and WHO's DOTS strategy. There is lack of government reimbursement for medications requiring the need for patient co-payment, and cost, and responsibility, shifting from the national to the regional and local level and to managed care systems—most of whom are not trained in public health or in the diagnosis and treatment of TB. We also find lack of longterm commitment on the part of government to managing the disease and low interest on the part of pharmaceutical manufacturers in developing new diagnostic tools and new therapies for treatment and prevention due to low potential for profitability.

In developing nations we find most of the industrialized nations' reasons plus: limited resources for TB medications; inadequate drug distribution and patient monitoring systems to ensure compliance (*Directly Observed Therapy*); failure to adhere to internationally recognized treatment regimens and The World Health Organization's DOTS strategy. We also find availability and widespread use of less expensive TB drugs that are not bioequivalent or efficacious—thus reducing cure rates and encouraging drug resistance; and "over the counter" availability of TB medications for self administration.

TB is Unique! With almost any other illness, responsibility for getting cured belongs solely to the patient. On the other hand, with TB, responsibility shifts 180 degrees to the health care provider and ultimately society. With TB, a decision to start treatment is a decision and obligation to cure the patient.

As described in the American Thoracic Society statement on treatment of TB: To Start to Treat is to Commit to Cure.

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"The prescribing physician, be he/she in the public or private sector is carrying out a public health function with responsibility not only for prescribing an appropriate regimen, but also for successful completion of therapy. Prescribing physician responsibility for treatment completion is a fundamental principle in tuberculosis control." [2]

One of the best descriptions of treatment compliance in TB is by Annik Rouillon in an editorial film in 1972 entitled *Default and Motivation*. "Default by the patient is in fact rarely an isolated phenomenon; in reality it follows or flows from other failures, insufficiencies or imperfections in the people or the system to whom or to which the patient has entrusted his fate... His behavior is... in large measure the result of the long chain of influences which he has undergone consciously or unconsciously within this system. It is the system that is mainly at fault if there is a large default of patients." [3]

"... to default is the natural reaction of normal, sensible people: The person who continues to swallow drugs or have injections with complete regularity in the absence of encouragement and help from others is the abnormal one." [3]

TB is transmitted by the respiratory route; the principal risk factor for acquiring infection is breathing. Most infected individuals develop a latent or persistent infection that can reactivate at any time during the individual's lifetime. 10% of infected individuals will develop active disease over their lifetime. It is estimated that there are currently 15 million people in the US and 2.1 billion people worldwide who are infected with the tubercle bacillus and whose infection could become active at any time. Compounding the impact of TB is the co-epidemic of HIV/AIDS. As is well known, susceptibility to TB is one of the earliest manifestation of immunosuppression in HIV infection.[4] As well, TB has been shown to be the attributable cause of death in a third of AIDS patients mainly in Africa. HIV accelerates TB: while the risk of developing TB for immunocompetent individuals is approximately 10% lifetime; for HIV infected individuals the risk is markedly increased to 10% annually. We can treat any patient with TB plus or minus HIV but HIV/AIDS seriously magnifies any deficiencies in TB control.[5]

I consider TB–HIV/AIDS the Ignored Connection. Most people infected with HIV in developing countries develop TB as the first manifestation of AIDS. TB is clearly a major accelerator of HIV disease and TB is by far the most prevalent infectious disease exacerbated by the HIV epidemic, which is then transmitted to people without HIV. The cure of TB patients with DOTS significantly delays the onset of AIDS in people with HIV infection. For example, in Uganda, efficient and speedy treatment and cure of TB has already been documented to slow down the spread and intensity of the HIV epidemic. Properly used DOTS cures 80% or more of TB patients whether they have AIDS or not so, rapid expansion of DOTS for TB is the one strategy that could be implemented today to prolong lives of the HIV infected, while we are gearing up to provide anti-retrovial therapy.

