The one approved vaccine against tuberculosis (known as the *Mycobacterium bovis* bacillus Calmette–Guérin (BCG) vaccine) and those currently in clinical trials are designed to protect against initial infection, as they incorporate *Mycobacterium tuberculosis* antigens that are expressed early in the disease process. However, they do not prevent the establishment of latent persistent infection or the reactivation of clinical disease — a major need both for infected patients and for reducing further transmission. Reporting in *Nature Medicine*, Aagaard and colleagues show that a vaccine containing antigens that are expressed in the early and late stages of tuberculosis protects against late-stage infection in both pre- and post-exposure mouse models.

The vaccine (termed H56) comprises a fusion protein (Ag85B–ESAT6–Rv2660c) and a cationic adjuvant (CAF01). Ag58B and ESAT6 are well known *M. tuberculosis* antigens that are secreted early in infection and have previously been shown to provide protective immunity. Rv2660c was identified in this study as one of the factors expressed at constant levels throughout infection. The authors proposed that simultaneous vaccination with these three antigens could produce multistage effects, enabling the immune system to mount a response to both the early and late phases of tuberculosis.

In the early stage of infection (<4 weeks after exposure), the mycobacterial loads in the lungs of H56-vaccinated mice were similar to those of mice vaccinated with the BCG vaccine. However, in the later stage of infection (24 weeks after exposure), H56-vaccinated mice had significantly lower numbers of bacilli than BCG-vaccinated mice. Moreover, H56 was an effective booster to BCG, as mice that received the booster had significantly lower bacterial loads 24 weeks after infection than mice vaccinated with BCG alone.

Importantly, in two mouse models of latent tuberculosis, H56 provided significant protection against reactivation of the disease. Detailed examination showed that H56 promoted the generation of antigen-specific, polyfunctional $CD4^+$ T cells in the lungs. These T cells, which were shown to express interferon-γ, interleukin-2 and tumour necrosis factor, are thought to be important for the quality and endurance of the immune response.

Together, these data show that immunization with an antigen that is expressed during the late stages of tuberculosis (together with early-stage antigens) enhances containment and prevents reactivation of the disease. The Statens Serum Institut, Denmark, have reported that H56 will enter clinical trials in South Africa in March 2011.

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ORIGINAL RESEARCH PAPER Aagaard, C. *et al.* A multistage tuberculosis vaccine that confers efficient protection before and after exposure. *Nature Med.* **17**, 189–194 (2011)