

## Why Tuberculosis Has Not Been Eradicated? Need for Vision and Bold Innovative Research

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### Abstract

Tuberculosis has not been eradicated despite advancements in science. Main reason is that research and its utilization have gone into a deep rut because of lack of vision and innovation. Knowledge about epidemiology of tuberculosis is patchy. Some paradoxes and unanswered questions have been highlighted. Finding explanations for these is essential to eradicate tuberculosis. Prevention, diagnosis and treatment of tuberculosis need overhauling. A systematic review is needed to identify facts, myths and gaps in knowledge about all these. Thereafter, new types of research which can answer relevant questions are essential to find explanations for many paradoxes and unanswered questions and to remove lacunae in prevention, diagnosis and treatment of tuberculosis because many decades of present type of research have failed. Only thinking out of the box and carrying out bold innovative research can find needed explanations. Emphasis ought to be on going ahead urgently with bold innovative research to find effective measures required for eradication of tuberculosis. Studies to ascertain factors contributing to spontaneous cure also deserve high priority. Suggestions to make a beginning in innovative research have been given. Some instances of ignoring research findings have been highlighted. Importance of utilization of research findings has been stressed. Any hesitation in funding bold innovative research is a pennywise and pound foolish approach without vision because economic cost of tuberculosis is many times higher than even spending huge amounts, if needed, on such research. Moreover, elimination of suffering from tuberculosis is invaluable.

**Keywords:** Vision; Innovative research; Research funding; Research utilization

### Introduction

Tuberculosis has been a major world health problem for centuries. It has not been eradicated despite advancements in science. Main reason is that research and its utilization have gone into a deep rut because of lack of vision and innovation. There is an urgent need to think out of the box and adopt innovative approaches. These approaches should cover research on epidemiology, bacteriology, biochemistry, prevention, diagnosis and treatment of tuberculosis besides utilization of research findings and funding of research.

### Epidemiology of tuberculosis

There are unanswered questions about epidemiology of tuberculosis. Infection by tubercle bacilli causes tuberculosis. Only few infected persons get tuberculosis. Why do the vast majority escape? Why interval between infection and disease can be weeks or many years? Is succumbing more often due to exogenous re-infection than endogenous reactivation? Why do many cases have spontaneous cure? Why do some non-specific infections by environmental *Mycobacteria* provide immunity [1-4].

### More unanswered questions and some paradoxes

In Chingleput [5] and Madanapalli BCG trials [6,7] incidence rate among vaccinated was higher than among unvaccinated during first five years and between 12½ years and 15 years but was the opposite during intervening period of 5 to 12½ years. In British trial [8,9]

incidence among vaccinated was higher than among unvaccinated for period beyond 12½ years but not so in earlier periods.

In Chingleput [5] prevalence rate was steady during first five years but declined steadily during next 10 years. Incidence rate declined during first five years but was constant during next 10 years.

Chingleput had high prevalence and incidence though it had high prevalence of non-specific infection which was expected to protect.

BCG cannot prevent primary infection [5]. But another study [10] claims that BCG protects against infection.

Filling up gaps in epidemiology and finding explanations for unanswered questions and paradoxes are essential to eradicate tuberculosis. For this, thinking out of the box and carrying out bold innovative research which can answer relevant questions are essential because many decades of present type of research has failed in all these aspects.

For a possible beginning, identify recently infected and earlier infected by repeated surveys. Subdivide them into vaccinated, doubtfully vaccinated and not vaccinated by questioning about vaccination and observation of BCG scar. Ensure that sputum examinations at all surveys provide culture results and biochemical details of bacilli including virulence. Comparing the results will show whether characteristics of bacilli differ between cases in these sub groups and clarify questions about infection and BCG.

Follow up for a few years to identify new cases. Comparing culture results and biochemical properties of bacilli for old and new cases in the sub groups may answer questions or suggest new questions.

Similarly, comparing detailed personal characteristics of infected and non-infected persons and cases (old and new) in the sub groups can show whether there are any enlightening differences. Characteristics used should be wide enough to cover demographic, physical, mental and environmental aspects as thoroughly as possible.

Detailed analyses as above after splitting results for the sub groups according to reaction to non-specific infections will answer questions about influence of non-specific infections on prevalence and incidence of tuberculosis, according to characteristics of bacilli, persons and cases.

