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COMMENTARY

Non-clinical factors associated with TB: important for DOTS impact evaluation and disease elimination

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Initial optimism that DOTS (Directly Observed Treatment, Short-course) would have a dramatic effect on TB incidence rates in developing countries has not been supported by the evidence accumulated so far. Indeed, where TB incidence rates have decreased, non-clinical socio-economic factors appear to have played at least as great a role. We postulate that in those settings with little or no decrease in TB incidence, there are likely to be common pathway blockages that interfere with the effectiveness of DOTS implementation as socio-economic factors evolve. Measuring socio-economic trends, as well as DOTS implementation, is important for understanding TB control and opens up the opportunity for broader public health engagement.

Keywords: Disease elimination, DOTS, Tuberculosis

In 1998, Dye et al. estimated the likely effects on key TB outcomes in developing countries if DOTS (Directly Observed Treatment, Short-course) targets were reached.[1] A mathematical model was validated against Dutch data (1950 to 1975). Assuming no HIV and an initial state of stable endemnicity (i.e., a prior constant incidence rate), it was estimated that the incidence rate would be reduced by 11% per year. Remarkably, this was higher than the 5–10% decrease per year across Europe after the introduction of chemotherapy in the late 1940s.[2]

It is important to note that clinically efficacious TB interventions in Europe and other industrialised countries were responsible for only a proportion of the observed decline. This is because, prior to the introduction of chemotherapy, the incidence of TB had already been falling at a rate of approximately 2–5% per year for half a century, having accelerated over the 1800s. Thomas McKeown argued that dramatic increases and later reductions in major infectious diseases in industrialised countries during the pre-antibiotic era, plus sharp spikes during the two world wars, were most likely due to changes in socio-economic conditions.[3] The practice of isolating TB cases in sanatoria may have played a role, although this is debatable when variation in implementation is considered.[4] The rate of decline of TB mortality in England and Wales, at least from 1853 to 1910, actually exceeded that of other poverty-related infectious diseases (e.g., diphtheria and cholera) and all-cause mortality, and was faster than reductions in social deprivation.[5] However, natural selection is likely to have played only a minor role.[6]

Variation in incidence rates of TB and of the implementation of DOTS in developing countries, along with several years of observation, made it possible to estimate the impact of DOTS in the presence of socio-economic and other factors. Dye et al.,[7] using data on 32 different measures from across 134 countries from 1997–2006, showed that the incidence rate of TB declined more rapidly in countries with a higher human development index, lower child mortality and access to improved sanitation. None of seven direct measures of the intensity of TB control (covering expenditure, case detection and treatment success) were associated with TB trends worldwide. Oxlade et al.,[8] using health services, economic and epidemiological data from 165 countries between 1990 and 2005, showed that a 1% increase in TB treatment success for sputum smear-positive cases under DOTS was associated with a decline in TB incidence of 0.9/100 000 persons over the 15-year period. However, a decline in TB incidence was only statistically significant for low HIV seroprevalence countries. Much stronger associations were found for changes in life expectancy (inverse association with TB incidence) and for HIV prevalence. Neither the per capita GDP in 1990 nor the relative change in per capita GDP were significantly associated with changes in TB incidence on multi-variate analysis.

Poverty is clearly a strong risk factor for TB. Various indices of deprivation (including housing, employment and ownership variables) correlated strongly with TB notifications in Liverpool city electoral wards in the United Kingdom.[9] A strong relationship was found between TB incidence and a 14 variable 'state' level social

capital index,[10] as well as low socio-economic geographical areas,[11] in the United States. An almost four-fold change in TB prevalence was found across three categories of a nine-component standard of living index in India.[12] Case control studies in Africa have reported mixed results when exploring poverty in relation to TB,[13] which may relate to difficulties in choosing the right measures and the relative uniformity of poverty in the populations under study.

Systematic reviews have provided estimates of relative risks (RR) in relation to TB for the following specific risk factors: heavy alcohol consumption (RR=2.9),[14] smoking (RR=1.5–3.3 depending on the comparison)[15] and diabetes (RR=3.1).[16] Dose response relationships have been identified for smoking and alcohol consumption,[17] and a consistent inverse relationship between TB and body mass index (BMI) has been demonstrated.[18] However, the RRs for protein energy and micronutrient malnutrition have not been estimated. There is also evidence that passive smoking, biomass fuel consumption[15] and outdoor air pollution are associated with TB,[19] in addition to a range of underlying medical conditions. Population attributable fractions have been estimated across 22 high TB burden countries for malnutrition (range 5.2–62.6%), smoking (2.7–29.4%), HIV (0.2–69.7%), diabetes (2.3–13.8%), heavy alcohol consumption (0.1–21.8%) and indoor air pollution (2.7–27.5%).[20] These estimates must be interpreted with caution and should not be added together to predict the effect of multi-component interventions. Perhaps only HIV truly meets the necessary assumptions: the causal relationship is clear, removal from a population would most likely cause reversion to the risk of the unexposed, and it is relatively independent from other TB risk factors epidemiologically. While multiple risk factors operate in populations simultaneously, there are obvious interactions between them that may result in mixed effects on TB incidence. For example, increased BMI is associated with type 2 diabetes.

An unstated underlying assumption in Dye's original prediction for developing countries was that the lack of any current effect on TB indices by other, mainly socio-economic factors, would provide opportunity for DOTS to have an even greater effect than in developed countries. DOTS, through acting directly or indirectly on the same elements of the TB epidemic, would be able to exert maximal effect. However, if common pathways are blocked, one could anticipate that DOTS effectiveness would in fact be blunted. For example, if delays to accessing the health system mean that all possible contacts of a TB case are exposed before the case is diagnosed, chemotherapy to passively detected cases will have little or no effect on *Mycobaterium tuberculosis* transmission. Some studies have found that active case finding leads to increased TB case detection and decreased incidence. However, the overall body of literature is weak and surprisingly inconclusive.[21] Common pathway blockages may be part of the explanation for disappointing DOTS impact, exposing the limitations of modelling predictions and the need to unravel the complexities around factors associated with changing TB indices.

In short, trends in TB should not be interpreted in isolation from other contextual factors. We propose three practical ways to accomplish this. In the presence of the most dramatic shifts in global development that have been seen in human history, it is essential that socio-economic factors be measured when gathering evidence of TB impact. Prevalence studies in particular should measure these other factors at the time of data collection, at individual and population levels. Second, and perhaps more important, given that these 'other' factors have at least as big an impact on TB as DOTS, we need to know more about them. As Lonnroth et al.[20] have outlined, more epidemiological research is needed to understand causality and strength of association of risk factors, interactions and heterogeneity need to be explored more fully, and multi-level analyses should be developed along with increasingly refined predictive models to guide intervention. These studies, and the related modelling, should also explore and help to define common pathway blockages to optimal TB control. Third, the operational assessment of a variety of public health interventions should include broad indicators, such as key TB measures, where appropriate. This more inclusive approach would promote collaboration and interaction across government and non-government organisations. Together these steps would facilitate understanding of TB within the broader context of public health and the global factors that affect its control.

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