

## Tuberculosis of the Future

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### Abstrak

Di awal dan sepanjang abad 20 ada beberapa kemajuan penting dalam penanggulangan tuberkulosis, termasuk ditemukannya vaksin dan pengembangan obat anti-TB. Tetapi, memasuki abad ke-21 ini TB ternyata masih merupakan masalah kesehatan penting. Bila tidak ada perubahan memadai, maka di tahun 2020 jumlah kasus baru akan meningkat menjadi 11 juta jiwa. Masalah TB yang utama meliputi kegagalan memberikan obat dengan baik, penemuan kasus yang lemah, vaksin yang tidak adekuat, meningkatnya resistensi terhadap obat, kegagalan pemberian terapi profilaksis dan migrasi penduduk, epidemi HIV serta infeksi nosokomial. Dalam hal perkembangan diagnosis di masa datang, diperlukan sarana yang mampu mendeteksi infeksi laten, meningkatkan kemampuan pemeriksaan sediaan langsung, memperbaiki diagnosis pasien dengan BTA (-) dan mendapatkan cara sederhana untuk uji kepekaan. Beberapa teknik diagnosis baru meliputi nucleic acid probes, amplification tests, high performances liquid chromatography (HPLC), gas / liquid chromatography (GLC), dan automated system for radiometric and non radiometric detection dan penggunaan molecular fingerprinting. Di pihak lain, obat baru juga amat diperlukan untuk memperpendek lama pengobatan, mampu mengobati resistensi ganda (MDR) serta dapat mengobati infeksi laten. Beberapa obat / bahan yang diharapkan punya efek anti mikobakterial yang baik antara lain adalah fluorokuinolon, oksazolidinon, nitroimidazol, tiolaktomisin, nitroimidazopiran dan isositrate liase inhibitor. Riset untuk menemukan obat baru memang terbentur pada aspek finansial dan perhitungan kemungkinan keuntungan yang tidak terlalu menjanjikan. Untuk menjamin proses penemuan penderita dan pengobatannya maka harus dilangsungkan program penanggulangan TB secara nasional dengan baik, dan juga di tingkat global. Integrasi program TB dengan penanggulangan masalah merokok serta program penanggulangan penyakit paru kronik mungkin dapat jadi salah satu alternatif. (*Med J Indones 2002; 11: 190-4*)

### Abstract

Beginning and during the 20<sup>th</sup> century there were several milestones in TB control, including the development of vaccine and chemotherapy. But, as we enter the 21<sup>st</sup> century, TB continue be a global public health problem and if there is no improvement in TB control, the number of new TB cases is projected to rise to 11 million by 2020. Problems faced include inability to deliver / assure chemotherapy, deficient case finding, inadequate vaccine, rising level of drug resistance, failure to employ preventive chemotherapy and migration, HIV epidemics and nosocomial transmission. As far as recent advances in TB diagnostics, there is a need to find a tool for identification of latent infection, detection of diseases in migrant and other high risk populations, replace or facilitate AFB microscopy, improve the diagnosis of AFB smear-negative cases, and simple tools for determining drugs susceptibility. New diagnostic technologies includes nucleic acid probes, amplification tests, high performances liquid chromatography (HPLC), gas / liquid chromatography (GLC), and automated system for radiometric and non radiometric detection and molecular fingerprinting approach. In the coming years new drugs are needed, especially to shorten the duration of TB treatment or otherwise simplify its completion, improve the treatment of latent TB infection and to be eliminate. MDR-TB. There are some problems in pursue tuberculosis research because of the high investment required to bring a product to market and lack of likely commercial returns. Some new drugs and molecules with promising antimycobacterial activity include Fluoroquinolone, Oxazolidinones, Nitroimidazole, Thiolactomycine, Nitroimidazopyran and Isocitrate lyase inhibitor. To deliver good case finding and treatment, effective TB control program should be implemented in the country, as well as globally. The integration of TB control program with tobacco control program and chronic respiratory diseases control program could be one of the alternative. (*Med J Indones 2002; 11: 190-4*)

