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FEATURE REVIEWS

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Host Genetics of Tuberculosis Susceptibility
Tania Di Pietrantonio, Caroline Gallant, and Erwin Schurr, Ph. D.

FEATURE REVIEW

Advances in Tuberculosis Research in the Past 10 Years: Solutions for a Global Problem

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INTRODUCTION

In the early 1990's the number of cases of active tuberculosis (TB) was increasing in almost every country in the world. In developing, or resource-poor countries, which will henceforth be termed "poor" countries, this trend was no different than the previous 50 years, despite the discovery of effective treatment, since it was inaccessible to most of those with disease. However in industrialized countries, meaning those with established market economies (a World Bank term), which will henceforth be termed simply "rich" countries, incidence had declined since the end of the 19th century. Therefore the resurgence represented a suabstantial change that had important consequences. Although there is no doubt that this resurgence resulted in increased human suffering, and death, it had an important benefit. The phenomenon resulted in heightened awareness, interest and funding for TB. Increased investment in TB was for research as well as for control. Both activities resulted in substantial advances in our understanding of TB - at cellular, individual and population levels.

This review will examine the new knowledge gained over the past decade (1992-2002) largely resulting from this increased funding. New knowledge in TB can be broadly grouped into five areas: a) understanding the epidemiology and transmission; b) new diagnostic tools; c) new treatment tools; d) new tools for prevention; e) new approaches to management of TB - at individual and population levels. For each category the major advances of knowledge and their implications will be reviewed below.

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EPIDEMIOLOGY AND TRANSMISSION

Because the incubation period of tuberculosis may range from weeks to decades, it is usually not possible to ascertain from a patient the source of their infection. As a result, much about the epidemiology of TB transmission has traditionally been inferred through indirect means, for instance by observing that close contacts of TB cases are more likely to have a positive tuberculin skin test than casual contacts. Even in outbreaks of active TB, the confirmation of epidemiologic links was difficult, as there were no reliable bacterial typing tools prior to the early 1990's.

The discovery in the late 1980's of the insertion element, IS6110, opened up new avenues of epidemiologic and public health investigation. This insertion element is present in virtually all isolates of M. tuberculosis - with a variable number of copies (ranging from 1-25) and at variable loci within the bacterial genome. This means that the DNA from a particular starin of M TB will have a unique number and location of these insertion sequences. Therefore when the DNA strand is cut at these insertion elements, the resulting pattern of the fragments of DNA produced after Southern hybridization with a probe for the IS6110 element, will be unique - like a fingerprint. Hence this technique, called restriction fragment length polymorphism or RFLP, is also called "DNA finger-printing". This technique is highly reproducible and theoretically there can be billions, even trillions of different DNA fragment patterns. The underlying premise of strain typing is that in an outbreak, all strains will have identical or highly similar DNA fingerprints reflecting their bacterial genotypes. Epidemiologically unrelated isolates should have different RFLP patterns.

RFLP-based studies can be categorized as: patient-based clinic-based, and population-based. In patient-

based studies, bacterial typing permits one to determine if a clinical relapse represents treatment failure (same bacteria) or exogenous reinfection (cure followed by new infection), or a false positive culture due to lab cross-contamination. At the patient level, this information helps the treating physician to decide whether treatment is needed at all, if supervision of treatment should be intensified, or an outbreak investigation is needed to find an infectious source.

