Vaccines to control tuberculosis in cattle

The age-old cattle disease has resisted rigorous control but the BCG vaccine may do better

By ***Anita L. Michel***

Tuberculosis (TB) has plagued humans around the globe for thousands of years and still causes 10 million new cases every year (*1*). The second leading cause of death from infectious disease in humans, TB also afflicts animals, domestic or wild. Bovine TB in cattle causes socio-economic implications due to decreased production, the compulsory slaughter of infected animals, and the associated stigma (*2*). The BCG (Bacillus Calmette-Guérin) vaccine, which has been in use for 100 years, is currently the only vaccine available to protect children against human TB (caused by *Mycobacterium tuberculosis*); there is no TB vaccine for livestock (caused by the related bacterium, *Mycobacterium bovis*). On page XXX of this issue, Fromsa *et al*. (*3*) provide field data from studies in Ethiopia that supports the use of the human BCG vaccine in cattle, which could help eliminate bovine TB.

There are several closely related human and animal-adapted TB-causing bacteria that can cross species barriers given favorable direct or indirect inter-species contact (*4*). The dire consequences of this zoonosis for human health were felt throughout Europe during the first half of the 20th century. In the UK, an estimated 50,000 new TB cases in humans were caused by *M. bovis* in the 1930s. The burden of *M. bovis* infection in humans mirrored the soaring prevalence in the cattle population, which can be attributed to the intensification of livestock production and the uncontrolled spread of bovine TB. Compulsory pasteurization of milk and bovine TB control programs were introduced in the period from the late 19th century and mid-20th century, respectively, and curbed the epidemic in both humans and cattle in high income countries.

In sharp contrast, bovine TB remains largely uncontrolled in low and middle income countries (LMICs), posing a risk to vulnerable communities with limited access to health and veterinary services. Additionally, bovine TB has a detrimental effect on the agricultural industry and the livelihoods of farmers. Some countries impose compulsory quarantine for infected herds, excluding them from trade opportunities, or even enforcing the slaughter of infected cattle without financial compensation (*5*). The socio-economic consequences are crippling for LMICs, and such measures are socially and culturally unacceptable, calling for urgent alternatives (*6*).

TB has always been and remains the largest infectious disease threat to captive wild animals in zoological collections (*7*). In free-ranging wild animals, TB may pose a conservation concern to endangered species (*8*), and certain wildlife populations can become permanently infected reservoirs that jeopardize bovine TB control (*9*, *10*). Under these circumstances, wildlife reservoir vaccination could help control bovine TB in cattle (*10*).

The BCG vaccine constitutes a laboratory-adapted live *M. bovis*. It is safe and can confer protection to children against human TB, so why is the BCG vaccine not used to protect cattle? The strongest argument was around the interference of the BCG vaccine with the official diagnostic test (the tuberculin skin test) that is employed in bovine TB surveillance, international trade, and bovine TB control programs, rendering this test unreliable. Additionally, numerous earlier studies reported that BCG induced partial instead of complete protection in cattle, which appeared to be limited to one to two years, necessitating revaccination with uncertain effects on protection. As a result, such arguments hindered the acceptance of BCG vaccination of cattle and thus the test-and-slaughter strategy (whereby all herds are repeatedly tested and infected animals are slaughtered) was considered to be a faster and more cost-effective way to eliminate bovine TB. Several countries, such as Germany and The Netherlands have indeed achieved eradication of bovine TB using this strategy, but many others lack the resources, the political commitment, or their efforts have been hampered by spillback of *M. bovis* from an infected wildlife reservoir (*11*, *12*).

The increasing costs of bovine TB control (larger herd sizes requires longer duration of control measures, which harms production) and an apparent failure to effectively lower the disease prevalence have led to a renewed interest in cattle BCG vaccination, especially in the UK (*13*), as an additional rather than a stand-alone approach. The development of a modified diagnostic test that differentiates vaccinated from infected animals (called the DIVA test) has made this a possibility (*14*). Moreover, a duration of 52 weeks for BCG-induced immunity was demonstrated (*13*), which covers most if not all of the lifespan of the modern commercial dairy cow.

Importantly, Fromsa *et al*. carried out a natural transmission study in cattle in Ethiopia in which vaccinated and unvaccinated susceptible cattle were in contact with infected animals. A two-stage study design allowed the authors to quantify the direct and indirect BCG vaccine efficacy. Indirect vaccine efficacy refers to the spectrum of protective effects of vaccines. Animals that are not fully protected (immune) may have a partial protection that leads to a reduced risk of them transmitting the disease and thus confers a benefit towards reducing disease prevalence. Indeed, their results show a superior indirect vaccine efficacy (74%) compared to direct protection (58%) and the total BCG vaccine efficacy was 89%. Using a transmission model tailored for the dairy sector in Ethiopia, the authors concluded that BCG vaccination of cattle has the potential to prevent the spread of bovine TB and could reduce the prevalence of the disease in this setting within 10 years, improving the prospect of elimination over a longer timeframe.

Together, these advances strongly advocate for the adoption of BCG vaccination into the control strategy for bovine TB. For various reasons, the 'test-and-slaughter' approach introduced decades ago in high-income countries did not achieve the reduction or elimination of disease that was expected. But, this realization has allowed the concerns of LMICs about this approach to enter the agenda. However, several questions are remaining with regard to BCG vaccination including the influence of disease prevalence, cattle breed, farming system and revaccination on vaccine efficacy. From a practical perspective, the costs and availability of the vaccine and the DIVA test reagents could become a limiting factor, especially in LMICs. Future field research will have to address the scientific knowledge gaps and should ideally encompass all promising candidate vaccines including inactivated *M. bovis* and subunit vaccines (*15*) so the needs of different settings and species in high income countries and LMICs can be met.

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