**Keywords:** tuberculosis, future and recent advances

January 1900 was a time of optimism regarding the control of tuberculosis. Koch had described the means

to stain and cultivate the bacillus 18 years earlier. And, in 1890 he had intimated that his immunotherapy would both cure and prevent the disease. The sanatorium movement was flourishing in Europe and beginning to gain momentum in North America. Indeed the first half of the 20<sup>th</sup> century appeared to justify the positive spirit. Calmette and Guerin

developed a vaccine which would ultimately be administered to billions of individuals around the world. And, by 1952, the triple therapy of isoniazid, streptomycin and PAS given for 24 months had been shown to produce predictable cures for more than 90% of consumptive patients. Chemotherapy was further refined over the next four decades until it was possible to effect cures in only 6 months in regimen entailing as few as 62 to 78 encounters.<sup>1</sup>

However, as we enter the 21st century, dark shadows have appeared over the landscape. Global annual incidence estimated by the World Health Organization (WHO) in the early 1990s was 8 million cases, and 3 million death per year.<sup>2</sup> Another WHO report stated that the annual case notification rate remained steady at around 60/100 000 from 1980 to 1998. It is likely that M tuberculosis will remain widespread well beyond 2010. TB will continue to be a sensitive indicator for public health. If present control efforts are maintained without improvement, the number of TB cases is projected to rise to 11 million by 2020, a total of more than 200 million new cases over the next two decades.<sup>3</sup> The global surveys indicate that human kind exit the 20<sup>th</sup> century with more cases and deaths from the White Plague than 100 years before<sup>1</sup> Pilheu stated that the incidence of TB is expected to increase, from 8.8 million cases in 1995, to 10.2 million cases by the year 2000 and 11.9 million by 2005. Three million deaths due to tuberculosis occurred in 1995, and 3.5 million can be expected in the year 2000.<sup>4</sup>

## PROBLEMS

What are the problems encountered ? The human immunodeficiency virus has appeared and amplified manifolds the morbidity and mortality of tuberculosis. Our inability to deliver adequate chemotherapy has spawned multiple regions under siege by multidrug-resistant strains of tuberculosis.<sup>1</sup> Gledovic et al mentioned that there are several reasons for TB increase i.e. interest of many unsolved problems of immunity, prophylaxis, therapy and microbiological identification of tuberculosis was lost and the lesson of microbial antibiotic resistance were ignored. Added to these are migration from high prevalence areas and the human immunodeficiency virus (HIV) epidemic.<sup>5</sup>

Iseman mentioned 6 elements that thwart the success of TB control in the 21<sup>st</sup> century. The first 3 elements are the major category, and the remaining 3 are the minor elements. The first one is inability to deliver / assure chemotherapy. Obvious future steps to over-

come this problem include more powerful drugs that could facilitate shorter regimen or extend the interval between doses to make DOT more practical and perhaps promises from depot delivery system. The second one is deficient case finding. Even with 90% treatment completion rates, if only one-half of the prevalent cases are detected, we will not favorably impact morbidity. This element problem should be overcome with developing of sputum culture capacity, and perhaps a study on blood test, urine or exhaled gas test to diagnosed TB as well as identify patients with either pulmonary or extra pulmonary TB. The third element is inadequate vaccine, which is the most destructive weakness of TB control strategy. The pursuit of improved vaccine should be a central priority of research funding. The fourth element is the rising level of drug resistance, which threatens to render tuberculosis untreatable for many patients around the world and will inevitably escalate the cost of medical regimens. For MDR TB, WHO recently announce DOTS-Plus strategy. Looking ahead, we are looking forward the novel antimycobacterial drugs which will be developed to replace those agents lost to drug resistance. The fifth element is failure to employ preventive chemotherapy which theoretically help curtail the on-going epidemics, and the sixth element is nosocomial transmission.<sup>6</sup>

Pilheu stated the most important causes of world-wide increase in tuberculosis are : 1) non compliance with control programs; 2) inadequate diagnosis and treatment; 3) migration ; 4) endemic human immunodeficiency virus (HIV); 5) ambulatory and self-administered treatment.<sup>4</sup> Schraufnagel mentioned that the recent successes of science and medicine have spawned the optimism that has spurred ideas about TB elimination. But, several questions raised. Short course, directly observed therapy is working, but is it enough ? New drugs are being discovered again, but will they be marketed and made available to those who need them ? Better understanding and use of old drugs and new dosing schemes are shortening and improving treatment of active and latent TB, but can this knowledge be applied ? The excitement of discovering the tuberculosis genome, but what will it take to eradicate TB ?<sup>7</sup>