The next plane of molecular epidemiologic study can be termed the clinic or outbreak-based study. At a clinic level, participants in clinical trials with apparent relapse could be distinguished from patients with recurrent disease due to re-infection. This is important because while relapse indicates failure of a treatment regimen, re-infection does not. Outbreaks are often useful to validate the bacterial typing systems, by demonstrating concordance between epidemiologic evidence of links between patients, and genetic homogeneity of strains isolated from those patients. In one highly-cited example from San Francisco, a TB outbreak was suspected in an AIDS hospice because of the occurrence of 14 cases in just under one year (1). Molecular typing demonstrated that 12 of the cases had the same bacterial genotype, but the first two cases had a different TB bacterial strain. Based on this, it could be calculated that the true outbreak involved 12 of the 14 cases, that the epidemic window was just over 3 months, and that the interval from exposure to active pulmonary TB (incubation period) was as little as 3 weeks. Subsequently, a large number of outbreak investigations have made use of bacterial typing, either to rule-out links early during the investigation, or to refine the definition of the outbreak. As a result, TB transmission has now been linked to a wide-variety of potential contexts, including airplanes, bars, lap-dancers, illegal gaming facilities, etc. While it has not always been possible to obtain independent epidemiologic confirmation of these outbreaks, the observation of identical bacterial genotypes in these venues provides compelling evidence that TB transmission is not restricted to traditional settings (home, workplace) that would normally serve as the focus of contact investigations.

Because of the observation that outbreak strains share identical genotypes in the face of diverse strains normally circulating in a community, the next step in epidemiologic study involved the collection of all isolates from a community for strain comparison studies. Here the goal was not to elucidate all potential transmission links, but rather to demonstrate whether 200 cases in a community represents mostly independent instances of TB reactivation (manifest as different genotypes) or a collection of repeated genotypes (suggestive of unsuspected outbreaks). In the first studies to employ this methodology, groups in San Francisco and New York found that about 30-40% of TB cases in their communities represented ongoing epidemic spread (2;3). Moreover, by identifying the epidemiologic features of TB patients with shared strains (deemed molecular clusters), they were able to determine that ongoing TB transmission in these American cities appeared to be greater in American-born, younger, males. Also, HIV co-infection appeared to be a risk factor for being a member of a molecular cluster. These data refuted the contention that TB in the US was the result of immigration policies and imported infections, but rather pointed to a local problem in TB control. A number of studies have employed a similar methodology to query the degree of ongoing transmission in a community, providing a great range in estimates. In Montreal, the vast majority of TB cases have unique RFLP patterns, indicative of reactivation disease (4). In contrast, in a study of gold miners in South Africa, the majority of TB was deemed by molecular typing to represent ongoing spread (5). A further refinement of population-based molecular typing studies was to perform a observational study looking at the impact of altered TB control activities on the degree of molecular clustering. Following the observation that TB was being preferentially spread among young, US-born males in San Francisco, the department of public health bolstered control programs in that constituency. Not surprisingly, over the next 5 years, rates of TB remained essentially stable in the foreign-born community of San Francisco, but a dramatic drop in TB rates and TB molecular clustering was observed in the US-born (6).

A second important use of information at a population level, is to decide whether vaccination is a tenable strategy. If re-infection rates are high among patients treated for TB, then vaccination may not be tenable, because vaccines are most beneficial when survivors of natural infections are immune to further infections. In early studies of reinfection, most of the hosts suffering from reinfection had advanced HIV/AIDS disease, therefore, it was perhaps not surprising that their immune system had failed to ward off a new assault by M. tuberculosis (7). Soon after, reinfection was also demonstrated in a relatively immune-competent patient with diabetes, however, reports remained anecdotal. In 1999, van Rie and colleagues reported that in a township of Cape Town, three-quarters of patients with a second diagnosis of TB had reinfection rather than relapse. This suggested that in a high incidence setting, persons who were unable to contain the organism on first exposure could be treated and cured, but were at significant risk of developing disease again on re-exposure (8).

Contemporaneous reports suggested that the risk of reinfection was considerably reduced where TB incidences were lower, therefore, the majority of second cases of TB in San Francisco and the Netherlands represented clinical relapse, while an intermediate result was observed in the Canary Islands (9-11).