Doubts (e.g., inability to strictly demarcate vaccinated and not vaccinated) should not stand in the way because, when we are in the dark, even partial answers and indicators will throw light for further research.

### **Need for deeper analysis of data from Chingleput trial**

Further analyses of data from Chingleput trial may throw light on some unanswered questions or, at least, help to form hypotheses for further study.

Whether massive doses of infection can reduce effect of BCG may be evident in areas with higher prevalence and incidence. To test this, group villages in study area according to low, medium and high prevalence at initial survey. For each group, calculate incidence rate among vaccinated and not vaccinated. Comparisons will show whether protection level decreases with increase in level of prevalence.

Similar analyses after regrouping villages according to incidence between 1st and 2nd surveys can be rewarding.

Comparison of incidence in villages with different levels of non-specific infection will throw light on protection by different levels of non-specific infection. Calculation of effect of non-specific infection among vaccinated and non-vaccinated may indicate to what extent different levels of non-specific infection mask effect of BCG.

### **Bacteriology and biochemistry**

For treating cases, it has been presumed that they have uniform properties. Research in bacteriology and biochemistry has neither correlated properties of bacilli with treatment effect and or self -cure nor suggested diet modifications. Innovative research is essential in these fields.

### **Prevention of tuberculosis**

BCG trials in some countries [8,9,11-14] and in India [6,7] gave conflicting results about efficacy of BCG and question efficacy of BCG trials.

In Chingleput [5], prevalence rate was very high for 45-64 years age group in all seven surveys (ranging from 1,519 to 2,095 per 100,000 compared to 694 to 875 per 100,000 for all ages). For 65 years or more, this rate was even higher (ranging from 1,775 to 2,233 per 100,000). Another study [15] confirmed that rates of prevalence and incidence steadily increased with age.

Most non-infected persons in vaccinated and control groups will be in 0-19 year age group initially. If trial period is less than 45 years, effect of very high incidence among them when they cross 45 years will be missed. Obviously, complete information about efficacy of BCG could not be obtained from any trial conducted so far because of

grossly inadequate follow-up period (much less than a minimum of 45 years required for studying effect of very high incidence rates).

Carrying out a variety of field investigations for even 15 years in a large population posed many problems due to migration of population and doubtful availability of large number of staff to continuously maintain uniformly good quality of work. These unavoidable changes distort quality of data.

Many socio-economic and environmental changes occur during a long period. These directly and indirectly affect pattern of incidence in any study and vitiate isolation of effect of BCG.

Because of all the serious problems mentioned above BCG trial can only be costly and wasteful.

One serious consequence of dilly dallying with BCG trials for many years was that adequate efforts were not made to find a better vaccine or preventive which can help to eradicate tuberculosis.

### **Indirect assessment of protection by BCG (or a new vaccine) and non-specific sensitivity**

Because assessment of protection by BCG (or a new vaccine) and non-specific infection is not possible through controlled trials, indirect methods have to be adopted. Information about prior BCG vaccination, BCG scar status and non-specific reaction for each case diagnosed can be useful. If substantial proportion of cases reported BCG vaccination and had BCG scar it can be concluded that BCG did not protect adequately. Estimate of protective effect of BCG is not needed. If substantial proportion of cases were reactors to nonspecific infection, it can be concluded that non-specific infection did not protect sufficiently. Protective effect of a new vaccine can be similarly studied by collecting information about vaccination status of cases.

### **Diagnosis of tuberculosis**

In the absence of effective prevention, to achieve progressive reduction in number of cases leading to eradication over a period of time, it is essential to diagnose and cure every year larger number of infectious cases (out flow) than the number of new infectious cases coming up (in flow). When this is not happening systematic efforts should be made to achieve it. For this, direct microscopy should be more effectively used to diagnose more cases. A study [16] showed that only 64% of cases can be diagnosed by microscopy of one sputum specimen and 72% from two specimens. Examination of six specimens can diagnose 95%. Microscopy of six specimens will lead to a substantial increase of 49% in number of cases diagnosed where only one specimen was examined and 32% where two specimens were examined. This is definitely worth the extra efforts. Non-utilization of this important research finding is one example of lack of vision. Further, to diagnose early cases which do not have enough bacilli in sputum at time of first approach, microscopy should be continued at suitable intervals (determined through research) so that remaining 5% of cases can be diagnosed without delay.

