OBSTACLES TO THE CONTROL OF MDR-TB IN INDIA

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The increasing worldwide prevalence of multidrug-resistant (MDR) strains of Mycobacterium tuberculosis represents a major threat to tuberculosis (TB) control programs.

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I. INTRODUCTION

This story begins with the 1987 publication of The World Bank Report “Financing Health Services in Developing Countries: An Agenda for Reform”. The policies recommended therein were strategically implemented in the form of cut in public health budgets and privatization of medical health services. The Epidemiological Bulletin of the Pan American Organization in 1991 reported the occurrence of almost 300,000 cases of cholera in 10 countries - the first cholera epidemic in the Americas in the 20th century(1). Cornia et al (2) compiled compelling evidence from case studies showing a direct association between cuts in Government expenditure on health and other social services.

A general deterioration in health status was observed in 10 countries as manifested by higher morbidity especially from infectious diseases such as diarrhoea, pneumonia and tuberculosis. In India, however, the sample surveys show no fluctuations either in the prevalence or incidence rates of TB(3) despite stabilization and Structural Adjustment Programmes implemented vigorously since 1993. Though this stability is partially attributed to a well conceptualized National Tuberculosis Programme (Banerjee, personal communication), the lack of a reliable epidemiological base raises doubts as to the veracity of this claim. Indeed it has recently been felt that multidrug resistant TB (MDR-TB) is on the increase and is likely to reach ‘menacing proportions’(4). Tertiary care hospitals in Western Maharashtra report prevalences ranging from 25-45% whereas community based figures are quoted to be between 3-11%.

II. CONTROL THROUGH DRUGS

The National Tuberculosis Control Programme adopted by the country in 1963 espoused specific drug regimens as the sole measures to control TB. These “magic bullets” could be availed of as domiciliary treatment thus excluding extended hospitalization and subsequent economic wage loss to tuberculosis patients. Four decades later we are left sadder and wiser probing for answers.

The traditional public health school still attributes this solely to a failure of the biomedical system viz. non-availability of anti-TB drugs, patient’s irregularity and drop out from treatment regimens and a strange lack of knowledge of TB drugs and their standard regimens among our medical practitioners. The Revised National Tuberculosis Control Programme (RNTCP) adopted since 1993 aimed to rectify drug related deficiencies and while aiming at least 80% drug availability. It also undertook the streamlining of sputum examination based diagnostic procedures and introduced a strategy of direct observed therapy (DOT). The latter implemented after an MDR-TB epidemic at a cost of $1 billion in New York for a small high risk population is now prescribed in all TB affected countries as the most cost effective and efficient method for the control of drug resistant strains.

However, during trials several negative aspects of the DOT strategy (DOTS) have manifested themselves. Firstly in view of the additional staffing required, it is expensive to implement. There is no reason to believe that such staff recruited in the public health system will function any more effectively than the existing ones. Furthermore patients find its burdensome to travel to a clinic for months to avail of...
the treatment and tend to stop treatment as soon as they feel better because of the inconvenience and problems of holding a job while under treatment and the loss of wages that this entails. On an average and Indian TB patient spends Rs. 120-165 per month on such free DOTS treatment. There are now increasing complaints of inferior quality drugs being distributed at DOT centres with staff ill-equipped to deal with either counselling or care of complications (5) resulting from drugs or of the disease.

By ignoring to recognize the patients’ felt needs, DOTS in India can hardly be expected to control the problem of tuberculosis as a whole, leave aside MDR-TB. In fact, its unintelligent application can encourage irregularity and even drop out of treatment, thus exacerbating the problem of MDR-TB. In this respect the growing concern of doctors and staff regarding treatment failure of patients on DOTS is justifiable.

The pointer that drug induced MDR is a reality is experienced in Africa where MDR-TB is less common than in other parts of the world as is the number of patients who are treated with anti-Koch’s therapy(6). More recently Hoffner has also observed the transformation from drug susceptibility to drug resistance in a strain of M.avium during the course of treatment(7). Even in the US, 12% of TB infections are resistant to at least one drug(6) whereas in South Africa, a study showed that at least 52% of drug resistant tuberculosis was caused by transmission of a strain that was drug resistant before initiation of treatment i.e. primary resistance(S).