The ominous emergence of multi-drug resistant TB is a global concern. In the US, multi-drug resistant strains were detected in 43 of the 50 states and the District of Columbia between 1993–1997 compared to only 13 states in 1991. In countries such as South Korea and China, resistance to Isoniazid is 10–15%, and in parts of Russia and Eastern Europe, resistance to Isoniazid is virtually 100% and MDR-TB rates are commensurately extremely high. Obviously, TB with resistance to INH and RIF is very difficult to treat. Treatment must be individualized and prolonged based on medication history and drug susceptibility studies so that clinicians unfamiliar with treatment of MDR-TB should seek expert consultation.[6]

The mechanism of MDR-TB is based upon random mutation probabilities for tuberculosis drugs which are Isoniazid—1 in 1,000,000 (10^6), Rifampin—1 in 100,000,000 (10^8), Ethambutol—1 in 1,000,000 (10^6), Streptomycin—1 in 100,000 (10^5). The likelihood of an organism spontaneously resistant to 2 antibiotics is the product of their probabilities (*i.e., for Isoniazid & Rifampin 1 on 10^{14} an exceedingly small number so highly unlikely*). So one can see that use of one drug knowingly or unknowingly, sensitive bacilli are killed, resistant bacilli multiply unimpeded, resistant bacilli become dominant. In order to counter MDR-TB is the WHO's DOTS strategy, which is a combination of technical and management components, ensuring availability of a diagnostic and treatment network easily accessible to the population. DOTS consists of government commitment; smear diagnosis; directly observed treatment; drug supply and record keeping.

It is also important to recognize well known remedies to improve completion rates: early intervention with Directly Observed Therapy and other adherence-promoting strategies such as closer monitoring of patients on self-administered therapy and assessment of adherence to therapy; exclusive use of fixed dose combination preparations of demonstrated bioavailability[7]; education of health care providers on identifying and addressing patient non-adherence[8], the use of adherence-promoting strategies, and use of DOT with short-course regimens; and active follow-up by ministry or NTP of patients on therapy with complete and timely reporting on completion of therapy from both public and private sectors. In other words, monotherapy EQUALS Resistance. DOT prevents monotherapy... therefore DOT prevents resistance. Fixed dose combinations of demonstrated bioavailability prevent monotherapy... therefore fixed dose combinations prevent resistance.

A word here about fixed combinations, which I understand are not used in Japan. The advantages are: acceptability by patient; prescribing is much simpler with far less error. They are easier for patient to remember how many tablets to take, their use ensures all drugs taken together on each occasion and dosages are more easily adjusted according to patient's weight. Most importantly, the number of pills swallowed is

reduced which obviously encourages a higher level of compliance and ultimately they ELIMINATE MONOTHERAPY! In other words, such drugs are preferentially advantageous and are increasingly being used with essentially no down side![7]

A very successful example of DOTS at work is in India[1], which remains a milestone in TB control. In the years since its program inception, over 20,000 medical officers and over 100,000 related personnel have been trained and over 3,000 laboratories set up for the diagnosis of TB. Each day in these clinics, which serve just about half of the Indian population, 1,300 patients start treatment. At any given time, more than 200,000 people are receiving treatment, most of which is directly observed. Over half a million people have been cured of TB at an incremental cost of the program since its inception has been about $50 million. At current rates of case detection, this works out to roughly $50 per patient cured.[9]

In looking at the global burden of tuberculosis, one should recognize that there have been no new drugs or no new tools introduced in recent years. The last new drug class specifically for TB — Rifampin was introduced in 1968 Europe, 1974 in the US and the most widely used diagnostic test — Tuberculin in 1890, and the ineffective most widely used vaccine — BCG in 1919. *Wouldn't one think that the largest killer of any single infection deserves better, newer tools?* There have been some improvements. Quantiferon–TB Gold has been recently approved by the US FDA. It uses antigens not found in BCG or *Mycobacterium avium* Complex (ESAT-6 CFP-10) and is more specific with no cross reactors. Similarly, Japan's Otsuka Pharmaceuticals has developed a very promising compound for TB Treatment.

In Japan, the global burden of tuberculosis reveals increasing risk for all. With the globalization of the economy has come a globalization of health risks; there are 500 million international travelers, 5,000 airports supporting international travel, and 49 million international travelers who enter the US each year. An increasing percentage of cases in the US (now 54%) is observed among the foreign-born. This strongly demonstrates that failure to develop measures to prevent and treat tuberculosis everywhere threatens our ability to control the disease anywhere.

