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Whole-genome sequencing of *Mycobacterium tuberculosis* as an epidemiological marker

DNA fingerprinting of *Mycobacterium tuberculosis* has revolutionised the study of the transmission of tuberculosis. Since the early 1990s, IS6110 restriction fragment length polymorphism (RFLP) typing and variable number of tandem repeat (VNTR) typing have progressed and are being used to answer longstanding epidemiological questions.1 DNA fingerprinting of *M. tuberculosis* isolates enables the visualisation of transmission and allows a much more sensitive investigation of this important aspect of tuberculosis control. Although having these possibilities is an advantage to tuberculosis control in daily practice, the findings of possible epidemiological links as shown with advantage to tuberculosis control in daily practice, the investigation of this important aspect of tuberculosis transmission and allows a much more sensitive marker, not able to understand how transmission occurred? Is it simply impossible to confirm transmission through interviews with patients? This apparent lack of resolution in typing is also related to the remarkable genomic stability of *M. tuberculosis*. In a study in the UK, a turnover of 0·5 SNPs per genome per year was noted, whereas in the Netherlands a highly similar rate of change of 0·36 SNPs was found.8,9

Another major concern that has not been sufficiently addressed and investigated generally is that *M. tuberculosis* isolates are not at all homogeneous populations. They comprise several populations with different SNP profiles.10 With the current WGS techniques only the SNP profile in the predominating population is visualised; however, this predominance might shift when the strain is passed on to another person.

In view of the concerns described above, WGS is also not an ideal epidemiological marker, but still undoubtedly a major step forward in DNA fingerprinting compared with the conventional RFLP and VNTR typing. In the molecular epidemiology of tuberculosis it would be ideal if at each transmission a minor, but recognisable, difference occurred in the DNA profile of *M. tuberculosis*. Such a difference would enable the deduction of all transmission...
Pulmonary hypertension is a pathophysiological disorder defined as an increase in pulmonary arterial pressure, as assessed by right heart catheterisation (mean pressure ≥25 mm Hg at rest). Pulmonary hypertension can arise in various clinical disorders, which have been classified by WHO into five clinical groups, on the basis of mechanisms, with different pathogenic, prognostic, and therapeutic features. The first group is defined as pulmonary arterial hypertension, whereas the third group encompasses pulmonary hypertension due to lung diseases or hypoxaemia, including hypertension due to chronic obstructive pulmonary disease (COPD), interstitial lung disease, and sleep-disordered breathing. In patients with COPD, the presence of COPD-associated pulmonary hypertension has been linked with reduced exercise capacity, impaired quality of life, and increased risk of mortality. Therefore, interventions that alleviate COPD-associated pulmonary hypertension are needed to improve symptoms, prevent right heart failure, and prolong survival.

Prostanoids, endothelin receptor antagonists, and phosphodiesterase type-5 (PDE5) inhibitors are the main treatment options for patients with pulmonary arterial hypertension. PDE5 inhibitors increase cyclic guanosine monophosphate (GMP), the final mediator in the nitric oxide pathway, in smooth muscle cells of the pulmonary artery, causing pulmonary arterial vasodilation. PDE5 inhibitors have proven effectiveness in pulmonary arterial hypertension, enhancing exercise capacity and quality of life. However, in patients with COPD-associated pulmonary hypertension, treatment with the short-acting PDE5 inhibitor sildenafil did not improve exercise capacity or quality of life. In The Lancet Respiratory Medicine, Andrew Goudie and colleagues investigate whether the long-acting PDE5 inhibitor tadalafil is beneficial in patients with severe COPD and mild pulmonary hypertension. Findings from this randomised, double-blind, parallel-group, placebo-controlled trial show that, compared with placebo, tadalafil did not improve exercise capacity after 12 weeks, as measured by the primary endpoint of 6 minute walking distance (between-group difference 0.5 m, 95% CI -11.6 to 12.5; p=0.937). Additionally, tadalafil did not improve quality of life, lung function (spirometry and diffusion of lung carbon monoxide [DLCO]), or serum B-natriuretic peptide, a biomarker associated with worse prognosis in patients with pulmonary hypertension. Why was tadalafil ineffective in patients with COPD-associated pulmonary hypertension in this trial?