## RECENT ADVANCES IN DIAGNOSTICS

The diagnostic needs in most industrialized countries are those support elimination phase TB control priorities,<sup>8</sup> and include tools for :

1. identification of latent infection in high risk individuals who will benefit from preventive chemotherapy – a replacement for purified protein derivate (PPD)
2. detection of diseases in migrant and other high risk populations through active case finding – a replacement for chest X ray and smear
3. detection of patients with early disease, low burden infection or minimal symptoms – a replacement for culture
4. identification of outbreaks and characterization of nosocomial and community transmission – a replacement for standard molecular fingerprinting
5. discrimination of patients whose mycobacterial infections are due to non-tuberculous species – a replacement for biochemical tests and single species probes.<sup>8,9</sup>

In developing countries, four areas of need should be address for a new diagnostic TB test that should be able to : 1) replace or facilitate AFB microscopy for the identification of smear positive cases; 2) improve the diagnosis of AFB smear-negative cases; 3) determine drugs susceptibility in cases where standard treatment fails; and 4) identify persons with latent tuberculosis infection. There are also several number of characterization that new tests should have in order, that include consideration of sensitivity, specificity, predictive value, speed, reliability, reproducibility and cost. The diagnostic test should also be safe, easy to use, robust and acceptable to both laboratory technician and patients.<sup>10</sup>

In diseases endemic countries, welcome new diagnostic tools would include:<sup>9</sup>

1. a replacement for smear which would yield conclusive result in < 2 hours, be simple enough, require little or no interpretation, function well in HIV infected individuals and specific enough to allow initiation of therapy. Such test should be sensitive enough to detect the great majority patients who are smear positive by expert microscopy;
2. a replacement of culture to augment smear for the evaluation of complex patients and to increase case finding. Such test should be sensitive enough to detect the majority of smear negative culture positive patients;
3. a screening test for active tuberculosis with very high sensitivity, even if only moderately specific, to eliminate symptomatic patients from TB diagnostic workup;

4. drug resistance detection tools for countries prepared to offer treatment with second line drugs;
5. a simple screening tool for latent infection that is specific for M tuberculosis.<sup>9</sup>

New technologies for the diagnosis of tuberculosis includes nucleic acid probes, amplification tests, high performances liquid chromatography (HPLC), gas / liquid chromatography (GLC) and automated system for radiometric and non radiometric detection of growth mycobacteria in liquid culture.<sup>11</sup> Several studies show the power of molecular typing when used systematically in a given population for an extended period of time. Unfortunately, the current methodology of molecular typing is technically demanding and laborious. However, new methods are emerging, and it is hoped that in the near future simpler and cheaper methods will allow small tuberculosis control units to carry out molecular epidemiological studies to monitor tuberculosis transmission and the efficacy of tuberculosis control programmes.<sup>12</sup>

Perkins<sup>9</sup> reviewed many recent advances in mycobacteriology. For smear microscopy, the first diagnostic upgrade that most TB laboratories should implemented is correctly performed smear microscopy, followed by high centrifugation and perhaps a zwitterionic detergent. For culture, the speed superiority and sensitivity of radiometric liquid culture system has been already established. Recently alternative growth detection methods for liquid culture employing oxygen quenching and redox reagents have been described too. For detecting latent infection, beside tuberculin skin test, new invitro assays have been developed, such as measuring of IFN- $\gamma$  produced by T lymphocytes. For serology, promising research development includes the availability of high purified recombinant antigens, improved understanding of the heterotypic nature of the humoral response to TB and the development of multi antigen test that maintain high specificity, novel M. tuberculosis proteins identified and characterized with the assistance of new genome sequence, the characterization of a number of nonprotein antigens and the development of improved and simplified test formats. Other recent advances is molecular detection of rifampicin resistance which will detect rpoB mutations, the cause of rifampicin resistance, and nucleic acid amplification (NAA) which have been found in most studies to be more sensitive than smear but less sensitive thn culture.<sup>9</sup>