From the numerous molecular epidemiologic studies of TB, important lessons have emerged. TB transmission often occurred where TB control efforts were inadequate or de-emphasized, such as New York in the late 1980's and in recent years in the former USSR. This highlights the limited perceived economic value of preventive health until the costs of neglect mount (12). HIV infection has been shown to be a powerful force in the spread of TB, but its effects on transmission are variable. This is because HIV co-infection accelerates the reactivation of TB in persons previously infected and accelerates the progression of new M. tuberculosis infection to disease. Studies of drug-resistance have been able to use molecular tracking to document risk factors for the acquisition of drug-resistance mutations within patients and the spread of resistant strains among them (13). Unfortunately, a sobering lesson has been that spread of drug-resistant strains has been greatly enhanced by the bringing patients together in hospitals, providing yet another example of where a community public health problem is unwittingly amplified within the health-care system. Fortunately, attentiveness to many of these issues has been associated with a recent decline in TB rates in the United States as a whole (14), and in certain high incidence urban settings (12). The challenge that remains is bringing these advances to other countries where TB continues unabated.

DIAGNOSIS OF TB—DISEASE AND LATENT INFECTION

Nucleic acid amplification (NAA)

This term refers to a technique in which the nucleic acid (DNA or RNA) of organisms is amplified, by as much as 40 orders of magnitude, after which a probe detects a target sequence of DNA or RNA unique to that organism. These probes are highly specific, allowing one to identify individual species of mycobacteria, and distinguish M Tuberculosis (the causative organism of active TB) from Mycobacterium avium or other "atypical" environmental mycobacteria (15). These are easily confused with M Tuberculosis , but have very different clinical and public health implications.

Nucleic acid amplification tests are highly sensitive, and can detect as few as 10 organisms in one mL of clinical sample (15). Over the past decade the technology has progressed to become more automated and more rapid. The technique used to take 4-6 hours, but now 40 cycles of amplification can be accomplished in 40 minutes (16). However this technology is still expensive, requiring complex equipment as well as highly trained technical staff.

The major advantage of this technique is that it is much more sensitive and rapid than the traditional technique of direct microscopic examination of a smear of sputum stained to detect Acid Fast Bacilli (AFB smear) to rapidly diagnose active tuberculosis (15;17-19). Compared to NAA, AFB smear is less sensitive as it detects patients only when they have more advanced disease. The disadvantage of NAA testing is that Mycobacterial culture still needs to be performed, because NAA is still less sensitive than culture. However, culture requires 4-8 weeks for a positive result using solid media (which are much less expensive and so are commonly used throughout the world) or 2-4 weeks using liquid media (which are only used in rich countries). Therefore, NAA tests offer the advantage of more rapid diagnosis of the majority of cases of TB disease.

Impact: At the moment NAA is only used in rich countries where the equipment and well-trained staff are available. In these countries, the greatest benefit of NAA techniques is for patients with a positive sputum AFB smear, in whom NAA can distinguish rapidly and accurately between active TB and diseases caused by environmental or atypical mycobacteria (20). This is important for infection control, public health and treatment reasons. Unfortunately, the limited sensitivity on AFB smear negative samples has prevented widespread adoption of this technique for screening of all samples.

In the long term, if the NAA process can be more automated, this will diminish requirements for highly trained staff. If the cost for materials and equipment continues to diminish, as it has over the last decade, then this technology could be applicable, at least for middle income countries (21). Since this includes most countries in Latin America, Eastern Europe and much of Asia, where more than 2 million patients with active TB are diagnosed each year, NAA could bring benefits to a large population.

Cytokines

Cytokines are inflammatory mediators produced by cells of the immune system such as macrophages, monocytes, and lymphocytes. When immune cells have been sensitized by prior exposure to M Tuberculosis, and then are re-exposed to those same antigens, they increase production of certain cytokines (22). This cell-mediated immune response, known as a Th1 response, is typical for tuberculosis and similar organisms and will result in increase of cytokines such as IFN(, IL-6, IL-12, and IL-18 (22-24). In contrast patients with

asthma or other atopic diseases will characteristically have a Th2 cell-mediated response and produce different cytokines, including IL-4 and IL-5 (25).

