
APPROACHES TO DRUG RESISTANT TUBERCULOSIS - INDIA AND BEYOND 1955-1992

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AARHUS
UNIVERSITY
DEPARTMENT OF CULTURE AND SOCIETY

NIELS BRIMNES
ASSOCIATE PROFESSOR, PH.D.

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MADRAS TUBERCULOSIS CHEMOTHERAPY CENTRE

Major Result:

‘A Concurrent Comparison of Home and Sanatorium Treatment of Pulmonary Tuberculosis in South India’, *Bulletin of the World Health Organization*, 1959

- Differences between home and sanatorium treatment were “surprisingly small”
- Standard regimen: INH + PAS
- Trials with INH alone – an alluring option, because it was far cheaper than other drugs



EARLY AWARENESS

BMRC note, 1955:

The Indian side was “very well aware of the danger of creating widespread resistant strains”

Project report, 1956:

A major purpose of Madras TCC “to gain information on the dangers involved in the creation of INH resistant tubercle bacilli during chemotherapy”

Project report, 1963:

up to 40 % (?) of first time patients carried INH resistant organisms



LAXITY

Meeting in New Delhi, 1957:

School 1:

Resistance to INH is serious (Britain and Commonwealth; Wallace Fox)

School 2:

Resistance to INH is “comparatively unimportant” (US, continental Europe)

WHO HQ (Johannes Holm): INH should be given alone and UNICEF funding would be available only for INH



CONTROVERSY BETWEEN FOX AND HOLM

Fox (clinical outlook): We must do everything to prevent resistance from emerging

- ▶ Multi drug regimens, elaborate patient monitoring

Holm (public health outlook): We need a simple, feasible and cheap programme

- ▶ Holm would “not be too afraid of a few complication if INH were given alone

CONTROVERSY BETWEEN FOX AND HOLM

Holm in 1957 (speech in Glasgow):

WHO's approach was: "not always appreciated by the clinician who wishes to do everything possible for his patient and therefore, when the question of chemotherapy arises, will accept only the drug or drug combination which is generally considered to give the best results, irrespective of the costs".

"I shall refrain from entering into a discussion of the controversial issue of INH resistance of tubercle bacilli and the importance of this in a public health tuberculosis control programme. I will only say that public health people are much less afraid of this than many clinicians seem to be"



THE NATIONAL TUBERCULOSIS PROGRAMME

Launched from 1962:

Assisted by WHO and UNICEF until 1975

Based on:

- ▶ district programmes (DTPs)
- ▶ Free drugs (ideally INH + PAS)
- ▶ Self-reporting patients ('passive case finding', 'felt need approach')
- ▶ Self-administering patients (monthly or bi-monthly collection of drugs)



DRUG AVAILABILITY

Calculations (district):

INH alone:

Case reduction: 20%

Cost: 20,000 Rs.

Full development of Drug Resistance

INH + PAS:

Case reduction 30%

Cost: 220,000 Rs.

Drug resistance reduction 80%

Later 1960s also: INH + Thioacetazone



DRUG AVAILABILITY

Maurice Piot (WHO Medical Officer), 1962:

“In order therefore, to provide treatment only for those who come forward for it, all the money now budgeted for anti-tuberculosis drugs for each centre in the Third Five Year Plan must be, of necessity, spent on INH. .. (...) .. the cost of a programme based on combined therapy, however desirable, remains today prohibitive, unless another cheap, effective oral drug becomes available as a companion drug”.

- ▶ *De facto* widespread employment of INH alone – ‘One is better than none’
- ▶ Longitudinal Study of INH resistance 1961-68: 10% → 20%

PATIENT REGULARITY

Patients completing treatment:

1960s 'model programme': 50%

1960s 'field conditions': 30%

1980s: 'field conditions': 27%



RARE WARNINGS

Frimodt-Möller (1962):

- ▶ Resistance is a “formidable problem”

Gryzbowsky and Styblo (1971):

- ▶ INH alone and INH + Streptomycin must be abandoned immediately



LAXITY (CONTINUED)

Pamra, Prasad and Mathur (1973):

- ▶ Pre-treatment resistance “of which so much is being made these days” was not an important factor in treatment failure

Fox (?):

- ▶ Pre-treatment resistance is “least important” among known reasons to treatment failure



LAXITY (CONTINUED)

WHO Expert Committee on Tuberculosis, 9th Report (1974):

“... it was at one time feared that primary drug-resistant disease ... might become a problem that would assume epidemiological importance. ... there is evidence that as the standards of chemotherapy improve the level of primary drug resistance becomes stabilized (p.9)

“The Committee emphasized that the importance of initial drug resistance as a cause of treatment failure has been much overrated.”



CRITICAL REVIEWS OF NTP

1975 ICMR report: resistance not highlighted

1988 ICORCI report: resistance not highlighted

1992 WHO, SIDA report: resistance finally highlighted as a problem



CONCLUSION

“Writing with the benefit of hindsight, the lack of concern over rising levels of drug resistance from the 1960s onwards does seem to be a severe flaw in the approach to tuberculosis in India and beyond.”





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