Tuberculosis - A Forgotten Plague

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In the 19th century and first half of the twentieth century, TB was a widespread and deadly disease, killing one out of four adults in Western Europe and North America, many in the prime of their lives. It was known as the White Plague because of the extreme anaemic pallor of those affected. The White Plague was only a blip in the timeline of TB, which has existed since ancient times. It was only in the latter half of the 19th century that TB was recognized to be a contagious disease. The causative organism, Mycobacterium tuberculosis was identified by German scientist Robert Koch who announced his discovery in 1882 on March 24 which is commemorated each year as World TB Day. Since then, progress in the discovery and development of diagnostic tools and treatment for this ancient disease has been slow. In 1993, the World Health Organization (WHO) declared TB a global health emergency. Twenty-eight years on, TB continues to afflict millions each year, and until the COVID-19 pandemic of 2020, it was the leading cause of death from a single pathogen globally.

The 2020 WHO Global TB report estimated 10 million new cases in 2019 of whom 7 million were notified. Of these, 84% were pulmonary cases and 57% were bacteriologically confirmed. Out of the 465,000 estimated MDR cases in 2019, only 44% were notified, and 38% enrolled into treatment.

TB is an airborne disease and is spread when a person with active disease in the lungs coughs and aerosolizes the tubercle bacilli in the form of micro-droplet nuclei (1-5 microns) which can remain suspended in the air for many hours. The likelihood of transmission depends on the host mycobacterial load and ability to generate cough aerosols, the virulence of the organism, the exposure environment, duration of exposure, and immunological status of the host.

Most persons exposed to Mycobacterium tuberculosis are able to eliminate the pathogen by their innate immune responses. Others will have evidence of T-cell priming as detected by a positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA) result. The majority of immunocompetent persons who convert their TST or IGRA test are able to contain the pathogen in a quiescent state (ie. without evidence of clinical or radiologic disease), referred to as latent TB infection (LTBI). One in ten immunocompetent persons with LTBI will progress to active disease - of these, ~50% do so 2-5 years after infection. The rest develop active disease many years later or may persist in a state of "subclinical" (asymptomatic) disease, with intermittent symptomatic periods. Some may exhibit spontaneous disease resolution. Very young children and persons who are immunocompromised have a higher risk of progression to active disease.

Incipient and Subclinical TB

It should be noted that the TST and IGRAs indicate immunosensitization to TB antigens and are poor predictors of risk of progression to active TB. The challenge is to identify persons with "incipient" TB, ie. those at the stage where the pathogen is metabolically active with impending progression to disease, so that they may targeted for preventive therapy. There has also been renewed interest in "subclinical" TB disease, a state where the patient is asymptomatic, but has radiographic or microbiological evidence of disease (1). A recent review of prevalence surveys since 1990 showed that 50% of prevalent bacteriologically confirmed TB was subclinical, ie. would not be picked up by the usual symptom screening (2). It is clear that in order to accelerate progress towards ending the TB epidemic, efforts must be directed to identify and treat these persons before they become obvious health threats in the community.

Why is TB still a global health threat today?

Persons with pulmonary TB are often diagnosed after a prolonged symptomatic period, by which time they may have transmitted the mycobacteria to their close contacts. TB is also unique among infectious diseases in that symptomatic/infectious disease manifests years after the transmission event, making it hard to track. The current standard TB treatment (which has been in use for 50 years) is 6 to 9 months duration, making treatment adherence difficult. The only vaccine we have against TB, the Bacille Calmete Guerin (BCG), does not protect from adult pulmonary disease, which drives the TB epidemic. Above all, TB has been largely neglected for much of the 20th century because it affected poorer nations and did not attract funding for the vital research for better diagnostic tools and drugs required for its control.

Why is TB often diagnosed late?

There are many possible reasons: the diagnosis of TB is not considered often enough; it presents insidiously with low-grade symptoms (eg. fatigue, weight loss); cough is a common symptom which is often ignored; it has protean manifestations, often mimicking other diseases. It is also a common misconception that disease activity can be ascertained on chest radiograph alone and that reported radiological "scarring" excludes active disease. As TB disproportionately affects the poor, the cost of investigations / medical consultation may also be a barrier to early diagnosis.

Data from the Singapore TB Elimination Programme (STEP) Registry as reflected on the MD 532 notification form show that, among sputum acid fast bacilli (AFB) smear-positive cases, the median duration of cough increased from 4 weeks to 8 weeks after 2005; and that 15- 20% of these cases had median duration of cough of 12 weeks, and 8% had median duration of cough of 24 weeks. We should try to diagnose TB earlier. TB should be suspected in persons with unexplained cough for more than 3 weeks.

It is TBCU's practice to obtain our patients' previous chest X-rays (CXRs) for comparison. It was noted at the TB Control Unit (TBCU) that a number of pTB cases had previous abnormal CXRs which were not acted upon before they presented with smear-positive disease. A retrospective study found that, of 254 smear positive patients seen over a 6-month period at the TBCU in 2014, 39 (36%) of 108 patients with previous CXRs in their electronic records had lesions compatible with PTB. The majority (69%) were abnormal 6 months or longer before their diagnosis of smear-positive PTB (3).

The rich and famous are also not spared the scourge of TB. Eleanor Roosevelt was diagnosed aplastic anaemia on routine testing in April 1960 at the age of 75. Two years later, she was started on prednisolone in view of worsening cell counts. She subsequently developed fever of unknown origin, for which she was started on empirical TB treatment while awaiting bone marrow investigations. She succumbed to a massive cerebrovascular accident 6 weeks later. Autopsy showed widespread mycobacteria, and her cultures grew drug resistant TB. It can be argued as to whether she already had TB when her aplastic anaemia was first diagnosed (4).