Case detection under current system depends on sputum examination of chest symptomatics seeking relief from health institutions. Only about 10% of them have tuberculosis. Many symptomatics stop visiting these institutions when the programme has nothing specific to offer to majority (90%) of them. This seriously retards case detection. To help chest symptomatics without tuberculosis (with a humanitarian approach) and to overcome the unpopularity which has retarded case detection, innovative research

should be carried out for diagnosing and treating millions of chest symptomatics without tuberculosis [17]. Ignoring this suggestion because of a compartmental approach is the second example of lack of vision.

Diagnosis based on x-ray examination has been in practice for a long time. In 1974, one study [18] showed that 87% of those diagnosed by x-ray examination alone are unlikely to have tuberculosis. Reported figures for case detection in 2006, 2008 and 2009 showed that only 13% were smear positive among those diagnosed on x-ray alone and repeatedly showed that about 87% of those diagnosed on x-ray alone could not be confirmed as true cases of tuberculosis [17].

An in-depth evaluation [19] found that, on an average, 6,90,000 cases were diagnosed by x-ray examination every year in India, of whom about 6,00,000 (87%) were unlikely to be suffering from tuberculosis. This unethical massive over diagnosis and huge wastage of x-ray facilities and drugs every year due to non-utilization of an important research finding [18] is the third example of lack of vision. The wasted funds could have been put to better use. Even more important, wrong diagnosis caused mental agony and permanent social problems to millions of people and their families. This human aspect also deserves serious attention [17-19]. This is also an example of Medical Council of India not utilizing important research findings.

Evaluation study [19] recommended that repeated sputum examination should be the main criterion for diagnosing tuberculosis. But wasteful x-ray examinations continued on a large scale in the questionable guise of detecting early cases. The only reliable method to diagnose early cases is to continue microscopy at suitable intervals.

A new technique (Xpert MTB/RIF) which can diagnose more cases than microscopy has been developed [20]. Large scale application of this technique has to depend on sensitivity and specificity of this technique and whether it can be organized and maintained on a large scale (like microscopy) to provide benefit to common people throughout the country.

Hardly any attempt has been made to effect technological improvements in x-ray examination. Menon VA (retired X-ray Engineer, National Tuberculosis Institute, India) has been unsuccessfully knocking at doors of number of scientific bodies for more than 25 years for funds to carry out a project for technological innovations! Not supporting this project is the fourth example of lack of vision.

Enormous over diagnosis by x-ray examination leading to unnecessary treatment still continues, particularly so by private medical practitioners and institutions. To prevent these and to increase detection of true cases, Medical Council of India should forbid use of x-ray examination by any registered medical practitioner for diagnosing tuberculosis and insist that microscopy should be done for up to six sputum specimens from each patient.

## Treatment of tuberculosis

Several studies have shown that (1) 25% to 33% of cases were cured without specific treatment for tuberculosis and (2) at least two-thirds of cases were cured with incomplete treatment [17]. Thus, a minimum of two-thirds of cases did not need the complete treatment which the programme forced on them. This large-scale unethical over-treatment has been continuing for years! This is the fifth example of lack of vision and another example of non-utilization of an important research finding.

A study to tackle this problem was suggested [17]. In this study, socio-economic, environmental and cultural status and information on physical, dietary, hygienic and other health practices; deficiencies (anemia, vitamin deficiency etc.) and mindset were to be collected for all cases irrespective of duration or regularity of treatment. They were to be followed up to ascertain whether their cure rate was influenced by any of these factors. Analysis of this study using discriminant analysis [21], would have helped to identify at least three categories of cases (those needing no treatment, short treatment and full treatment) and helped to substantially reduce or even eliminate unethical treatment practices. But this study, which deserved highest priority, was not carried out. This is the sixth example of lack of vision. This study would have also led to large savings in cost of drugs.

One argument against increasing case detection is: why should we diagnose more cases when we do not have resources to treat currently diagnosed cases? This question ignores the fact that currently bulk of resources are wasted to unnecessarily treat millions of wrongly diagnosed cases [17-19] and to force complete treatment on 66% of cases who do not need it [17].