Cytokines may be useful in two ways. The first is for the measurement of response by certain Th1 immune cells to specific M Tuberculosis antigens. In patients with prior sensitization to M Tuberculosis (i.e. patients with latent TB infection), lymphocytes or other immune cells will respond with increased production of IFN(when these cells are exposed to M Tuberculosis antigens (26). Patients who have been sensitized by other mycobacterial organisms such as M Avium or the BCG vaccine, should not respond with increased cytokine production if exposed to highly specific M Tuberculosis antigens (27;28). The uncovering of genes uniquely present in M. tuberculosis through the tools of comparative genomics has greatly facilitated the search for such M. tuberculosis-specific antigens (29). The adoption of such antigenic proteins in the coming years may permit the detection of a cytokine response that is more specific than the tuberculin skin test in detecting latent infection with M tuberculosis.

The second use may be through identification of a pattern of cytokine response that is typical and specific for active disease due to M Tuberculosis. If such a pattern could be identified, this might be useful to distinguish patients with active TB, from those with other active pulmonary diseases such as pneumonia, asthma, bronchitis etc. However, this idea is purely speculative, as there is very little supporting data at this time.

Impact: At the present time measurement of cytokine response is limited to rich countries because this is very technologically complex requiring expensive equipment and highly trained staff. However the potential long range impact is considerable. If a test to detect patients with latent TB infection was better than the current standard of the tuberculin skin test, this would have far ranging implications as the TST is open of the most commonly used tests in clinical medicine world-wide. Another impact would be the identification of persons with LTBI who are at increased risk to develop active disease. In a small study of household contacts in Ethiopia, individuals with heightened cytokine response to certain M Tuberculosis antigens had significantly higher incidence of active TB within 2 years than those who did not (30). If confirmed in other patient populations, then the cytokine response detected may be useful not only to detect LTBI, but also to identify those with LTBI who have the greatest risk of developing disease. This information would be useful to target interventions, such as LTBI therapy, to persons who are the most likely to benefit.

A further impact of research in cytokines has been to provide insights into the pathogenesis of reactivation of active TB disease. For example, TNF" is an important cytokine, and inhibitors of this mediator represent a novel, and highly effective therapy for patients with two inflammatory disorders - rheumatoid arthritis and Crohn's disease (31). Shortly after TNF" inhibitors were introduced into clinical practice, a number of patients developed disseminated tuberculosis (32). These patients presented soon after their first course of therapy, with clinical features similar to patients with advanced HIV infection and active TB (32). This suggests that when TNF" is inhibited, a profound immune defect results, which causes a susceptibility to TB reactivation. Understanding the role of cytokines in the pathogenesis of reactivation of TB, may lead to new therapies involving very different mechanisms than the traditional antibiotics.

The greatest barrier to widespread use of cytokines is the cost and complexity of their measurement. If the cost can be reduced and the techniques simplified, then cytokine-based tests may be useful in the near future to accurately identify those with latent TB infection, particularly those at high risk of disease.

TREATMENT OF ACTIVE DISEASE

Almost all the first and second line drugs currently used for TB were discovered and introduced in the 1950's and early 1960's. Rifampin, introduced in 1970, was the last new drug for more than 20 years, as there was no interest in development of new drugs for TB. However, in the past decade a whole new class of agents - the quinolones - have been found to have significant anti-tuberculosis activity. The most recently marketed agents, such as Moxifloxacin, have very high in-vitro activity against M Tuberculosis. Randomized trials are now underway to test the efficacy of this agent in the treatment of active TB.

