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EDITORIAL

Tuberculosis research: Quo vadis

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Despite 142 years of ongoing research, since Robert Koch discovered the tuberculosis (TB) bacillus, TB continues to flourish in the most vulnerable parts of the globe in Asia, Africa and South America (1). Indeed, progressive socio-economic measures (nutrition, housing and environment) have shown to be more effective than research in disease elimination in affluent areas of the globe (2). Undoubtedly, however, areas undertaken in recent research studies underscore new knowledge that may yield far-reaching impact on disease control, if not elimination. This editorial aims to highlight such specific studies and their impact.

Non-medical determinants

Little attention was paid to research on socio-economic measures. In this regard, two studies, viz., Bhargava et al. (3) and Shin et al. (4), stand out. Additionally, McKeown's famous graph (5) showed a dramatic decrease in TB even in the absence of drugs with good housing and a balanced diet. With the recent RATIONS (Reducing Activation of Tuberculosis by Improvement of Nutritional Status) trial in rural Jharkhand, the problem of undernutrition as a primary cause of TB was brought into the limelight though with nutrition supplementation only 54% of patients reached the desirable weight gain at 2 months of treatment (6). This poses several puzzling questions which need to be answered to establish nutrition as an effective control/prevention tool. Environmental pollution studies and its effect on TB incidence are also gaining ground with emphasis on particulate matter 2.5 and even smaller particles (7). However, the concept of healthy housing with optimal access to light and ventilation has been overlooked in India though it is prevalent in some countries of South-East Asia (8). In a study in the slums in Mumbai air exchange of 1-2 every 13 hours was seen to be the norm as opposed to the desired 6-7 per hour (FMR unpublished study). Transmission of all respiratory diseases is inevitable and will be continuous with such a large ventilation deficit and will continue to take place with compromised ventilation.

Drugs and mutations

The most singular outcome of biomedical research in TB has been to identify new and repurposed drugs for use against the TB bacillus. From rifampicin in the early 1970s to bedaquiline (BDQ) and delamanid in 2012 and 2013, the trickle of new drugs is envisaged as a powerful means of disease control but one that has a window of time before drug resistance sets in for a single drug/drug combination. One of the most singular findings in recent years is the theme that resistance to any drug can occur even before the drug is put to use by the disease programme. Extensive drug-resistant TB was detected in KwaZulu Natal even before the same drugs were deployed, through natural selection (9). Similarly in a cohort in India, mutations bestowing high minimum inhibitory concentrations (MICs) to BDQ such as Rv0678: c.141_142dupTC, p.Glu55Asp, p.Leu117Arg, p.Gly162Glu; atpE: p.Glu61Asp, p.Thr51Ile, p.Ser37Ala; pepQ: p.Pro69Leu, p.Arg7Gln; mmpL5: Ile948Val, Thr794Ile, Asp767Asn (FMR unpublished data) were seen in patients not exposed to BDQ. Does the presence of such natural mutations signify a natural tendency for resistance amplification? This is a powerful phenomenon to study the evolution of drug resistance in the coming years.

Another paradigm has been the linkage of gut microbiome to the phenomenon of drug resistance in an individual (10). Modulating the microbiome towards greater diversity and speciation offers a novel way to combat the emergence of drug resistance that needs to be explored with incisive studies, especially since a disturbed gut microbiome continues to exist for over 1.2 years post-anti-TB treatment (11). The use of complex compounds in phytomedicine indicates another approach to minimizing drug resistance. These complex structures in plant products may retard the development of drug resistance to conventional anti-TB drugs by stabilizing the gut microbiome or may have anti-bacterial action directly vs drug-resistant bacteria. This would provide a relatively cost-effective approach to the treatment of drug-resistant TB. Though no scattered studies provide positive indications (12-14), rigorous in-depth research is required.