## Need for vision and bold innovative research

Eradication of tuberculosis needs vision and keeping windows open for ideas to flow in. Open windows will also help to throw out discordant ideas. Emphasis should be on bold innovative research to find better method of prevention, improve quality and quantity of case detection, remove unethical treatment and find better treatment. Studies to ascertain factors contributing to spontaneous cure deserve even higher priority.

It is essential to ascertain factors which influence behavior of tuberculosis cases, chest symptomatic and health care providers and how these influence trends in prevalence and incidence of disease, so that all these can be considered for planning an eradication programme. A suggestion (in a "special article" [22]) to carry out a comprehensive, multipurpose, national sample survey with repeated rounds, which alone can provide a complete picture was ignored. This is the seventh example of lack of vision.

Frequent occurrence of self-cure and cure with incomplete treatment [17] endorses the possibility of finding some element in food that can inhibit growth of tubercle bacilli in the body. Identifying a biochemical element capable of inhibiting growth of tubercle bacilli and which food item (vegetable, fruit, nut, egg, meat or fish) contains this element deserves highest priority. If prevalence of tuberculosis is less among those consuming this food item, it can be a preventive measure also.

Making an inhaler which contains a biochemical element capable of inhibiting growth of tubercle bacilli will lead to effective cure of pulmonary tuberculosis which includes vast majority of cases.

Deep inhalation and maximum exhalation during pranayama and kapalbhati (yoga exercises) lead to lung movements which improve lung condition. Doing this sufficient number of times each day (determined through research) might help to accelerate curative effect of treatment of pulmonary tuberculosis and/or self-cure. If prevalence of pulmonary tuberculosis is less among those practicing pranayama and kapalbhati, these can be a preventive measure. Study of these aspects should get highest priority.

These are four examples of bold innovative research with highest priority for coming out of the rut of deep rooted ineffective thinking.

More such innovative research should be identified following the exhortation by Albert Einstein that “The important thing is not to stop questioning”.

Large number of scientists has put in lot of efforts to carry out research and huge amount of funds have been spent. But most of these have been wasted because findings were not utilized. For example, suggestions about (1) conducting comprehensive, multipurpose, national sample survey [22] which alone can provide a complete picture for planning an eradication programme (2) stopping use of x-ray examination to prevent colossal wrong diagnosis [17-19] (3) increasing case detection by examining six sputum samples [16] and (4) study to overcome unethical over treatment [17] were ignored. Non-utilization of research findings is due to lack of vision about eradication of tuberculosis and inability to think out of the box to achieve eradication. National and International Research Authorities, staffed by scientists with open mind and broad vision to eradicate tuberculosis, should be set up to visualize and/or approve meaningful research and to constantly review utilization of research findings. Their recommendations should be fully accepted and implemented by all governments if they are serious about eradicating tuberculosis.

Hesitation in funding bold innovative research shows a pennywise and pound foolish approach without vision because economic cost of tuberculosis is many times higher than even spending huge amounts, if needed, on such research. Moreover, elimination of suffering from tuberculosis is invaluable.

We can make progress only if we think out of the box and ask questions, discuss these freely and objectively and carry out scientific studies to find proper answers [23]. While asking questions we should not take the attitude of a frog in the well, for which universe consists of the well only. We have to ask lot of questions within and beyond the well, with an open mind.

A basic general obstacle which retarded development of innovative research is defective education [24]. Adequate attention is not given to development of analytical/logical thinking. Attempts to dovetail aptitude with selection of fields for education and skill development are scarce. This often resulted in calamity of square things being squeezed into round plugs. Research jobs are often taken up by persons without any aptitude for or interest in these but only to earn a salary. These are not conducive to development of innovative scientific research. Holistic education suggested in that article [24] will build up an environment conducive to development of innovative scientific research.

I believe scientists’ intuition had a role in most scientific achievements. Because one-third of cases had self-cure and another one-third were cured without complete treatment, I intuitively feel that regular consumption of a food item and practice of pranayama and kapalbhati are the best tools for prevention and treatment of tuberculosis. I urge that topmost priority should be given to innovative research on these aspects.

## Conclusion

Why tuberculosis has not been eradicated?

Because of lack of broad uninhibited vision to eradicate tuberculosis by giving priority and commitment to funding and carrying out bold innovative research and utilization of research findings.

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