When Rifampin was introduced, the duration of standard therapy of tuberculosis could be reduced from 18 to 9 months. When Pyrazinamide (PZA) was introduced, total duration could be further reduced from 9 to 6 months (33). With Moxifloxacin it is hoped that the total duration of therapy can be reduced further to only 4 months. Shortening the total duration of therapy is very important, because longer therapy is associated with poor patient compliance necessitating closer supervision, including directly observed therapy, which is more costly

A second new drug is Rifapentine. This is a rifamycin with a very long half-life, allowing it to be given once a week. Once weekly therapy allows highly intermittent directly observed therapy (see Section 5 below), which results in far fewer total doses of therapy - thereby reducing drug costs and the cost of supervision of

therapy.

Impact: At the moment these two drugs are still much more expensive then standard first line anti-TB drugs and so are accessible only in rich, and middle-income countries. However the cost of standard first-line anti-TB therapy has been substantially reduced over the past decade (see section 5 below). Therefore it seems likely that greater use will result in lower costs for these new agents, making them more accessible for use in poor countries.

VACCINATION AGAINST TB—BCG AND NOVEL VACCINES

BCG vaccines have been administered since 1921 and currently, over 100 million infants receive BCG at birth each year. The goal of BCG vaccination of newborns is to prevent invasive forms of infantile TB, most notably miliary TB and TB meningitis. As such, BCG vaccines are generally provided in high incidence countries, where infantile exposure to TB is most likely, and in Canada, is restricted to high risk communities, such as Aboriginal communities where there is documented high incidence of TB.

While it is generally stated that BCG vaccines provide high rates of protection against infantile TB and limited protection against contagious forms of TB in adults, resulting in some benefit at the level of the individual but limited impact in stemming the epidemic (34). However, according to the principles of evidence-based medicine, this view does not stand the test of critical analysis, as there has never been a randomized trial of provision of BCG to newborns. Furthermore, in a number of clinical trials of BCG vaccination in adults, there has been significant protection (up to 80%) against pulmonary TB, and in certain studies, TB-associated mortality and all-cause mortality (35). Unfortunately, the results of BCG trials have been so variable that accurate estimates of BCG protective efficacy are hazardous. In the largest study, involving over a quarter of a million subjects, BCG vaccination was no better than injection with saline placebo (36).

Given the resurgence in TB in the last decade, along with the emergence of drug-resistant forms of M. tuberculosis, increasing attention is being directed to the development of an improved vaccine against TB. In early years, efforts were focused on a subunit vaccine, with the view to reducing the risks associated with live, attenuated vaccines in countries often suffering from a high burden of HIV/AIDS. However, most of these candidates have been less protective than BCG in animal models, and the best subunit vaccines have equaled BCG in laboratory studies. More recently, two studies have published for the first time evidence of a vaccine that is more protective than BCG in animal models. Curiously, both are not just live vaccines, but in fact, recombinant variants of BCG vaccines.

After the original introduction of BCG vaccine in 1921, a number of different manufacturers began their own stocks of BCG, resulting by the mid 20th century in a family of vaccines that had evolved in vitro for 50-60 years. By genomic study of these vaccines, it has been possible to demonstrate genetic decay in these vaccines, with regulatory genes and antigenic proteins over-represented in these genetic events (37). This has understandably raised concerns, as the usual role of a live attenuated vaccine is to present antigens to the host immune system, therefore, a vaccine that has shed antigens may have limited utility as an immunizing agent. Recently, two groups have tried to improve upon BCG by over-expressing antigenic proteins of M. tuberculosis. Horwitz et al used the Tice strain of BCG as a means of producing high quantities of the antigenic protein 85B (38) . Guinea pigs are vaccinated with regular BCG Tice or the recombinant BCG, followed by challenge with fully virulent M. tuberculosis. In studies of the growth of the virulent M. tuberculosis and in time to death, the recombinant vaccine is consistently more protective (39). Notably, the recombinant vaccine does not appear to produce more pathology, in other words, the vaccine is no more virulent than the parent BCG. In a different approach, Stewart Cole's group took the Pasteur strain of BCG and added back a region of the genome that is consistently missing from all BCG strains. This region encodes two important antigenic proteins, named ESAT-6 and CFP-10. In mouse and guinea pig studies, the addition of this region did not materially increase the virulence of the BCG Pasteur, however, subsequent challenge of animals with virulent M. tuberculosis resulted in less dissemination of the virulent strain and less tissue pathology (40). While the exact mechanisms for these improvements in BCG vaccines remain to be determined, the important advance is that something better than BCG has finally been created. Hopefully, human phase I/II studies will proceed in coming years so that one can eventually field test these and other promising new candidates.