TB in the private sector remains a large problem globally, including the USA. In a classic survey in Bombay, India, Uplekar assessed TB treatment regimens utilized by 105 private physicians[9]. He found 100 MD's prescribed 79 different regimens (most inadequate and unnecessarily expensive); 67 used drug company reps for TB information source. He concluded that national TB programs need to establish effective communication with private practitioners including proper reporting of cases. Other studies also show inadequacies in Physician Practices. The major recurring practice is: delays in diagnosis and errors in screening and treatment which resulting in increased risk and likelihood of disease transmission; increased morbidity (i.e. more advanced and complicated disease resulting in lengthened hospital stays and increased medical costs); and development of multi-drug resistant TB.

In the Western Pacific Region of WHO[1], 1,000 people die of TB every day: 360,000 people die of TB each year; one third of the world's TB sufferers live there; three out of four TB patients are between 15 and 54 years old, the most economically productive age group; and the average treatment success rates for DOTS patients is 96%, more than twice as successful as non-DOTS treatment. The question rises, how do we get TB on the radar screen of those who need to consider it? Given the strong base of support and technical expertise that JATA and RIT have built in Japan, there is a huge opportunity to increase support for TB efforts globally and within Japan by utilizing JATA's network of national volunteers and chapters, and the many experts that come to RIT from all over the world. This can build on delivering Japan's commitment at the 2000 Okinawa G-8 Summit to provide $3 billion over 5 years to fight AIDS, TB and Malaria. There are numerous opportunities such as generating media on TB locally and nationally and educating Diet members and key government leaders about why TB is a major global problem. Educating journalists about TB is critical. Key messages include: making the links to Asia, to countries in the news like Indonesia, between TB and AIDS; and most importantly, *where is the outrage over a presentable, curable disease being responsible for so much illness and death?* How does one accomplish these objectives? Local volunteers and chapters reaching out to the press and to Diet members with letters and background information; meetings, local events; bringing international TB experts who come to RIT to meet with Japanese press. In the US, a very low burden country, there have been 2–3 outbreaks of TB weekly, resulting in a peg to hang news on.

The World Health Organization has created a proposed 2005–2015 "global strategy to stop TB"[10]: reinforcing DOTS to improve case detection and cure through effective patient-centered care for ALL, and especially the poor; adapting DOTS to respond to TB-HIV, MDR-TB, and other special challenges; engaging all care providers — public, non-governmental and private — to provide the Intenational Standard of TB Care; empowering patients and communities to demand, and contribute to, effective care; enabling and promoting Research and Development for new drugs, diagnostics and vaccines and they have enhanced the DOTS Strategy: government commitment with long-term planning, adequate human resources and sustainable financing to reach World Health Assembly and Millenium Development Goals targets; diagnosis through bacteriology (microscopy first, and culture); standardized treatment under proper case management conditions, including DOT, and full patient support for all treatment of MDR-TB; an effective drug supply system (including 2nd line drugs) and laboratory network; and adequate recording and reporting of cases and outcomes.

But we need to get others to make our case for us as we

cannot ask for ourselves. For years the "TB Community" was the only group speaking out on TB issues (if they got a chance). However, obvious self interest is not helpful when speaking to the greater community; it is needed to urgently engage with others to speak out such as RIT; JATA; RESULTS.

Finally, here is my prediction about the state of Global TB[11]: The continued rise of the TB in the world and the leveling off of tuberculosis in the US portends a significant global resurgence of TB followed by a frightening resurgence of MDR-TB still diagnosed and treated with old tools. The resurgence will continue unabated followed by subsequent transmission to healthcare workers and through that vector to the community at large. Subsequent global re-establishment of control of tuberculosis will then entail more staggering costs, both in cash and hysteria than has ever been contemplated. The TB community's success in turning this around once again will depend on energizing others to make our case.

Question:

What is the most important ingredient in ANY TB control OR elimination local or international program?

Answer:

Political will[12].

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