## NEW TB DRUGS DEVELOPMENT

There are three reasons usually given for needing new tuberculosis drugs : 1) to improve current treatment by shortening the total duration of treatment and / or by providing for more widely spaced intermittent treatment; 2) to improve the treatment of MDR TB, and 3) to provide more effective treatment of latent tuberculosis infection (LTBI) in programs that are able to implement this practice.<sup>13</sup> The Global Alliance for TB Drug Development<sup>14</sup> have a mission to accelerate discovery and/or development of cost-effective new TB drugs that will:

- shorten the duration of TB treatment or otherwise simplify its completion
- improve the treatment of latent TB infection
- be effective against MDR-TB

Most pharmaceutical companies do not pursue tuberculosis research because of the high investment required to bring a product to market and lack of likely commercial returns. To stimulate the interest of industry in new TB drug development, the public sector itself must initiate the dialogue needed to address the following financial impediments:<sup>13</sup>

1. Drug development is costly. It is estimated that the average cost of developing a drug, from laboratory to market is \$300 to \$500 million
2. Market size is insufficient. The industry estimates that the tuberculosis market is less than \$150 million, and targets for many companies want to generate \$200 million per annum. Most cases are in developing countries is another great concern, related to ability to pay and insecurity about patent protection
3. Pricing pressure are strong. The total cost for a standard treatment regimen currently is as little as \$11, which, when combined with the numbers of patients treated is too low to generate interest.

But, although the cost involved in the development of new drugs is enormous, it will be far outweighed by the reduction in cost of management of TB with less expensive drugs and shorter duration of treatment. Table 1 will provide some new TB drugs and or some of the molecules having antimycobacterial activity with the potential to be developed into new drugs.<sup>15</sup>

Fluoroquinolones constitute the most recent class of drugs offering hope in the control of TB. Ciprofloxacin, ofloxacin, levofloxacin and sparfloxacin are effective against *M. tuberculosis* with in vitro minimum

inhibitory concentration (MIC) range of 0.1 to 4 µg/mL. Fluoroquinolone offers favorable pharmacokinetic profile for the treatment of TB. Some of the new quinolones under research for TB treatment are trovafloxacin, moxifloxacin, T-3811 ME and PD 161148. Oxazolidinones represents a new class of synthetic antibacterial agents that intervene in protein synthesis by binding to the 30S subunit and prevent the formation of the 70S initiation complex. Preliminary studies have shown that that the compound PNU 100480 is as active as INH. The orally active agent CGI 17341 (5-nitroimidazole series) has comparable activity to that of INH and rifampicin, and it is able to inhibit both drug susceptible and MDR strains. Thiolactomycin specifically inhibit fatty acid and mycolic acid biosynthesis, and the target of this molecule is the same as for INH eventhough it does not share the same activation process and it might effective against INH resistant strains. Nitroimidazopyran derivate of PA 824 is active against MDR strains and against both active and static phase of *M. tuberculosis*. Thereby has a significant potential for reducing the duration of therapy.<sup>15</sup>

Table 1. New TB drugs / molecules with antimycobacterial activity

No.	New drugs / molecules
1.	Fluoroquinolone
2.	Oxazolidinones
3.	Nitroimidazole
4.	Thiolactomycine
5.	Nitroimidazopyran
6.	Isocitrate lyase inhibitor

## TB CONTROL

Achieving the dream of tuberculosis elimination requires ideals and ideas, ability and agility, foresight and fortitude. Up to now, DOTS strategy remain the most important tool for TB control in the world. But, changing gear may be needed. One very important tools will be high effective vaccine, which make TB control much easier. As for a DNA-based tuberculosis vaccine, as promising as the experimental result may be, in practice things are not going to be easy yet. Other issues in TB control include integration of TB control with the national programmed for chronic respiratory diseases (CRD) control, and or integration of TB control with tobacco control. Smoking may increase TB infection rates, TB incidence rates as well

as TB death rates. Smoking is also the common risk factors for most of chronic respiratory diseases, such as bronchial asthma, chronic obstructive pulmonary diseases (COPD) and lung cancer. For a country with limited resources like Indonesia, integration of TB control, tobacco control and CRD control programme should be one of effective and efficient alternative.

The global TB control approach is the only means to achieve long term reduction in global incidence and reduce vast pool of persons with latent infection who will otherwise continue to be a source of transmission for century

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