Bacille Calmette Guerin (BCG) vaccine

The BCG vaccine, introduced in 1921, is the only vaccine in use today for TB. It is a live attenuated vaccine derived from the M bovis substrain. BCG is the most widely used vaccine globally, with at least 90% coverage in 113 high TB incidence countries. Its effect is in the prevention of TB meningitis and disseminated TB in very young children. Shortly after its introduction, it was reported in Sweden that BCG vaccination reduced child mortality unrelated to TB, but this was not studied until 70 years later when reports from Africa and Asia showed the same effect in reduction of acute respiratory illness and mortality. Recent research suggests that BCG offers cross-protection against viral infections due to "trained immunity" which is the induction of immunological memory in innate immune cells (natural killer cells, monocytes and macrophages) mediated by epigenetic and metabolic rewiring; and heterologous immunity. This has led to interest in its use against the SARS-CoV2 virus.

To date, there are 14 vaccine candidates for TB in the clinical trials pipeline (5). This compares poorly to COVID-19 which has at least 3 highly effective vaccines rolled out within a year of the pandemic, and at least 50 on-going vaccine trials. Unlike vaccine preventable diseases whereby protective immunity is achieved by inducing neutralizing antibodies, for TB, a strong cellular immune response is necessary. Till today, there is still incomplete understanding of the nature of protective immunity to TB. There is a lack of validated, predictive animal models of TB infection and disease, and lack of validated biomarkers that can act as prospective signatures of risk of developing TB or as correlates of protection.

The results of a Phase 2b trial on the M72/ASO1$_E$ candidate vaccine (GlaxoSmithKline) were published in October 2018. This showed a vaccine efficacy of 54% over 2 years in preventing progression of LTBI to pulmonary disease in adults without evident safety concerns. This

fulfilled the WHO Preferred Product Characteristics of new tuberculosis vaccines for adolescents and adults (6). The final analysis published in 2019 showed vaccine efficacy of 49.7% at month 36 and sustained immunogenicity among those vaccinated for at least 3 years (7).

Molecular genotyping

Universal spoligotyping and MIRU-VNTR typing of M. tuberculosis complex (MTC) isolates was performed by the Central TB Laboratory (CTBL) for the STEP from 2013 to 2020. These molecular typing techniques, in conjunction with epidemiological investigations, have helped to determine recent transmission and identify outbreaks for public health action. They are also used to distinguish between relapse or re-infection in previously treated TB cases, to detect false positive TB cases (eg. due to cross-contamination / mislabeling) and identify and monitor the circulating strains in different population groups over time.

Relapse vs re-infection among recurrent TB cases in Singapore

Persons with previously treated TB contribute to ~8% of incident TB cases locally and globally. These cases are conventionally referred to as "relapse" cases, on the assumption that their disease recurrence is due to reactivation of the infecting strain of the first episode. However, with the availability of molecular typing methods, exogenous re-infection is increasingly recognized as an important cause of recurrent TB, especially in high TB incidence countries with high HIV burden.

In a TBCU study of recurrent cases of culture-positive TB over a 10-year period, spoligotyping and MIRU-VNTR typing of both disease episodes showed the relative contribution of exogenous re-infection and relapse to be 43% and 57% respectively. The median time between disease episodes was significantly longer for re-infection cases compared to relapsed cases (49 months vs 22 months). Compared to controls, patients who relapsed were significantly more likely to be sputum smear-positive and to have concomitant PTB and extra-pulmonary PTB in their first disease episode.

Universal spoligotyping and MIRU-VNTR-typing in Singapore

Spoligotyping performed on 8,691 (72%) of 12,407 MTC positive cases over 8 years showed the Beijing spoligotype to be the most common strain in Singapore (accounting for 47%), followed by the East African Indian (EAI) strain (accounting for 25%). The Beijing spoligotype accounted for the majority of cases from Singapore, Malaysia, China, Myanmar and Vietnam, and for a small minority of cases from India and Bangladesh. The EAI spoligotype accounted for 83% of cases from the Philippines. 55.3% of the 8,691 cases were distributed into 883 clusters. The percentage of cases due to recent transmission as calculated using the N-1 method was 45.2%.

Whole Genome Sequencing (WGS) for MDR-TB cases in Singapore

The advent of next generation sequencing has made WGS faster, more affordable and accessible. Spoligotyping and MIRU-VNTR typing on the isolates of 290 MDR-TB cases diagnosed in Singapore from 2006 to 2018 identified 108 cases in 24 clusters, 22 of which were of the Beijing spoligotype. WGS performed retrospectively on the majority of these isolates decreased the number of clusters from 24 to 9, and the number of clustered patients from 108 to 43. WGS also re-defined one large MIRU cluster into three separate clusters. Using WGS, we were able to more accurately define the spread of MDR-TB in Singapore (8). Transmission was demonstrated in unusual settings such as among regular patrons of two cybercafes and residents of a public housing block.

Starting November 2020, universal WGS has been performed by the National Public Health Laboratory for the STEP. Besides its higher resolution in identifying transmission links, WGS further allows inference as to the direction of transmission between cases. WGS also provides information regarding drug resistance prediction, which is very useful to the clinician for individual patient management.

In conclusion, TB may be forgotten by some, but it is certainly not gone. Singapore is a little dot, surrounded by high TB incidence countries. It behooves us to think globally while acting locally to control TB in our country.

References

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