The paradigm of drug induced resistance is supplemented with one other. Whilst ineffective public health policies are contributory to the rise of MDR-TB, the Amsterdam Declaration of 1999 recognized that TB is linked more strongly with poverty and rapid social change more than any other major disease. 98% of annual deaths from TB and 95% of new cases are in the developing countries (6) many of whom face a dual onslaught of HIV-infection and MDR-TB. Rising poverty, the inability to consume two square meals a day has several implications for MDR-TB.

Basu et al(9) highlighted that efficacy of drugs including Anti Kochs Treatment(AKT) is dependent on a ‘minimal’ nutritional status having yet an ill-understood interplay with host immunity. In any event, the patient will shop for alternative treatment, face several episodes of unresolved disease and eventually die. Even if on the other hand, an appropriate second-line treatment is prescribed, its efficacy will not exceed 50%. This fact will not reveal itself until the patient has spent at least Rs. 1,00,000 - 1,50,000 on treatment besides the additional loss of wages and time incurred. The social implications will be gross financial indebtedness for the patient and the family, stigma and possibly the death of a wage earner.

Mismanagement in use of antimicrobials in India through self-prescribing, over-counter sales and medical malpractice will further ensure that primary resistance to even second-line drugs is likely to be high. The frequency of hearing reports of resistance to second-line drugs such as kanamycin is increasing particularly in HIV-TB patients(10). The immunocompromised and debilitated condition of HIV patients, as in nutritional deprivation only serves to underscore the importance of nutrition and intact immune resistance for effective drug action.

The probability of controlling drug abuse/misuse particularly in developing countries is extremely poor. The unethical drug promotion practices of the pharmaceutical industry in search of profit adds to this problem. Even in the U.S. state legislation to govern prescriptions has been opposed by physicians as interference in professional judgement(11). One way of curbing this could be to link misuse of drugs statewise with receipt of central funds earmarked for public health. A selective withdrawal of some government subsidies in drug production, purchase and distribution maybe another avenue of control provided that it does not bring about inequitable accessibility to drugs that are needed. Rational use of AKT and second-line drug regimens depend on accurate surveillance but in the presence of a poor public health system a mere surveillance network however efficient, cannot be the sole panacea. The technical arm needs to be supported with the widespread creation of awareness, together with an accessible, accountable and well integrated health system reaching to the grass root level. Last but not the least required is a strong political commitment of governments to the welfare of all its citizens that allow practices like production or parallel imports of cheaper drugs and curbing of anti competitive licensing to come into their own.(12)

Technical inputs such as early diagnosis and identification of contacts cannot by themselves affect the transmission of TB (and MDR-TB) or diseases that are precipitated by socio-economic malaise. Firstly, the sensitivity of diagnostic tests in chronic diseases such as TB is less than satisfactory. Secondly stretched financial resources go ill with screening of populations and development of increasing sensitivity in diagnostic tests that are basically expensive. A very modest decrease in patients’ numbers in the U.S. between 1955 and 1992 was attributed to a 25 fold
increase in spending from $3 m to $75 m on tuberculosis research. A nation with a crunch in financial resources for overall health is likely to have poor socio-economic indices and a population with a high element of relative risk. Therefore, even in communities that implement essential public health elements of TB control, ongoing transmission of TB is bound to continue for a long time to come. (14)

Despite mounting doubts, the RNTCP using DOTS claims to have successfully treated approximately 80% of patients in 20 districts of 15 states in India(15). Treatment success rates are claimed to be more than double and death rates less than a seventh to those of the previous programme. A give away figure is the success rate of 80% achieved in patients with extra pulmonary tuberculosis!! In a country where diagnosis of extra pulmonary TB is largely on the basis of symptoms and clinical signs, with no consensus on laboratory based diagnosis, the figures of the so-called "cure rates" achieved are hard to comprehend.