Diagnosis

TB is well recognized as a respiratory disease spread through the air through microdroplets, especially in vulnerable communities. The ability to capture and detect such infectious droplets through masks (15,16) or through capture chambers (17) has given a profound scenario of disease biology. Increasing evidence has been generated in very recent years in even non-symptomatic individuals where disease in the preclinical stages shows the capture of such infectious droplets (18). This leads to a paradigm change in understanding the transmission of TB through non-symptomatic individuals, say, within a household in vulnerable communities and

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which can also be utilized effectively during active prevalence surveys.

The pipeline of novel TB diagnostics has never been richer. Several large consortia funded by the United States Agency for International Development, National Institutes of Health and Unitaid are currently undertaking validation study of these diagnostics for ensuring that the best are put to use. The future will stress self-sampling and self-testing technologies, which are likely to have wider acceptability.

Surveillance

The epidemiological research in TB is likely to be transformed in the coming years through increasing use of surveillance methods be it for antimicrobial resistance (AMR), mutations, clinical profiles or drug responses. The ability of countries to sustain continued data collection and rapid analysis would allow the use of key data that can be used for disease control.

Genomic surveillance and questions on how the environment fashions *Mycobacterium tuberculosis* (M.tb) response could not have occurred without the explosion in the field of bioinformatic tools and their application. For instance, Fastlin facilitates ultra-fast and accurate mycobacterium complex lineage typing, whereas Mykrobe can predict AMR in minutes (19,20). MTBseq is a comprehensive pipeline developed for whole-genome sequencing of M.tb complex isolates (21). These have been invaluable in ascertaining strain differences and in detecting transmission of TB in hyperendemic areas or examining tissue tropism of strain in extrapulmonary TB. We anticipate the generation of crucial knowledge in the coming years through deciphering the language of the cells.

Operations research

In operations research, the engagement of the private sector has become a key theme in recent times taken up on a global basis through the formation of public-private learning networks led by McGill University in Toronto. The Public Private Interface Agency (PPIA) introduced by the Gates Foundation in India around 2015 showed some early gains for patients accessing a PPIA-engaged physician at the first point of call (22). Whether this has translated to its successor, the Private Provider Support Agency (PPSA) overseen by the Government of India, remains to be evaluated.

The PPSA as of now is run on bureaucratic rather than functional lines, the emphasis being on orienting non-governmental organizations (the middle link between the National Tuberculosis Elimination Programme and the community) rather than sensitization and education of private sector physicians. The PPSA needs evaluation to fine-tune a potentially effective solution to early diagnosis, correct treatment and follow-up of TB patients buoyed by support mechanisms of direct cash benefit transfer for nutrition to patients.

The pioneering differentiated care model introduced by the Indian state of Tamil Nadu in 2022-2023 (23) is an innovative step today open for wider dissemination nationally and globally. It takes into account severe undernutrition, impaired lung function and overall functionality. This model if researched well will provide crucial learnings on approaches to reducing mortality and enhancing patient care infrastructure.

An excessively strict adherence to national guidelines for disease control paradoxically retards innovative insights in clinical and microbiological research and also adversely affects patient outcomes. Structures must be instituted to examine result discrepancies so that new paradigms of knowledge can be created.

Encouraging a comprehensive and open approach

With an eye on equitable access to knowledge and treatment, research should increasingly focus on to what extent and circumstances users stay out of the service technology net. The upfront GeneXpert (24) initiative and the SMaRT-PCR initiative (25 and Online) in diagnostic technology validation is a step in the right direction where technical performance is supplemented with an inquiry into community-level acceptability and feasibility. Two areas of applicability of such an approach are paediatric TB and post-treatment rehabilitation, an area almost completely ignored today in India. The next couple of years will give a comprehensive view of how novel technologies need to be translated for field conditions.

With the advent of big data technology globally, there comes the responsibility of open data sharing that can ward off common global threats. The trend of overt protection of country data needs to be eschewed if the common good is to be realized by the use of big data. Such global cooperation is a desirable but still yet distant goal.

Abbreviations

TB, tuberculosis; BDQ, bedaquiline; M.tb, *Mycobacterium tuberculosis*; PPIA, Public Private Interface Agency; PPSA, Private Provider Support Agency

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