THERAPY FOR LATENT TB INFECTION (LTBI)

In North America, the current approach to LTBI is to identify those at increased risk of reactivation of TB disease, screen them with TST, and to offer therapy of 9 months of INH (9INH) to tuberculin reactors. The long duration of LTBI therapy (previously referred to as preventive therapy), reduces compliance, often to less than 50%. As a result, non compliance is the most important factor reducing the effectiveness of this

therapy. In addition 9INH has significant side effects which are uncommon but can be serious, and even fatal. For this reason, patients must be intensively educated and motivated at the start, and then followed closely throughout treatment. This adds substantially to the cost of care.

Therefore the search for a shorter, safer and equally efficacious therapy has been very active for the past decade. The shortest preventive therapy regimen investigated to date has been two months of daily, self-administered Rifampin and Pyrazinamide (2RIF-PZA). This regimen was highly efficacious in a mouse model of latent TB infection. In several randomized trials among HIV positive patients, 2RIF-PZA had similar efficacy as 6 or 12 months of INH (41). However among HIV negative patients, under programme conditions, or in randomized trials, tolerability and completion rates with 2RIF-PZA were low and major adverse events unacceptably frequent (42-46). As a result, this regimen should be used with caution in highly selected patients.

Two other options are available: three months of INH and Rifapentine (3INH-RPT), taken once a week under direct observation, and 4 months daily self-administered Rifampin (4RIF). The 3INH-RPT regimen has the advantage that, in total only 12 doses are given, reducing the cost of therapy and followup as well as burden to patients. However it must be given under direct supervision, which is cumbersome. The 4 RIF regimen appears to be well tolerated, and has good completion rates. At present there is insufficient data regarding the safety and efficacy in preventing reactivation of active TB of both regimens. Therefore neither can be recommended for routine use now.

Shorter therapy will likely result in better compliance if the therapy does not have unpleasant side effects. Costs should be lower, unless follow-up has to be more intensive. Compared to 9 months INH, if a shorter regimen has fewer adverse effects, and equal efficacy then the shorter regimen will be more cost-effective, and have a better risk-benefit profile. This would make it much more acceptable for widespread use, and so potentially have a large impact on a population level in many countries.

Impact: At the present time therapy of LTBI is only feasible in rich countries. This is primarily because of the high cost of follow-up and the relatively low benefit. In poor countries and even in middle income countries resources are barely sufficient to diagnose and treat all patients with active TB disease. Diversion of these scarce resources to provide therapy of latent TB infection would be inappropriate. However if regimens can be found that are effective, shorter, and safer, and with high completion rates then therapy of LTBI would be applicable in middle income and could be considered for very high risk patients (such as HIV infected) in poor countries. Provision of therapy for latent TB infection on a population basis may accelerate reduction of incidence of active TB in many countries.

TB CONTROL

DOTS (Directly Observed Therapy - Short course):

Many advances in diagnosis and therapy of TB disease are based on studies conducted in poor countries. The DOTS approach is a good example. This approach is based on a successful approach to TB control developed in Tanzania by Dr. Styblo and colleagues of the IUAT. This approach emphasizes smear microscopy for diagnosis, therapy for 6-8 months (short-course) with standardized, Rifampin-containing combination regimens, a secure and stable supply of the necessary drugs, and directly observed therapy - meaning that someone, often a health care worker, actually observes the patient take therapy (47;48). This approach was based on sound epidemiologic principals and years of practical experience and has been shown to be highly cost-effective (49) and results in slow but steady decline in incidence when applied on a country wide basis (50).