Diagnosis of even pulmonary tuberculosis by simple sputum examination till recently enjoyed an average national sensitivity of only 25%(5). This was true also of the municipal wards in the island city of Bombay as recently as 1998. Yet case detection rates for the first two quarters of 1999 show up as 43.27/100,000 with a target of 50/100,000 for sputum positive cases. The cumulative figures for sputum positive and negative pulmonary tuberculosis, on the other hand are 135/100,000 exceeding the target of 132/100,000 (Rangan, Personal Communication)! Whilst external experts dubbed the performance of Bombay Municipal Corporation (BMC) microscopy centres as "abysmal", the BMC technicians negated any effort at monitoring or upgrading of their performance. These "gratifying" cure rates originate from these very public microscopy centres. This echoes the lament of D. Banerjee(16), where he states that "a major obstacle to assessing the performance of the RNTCP is that very scanty information, and that too of questionable validity, is available”.

Datta and Mohan(17) similarly indicate the lack of any reliable epidemiology of MDR-TB in India. No continuous quality control between even referral laboratories has been undertaken. The test procedures are never fully disclosed and no effort is being made to evolve rapid tests for screening for drug resistance. The problem of MDR-TB will never be reflected accurately in the RNTCP since claims indicate that about 30% of patients (probably a large part comprising of problematic cases) are turned away from the DOT treatment centres(5) by virtue of their place of residence or disease complications or previous history of refractoriness to anti-TB drugs. The terms DOTS treatment and DOTS coverage are therefore not always synonymous.

The increasing worldwide prevalence of multidrug-resistance (MDR) strains of Mycobacterium tuberculosis represents a major threat to tuberculosis (TB) control programs(18). Although data on drug-resistant TB are lacking in India due to the absence of a reliable surveillance network, a World Health Organization survey in 1997 in the state of Tamil Nadu (19) and a limited study in an urban tertiary care center in Bombay (20 reported figures of 7.1 and 58% prevalence of multidrug resistance, respectively, indicating that MDR TB may pose significant problems. The figures of multi-drug resistance in rural parts of India derived from micro studies in well-run programmes are reportedly low at 2-3%. This may not be a cause for complacency as it may merely reflect a situation of inaccessibility to health care and drugs as in Africa. Paramsisvam and others in 2002 presented a longitudinal surveillance of drug resistance in two districts. In new cases resistance to any one drug was 28%, to isoniazid 23% and Rifampicin 2.8%. These figures were tremendously amplified in previously treated cases where overall resistance to Isoniazid and rifampicin were 81, 69 and 69% respectively. The significant biological pressure that drugs therapy (particularly of the intermittent type) experts is obviously significant.

The design of strategies for the management of MDR TB depends on an understanding of the development and spread of resistant isolates. Well-documented outbreaks in settings of low endemicity demonstrate the efficacy of MDR TB isolates in generating new incident cases(22), but less is known about the ability of resistant isolates to compete with other strains of M. tuberculosis in areas of high endemicity.

In a recent study conducted in Bombay (23), the detection of 36 different spoligotypes among the panel of drug-resistant isolates is consistent with a high rate of secondary, or acquired, resistance in this population, reflecting the problems of efficient TB control in a metropolis with overburdened health facilities (D.D’souza, N G Mistry, B A Rajgor, and N H Antia, submitted for publication). However, the sharing of a single spoligotype by 29% (19 of 65) of the isolates (cluster 1) suggests an important role for the transmission of a dominant resistant clone. While alternative genotypic techniques (24,25,26) are required to determine whether cluster 1 indeed represents a clonal population, this study may provide
the basis for a systematic and extended study of MDR TB strains in India.

III. BEYOND DRUGS

The current stage of globalization, dating from the 1960s is distinguished by the geographical breadth it encompasses, the frequency and intensity of human interactions that are taking place and the degree to which thought processes have been made subservient to these interactions. The impact on human society and its health is unprecedented(27). Atleast 30 new infectious diseases have emerged in the last 20 years.

Globalization creates pressures on national governments to integrate and compete within a grossly unequal global economic system. Deacon(28) writes “Economic competition between countries maybe leading them to shed the economic costs of social protection in order to be more competitive (social dumping) unless there are.... global regulations in place that discourage this”. Some of the forms that this dumping has taken are reduction in public expenditure on health and undermining of effective regulation of environmental pollution notably in the need-based world of which India is a glaring example.

