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NEEDS IN TUBERCULOSIS RESEARCH*

R. Prabhakar[1]

Tuberculosis is still a major health problem in developing countries. It is also emerging as a major infectious disease in the developed countries due to AIDS epidemic. Its pathogenesis, immunology and molecular biology are still incompletely understood. The development of new drugs to fight tuberculosis ceased over two decades ago. The variable efficacy of BCG, found in different trials, still remains an enigma. And, it is likely that its epidemiology is also different, in some aspects, in developing countries compared with the developed ones. Sometime ago, it was said that the application of current knowledge about tuberculosis was lagging so far behind its application in the field that the focus should shift from more and more research in tuberculosis. That saying appears to have lost its validity under the present circumstances, especially when the WHO has declared a global war on the "neglected epidemic". The following horizons in different aspects of tuberculosis can be recognised in respect of research needs in tuberculosis.

Epidemiology

Infection

Setting up of surveillance systems to assess the impact of control programmes. Monitoring of changes in tuberculosis infection (or prevalence of infection) (a) Sequential tuberculin testing surveys among children; (b) Surveys among sentinel populations of young adults.

Disease

Case control studies to identify the factors responsible for progression of disease. Application of new methods to characterise strains of tubercle bacilli - DNA fingerprinting. Studies to determine the impact of HIV infection on TB. Tuberculin surveys amongst close contacts of tuberculosis cases. Effect of preventive chemotherapy on the infectiousness.

Diagnosis (Case-Finding)

1. Improvement of case-finding:

   KAP studies on tuberculosis
   Integration of tuberculosis services into primary health case
   Health Education
   Active case-finding focussed on high risk populations
   Improving the diagnosis among patients presenting at health care facilities.
   Increased involvement of private practitioners and traditional healers

2. Improvement in currently used technologies:

   - Improvement in smear microscopy
   - Slide cultures
   - Improved culture techniques, including development of a simple non-radiometric technique of detecting mycobacteria prior to visible growth

3. Development and in-service evaluation of new technologies for the diagnosis and prediction of:

   (a) early disease;
   (b) relapse;
   (c) prognosis of tuberculosis, that have potentially

   (i) greater sensitivity
   (ii) higher specificity
   (iii) greater rapidity
   (iv) greater cost effectiveness, and
   (v) greater applicability to developing countries

4. Improved methods for diagnosis of *M. tuberculosis* infections. The criteria required for a new diagnostic test include

   (1) Cost-should be less than US $ 0.50 per test

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[1] Director, Tuberculosis Research Centre (ICMR), Madras

(2) Speed-result should be available within two hours

(3) Sensitivity and specificity - should be 99% when compared with culture

(4) Simplicity-should be adaptable to use in field conditions in developing countries

(5) Reliability and reproducibility

(6) Safety and acceptability to both users and providers

(7) Not invasive (short of a finger stick)

(8) "User friendly"

5. Approaches in development of new diagnostic test(s):

(a) Detection of the response of the host to the bacilli. The first immunodiagnostic tuberculin test is unable to distinguish active tuberculosis from past sensitisation, BCG vaccination or environmental mycobacteria.

(b) Serologic tests are based on the binding of an antigen to its specific antibody in serum. ELISA test is the choicest of all serological tests.

(c) A very high specificity is required for any new test to be applied to the patients of mycobacterial disease. In competent laboratories, the existing methods of sputum microscopy and culture have specificities approaching 1, and this sets the standard that must be matched by new diagnostic tests. The specificity of immunodiagnosis depends on the specificity of the antigens and antibodies used. Diagnostic PCR is a technique of DNA amplification that uses specific DNA sequences to serve as markers for the presence of micro-organisms. The genetic marker most commonly used is mycobacterial insertion element - IS 6110 - DNA piece of uncertain functional sequence present in *M. tuberculosis, M.bovis, M.microti* and *M. africcanum.*

Treatment and Case Holding.

Improvement of patient adherence to treatment crucial in developing countries.

1. Studies to improve
   - the present delivery system of chemotherapy
   - alternatives to hospitalization
   - DOT (directly observed therapy) in the initial intensive phase of SCC
   - novel drug delivery (e.g. calendar, blister packs)
   - impact of participation by the private sector
   - community participation

2. Studies to
   - improve treatment adherence
   - evaluate incentives and enablers
   - select potentially non-adherent patients for supervised chemotherapy

3. Cost-effectiveness analyses of various regimens of SCC.

4. Surveys of consumer satisfaction

5. Surveillance of initial resistence to Isoniazid, Streptomycin, Rifampicin and Ethambutol

6. Development of new therapeutic modalities: New drugs like
   - Long acting Rifamycins: Rifapentene, Rifabutin
   - Quinolones: Ofloxacin, Ciprofloxacin; Sparfloxacin.
   - B lactamhse inhibitors: Amoxycillin, Ticarcillin and Clavulanic acid
   - Newer Aminoglycosides
   - Clofazimine

Prevention

1. Efficacy and operational studies, including analysis of cost-effectiveness to define the

role of preventive chemotherapy in high-risk populations.

2. Revaccination with BCG vaccine

3. New forms of preventive therapy, new drugs, immunotherapeutics, depot preparations

4. Development and testing new anti-tuberculosis vaccines including understanding the immunology and molecular biology of the bacillus

5. Additional studies with BCG:
Neonatal vaccination, studies of additives to BCG (e.g.killed *M. vaccae);* safety of BCG vaccine in HIV infected persons.

Economic, Social and Operational Research

1. Problems at the Tuberculosis Clinic level:

- inadequately trained, poorly supervised and over-burdened, health manpower
- incorrect or incomplete information available to the public on tuberculosis symptoms and risks
- deficiencies in the quality of diagnosis, despite efficacious technology
- inadequate cooperation and referral arrangements with private providers of services
- Poorly designed or completed registries and notification forms
- drug supply problems leading to intermittent shortages
- improper prescribing patterns, and lack of follow-up
- difficulties in motivating patients and ensuring compliance
- lack of staff, transport and information systems to follow up all patients who do not adhere to treatment.

2. At the national or provincial control programme levels

- increasing competition for scarce health sector financial resources
- the low-priority status for tuberculosis despite the continuing heavy burden of disease

ineffective negotiations for low-priced purchase of drugs, and poorly managed distribution and quality control system

- incomplete management information system
- lack of control over prescribing and sale leading to drug resistance and chronic excreters
- poorly planned and executed integration of tuberculosis control programmes into primary health care systems, including
- lack of supervision and training
- lack of health services management

3. How to

make efficient and effective use of existing technologies
improve the delivery system infrastructure
increase patient and provider motivation and compliance
appropriately adapt new technologies to operational settings
expand programme coverage
increase political and financial support for tuberculosis control efforts

4. Studies focussed on

cost-effective diagnostic and treatment strategies that are appropriate and feasible
improvement of health service infrastructures for tuberculosis control
role of hospitals in tuberculosis diagnosis and treatment
development of strategies for enhancing the cost-effective use of hospitals
scope of private sector involvement in diagnosis and treatment (including traditional healers)
KAP of providers
development of models for integrating tuberculosis control into related control services.