In 1993 the World Health Organization adopted the DOTS programme and promoted its application in all countries. Because of this, the DOTS programme is now applied in most countries, although often to only a small part of the total population. As a result, currently less than 1/3 of the total world's population has access to diagnosis and effective therapy using this approach. An important element of the DOTS approach is standardized therapy with 4 highly effective first line TB drugs - Isoniazid (INH), Rifampin, Pyrazinamide (PZA), and Ethambutol (48). As a result of the increased use of standardized regimens with these 4 drugs, their price has fallen dramatically. Ten years ago the cost of a full course of therapy was approximately $60 US, but now costs less than $10, even for high quality drugs purchased from international manufacturers. As a result TB therapy is even more cost effective and more accessible to the world's poor.

DOTS Plus:

The emergence of drug resistance in almost all countries, has been one of the most major challenges to global TB control. Drug resistance, particularly multi-drug resistence (MDR) defined as resistance to at least INH and Rifampin, is the result of inadequate treatment (47). This occurs because of selection of inadequate regimens, poor quality drugs, or interrupted therapy. The latter occurs because of interrupted drug supply or

patient non-compliance. In some countries, 10-20% of patients with a history of prior therapy, have MDR-TB (51). In these same countries as many as 5% of patients who have never been treated before have MDR-TB (51). This implies substantial transmission of MDR-TB strains in the community - amplifying the gravity and extent of this problem.

Therapy of patients with drug resistance requires use of second line drugs, for 12, 18, or even 24 months depending on the pattern of drug resistance and extent of disease. As a result therapy of patients with MDR TB has been estimated to cost $7,000 - $10,000 US per patient, for the drugs alone. This is far more expensive than the $10 required to treat patients who have drug sensitive organisms, and may not be feasible for national TB control programmes in many poor countries. Therefore the IUATLD and WHO had recommended a standard re-treatment regimen of 8 months duration which did not include any of the expensive second line drugs (48). However this standardized re-treatment regimen is only moderately effective for previously treated patients and completely ineffective for patients with MDR strains. In such patients the standardized re-treatment regimen will actually worsen their drug resistance pattern.

For a number of years the approach to patients with MDR-TB was very controversial. The WHO argued that treatment of a handful of MDR TB patients could divert scarce resources, and mean that treatment would not be available for hundreds of previously untreated patients. However others argued that it was unethical to offer treatment that was almost certain to be ineffective. These patients posed a real humanitarian crisis.

To resolve this, the "DOTS-plus" approach was developed. Although there is still no single standardized regimen with documented superiority, the DOTS-plus approach emphasized a standardized and strictly observed therapy with second line drugs for prolonged periods. As with DOTS approach, a standardized international approach has enabled bulk purchasing which has resulted in more than 90% reduction in cost of the second line drugs needed. This has made therapy of MDR TB more accessible in middle-income and poor countries. Nevertheless the costs of more than $500 US per patient, makes provision of this therapy beyond the capacity of most national programmes in poor countries.

Treatment of MDR-TB remains one of the most important challenges for the next decade. It is encouraging to note that in regions where DOTS has been implemented and strictly followed the incidence of MDR TB has slowly fallen (12;52). This implies that generation of new MDR cases can be stopped by a good DOTS programme. If this can be combined with access to effective DOTS plus regimens, then the problem of MDR-TB could be controlled.

CONCLUSIONS

Much has been achieved over the past decade to advance our knowledge of the epidemiology, transmission, diagnosis, therapy, prevention, and management of tuberculosis. The advances in knowledge have resulted in greater changes in patient management and TB control in rich countries. However, there have been substantial improvements in access to diagnosis and therapy in poor countries. The challenge for the next decade is to ensure that we continue to invest in TB research in, to advance our knowledge, while also looking to apply this new knowledge in the most cost-effective and practical manner in all countries of the world.

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