The result has been a long term deterioration of our public health system including the capacity to prevent, control and treat communicable diseases. Within this framework inadequate social welfare, public health systems and a rapidly burgeoning uncontrolled private medical and pharmaceutical sector are the main causes of drug resistance, together with incomplete and inappropriate use of medication and unregulated promotion and sale of antibiotics. More that this however, is the reality of an evolving world view that propagates a seemingly rapid global culture of reform but which excludes populations without financial resources from available medical technologies and drugs such as HIV triple therapy or regimens for treating MDR-TB or anti malarial medication(18).

Like Richard Horton, we have to put the major share of failure at the door of our government, policy makers, national health infrastructures and market mechanisms, that degenerate caring human beings into unfeeling and uncaring machinations. The last answers why rates of patented basic drug prices have risen from 5 to 67%(30); why our laboratories underreport positive TB smears by 80%, why poor quality, often unnecessary and even dangerous drug cocktails, are prescribed for patients by private practitioners, why government deregulates drug policies, or why poor patients need to discontinue their AKT. Horton(31) calls it a “displacement of collective responsibility and turning away from the consequences of a globalizing world - thinking it fragmented into myriad pieces with their own fate, autonomy and responsibility”.

In the event of deliberate misleading and the absence of caring and commitment by the government, industry or the affluent classes, it is intriguing that Dr Kochi of the WHO once again focuses on a $ 300 million endowment fund to buy TB medication in the stop-TB declaration(6). He fails to qualify however whether these drugs will be made available to need-based countries once again through mega loans of The World Bank which will help to re-establish the cycle of poverty, destitution and disease. The situation for TB may in the near future mimic the HIV-endemic nations of Africa which are currently being “persuaded” to avail of U.S. loans for procurement of anti-HIV drugs from U.S. pharmaceutical companies(32).

It is now imperative to simultaneously also question the facile supposition that sufficient drugs, or even new drugs, will stem a disease for whose sufferers there is no concern, leave aside caring. Decrease in the quality of drugs, mismanagement of supplies, inequitable pricing and the pressure of multidrug induced resistance will continue to near their head time and again, the last with ever increasing virulence(8). Perhaps these adheres to Styblo’s contention that whilst socio-economic development leads to an annual decrease in TB upto 4% per annum, effective chemotherapy can increase this rate to 14%(23). But the operative word is “effective”. Socio-economic conditions and the changing nature of germs now continuously ensure that drugs will become less and less effective. The post antibiotic era for TB is beginning. We wish it away only at our peril.

IV. EPILOGUE

It is indeed convenient and easier to analyze the emergence of MDR-TB in India (and globally) in the sole context of a biomedical model and logistics of drug
supplies. This stance suits international agencies and researchers who can then tinker with outcome projection models, divert resources into research for new drugs (which a naive “Roll back malaria” type programme advocates every three years!). A convenient strategy which draws attention away from the underlying pervasive common theme of poverty, to which occasional lip sympathy is or is delicately not mentioned at all. To admit in the present climate that a large group of adverse health conditions are basically the result of reduction in disposable income amongst the world's poor and admit that development policies have an unintended or intended consequence of exacerbating poverty, requires qualities of caring and a strong moral fibre: indeed it may even be expressed by a few that in the “larger benefits” of globalization, some outcomes such as marginalization are inevitable and an outcome of the trickle down theory of development.

This paper does not reject completely the biomedical model. The initial discussion is focussed on drug action and its nuances but it does not end there. Its aim is to show that even within a narrow technical purview there are issues of caring, costs, poverty and misleading. Refusing steadfastly to recognize this, international funders harp only on drug and vaccine based techno-managerial solutions and associated research. Because the issues are complex, the causal linkage between consequences of Adjustment Policies and health status of the poor is difficult to formulate and gets bogged down in academic semantics, arguments and eventually convenient confusion(34). It is hoped that the new strategy of policy-oriented monitoring of equity in health does not suffer the same fate. As Braveman(35) states “Better data and methods are needed to monitor equity, but in virtually any country,..., even the poorest nation with most meager data... far more could be done now with existing data and simple methods”. We would, on the basis of our experience, also add existing financial resources.

Therefore, any technical strategy needs to address the formidable national and international political obstacles to the achievement of Health for All, if it is not to become a convenient rhetoric for continuing ‘more of the same’. Even tragedies such as MDR-TB have their uses in serving as models to highlight these obstacles.

REFERENCES


