News & views

Medical research

Tuberculosis vaccine finds an improved route

Samuel M. Behar & Chris Sassetti

A widely used vaccine against tuberculosis has now been shown to provide almost complete protection when injected intravenously. This is a striking improvement over vaccination through the typical intradermal route. See p.95

Tuberculosis is the deadliest human infection, killing 1.5 million people in 2018 alone (go.nature.com/2kbuiq). It is widely accepted that an effective vaccine against the bacterium responsible, *Mycobacterium tuberculosis*, would be the most practical way to control the disease. However, the pathogen is often able to resist the immune responses elicited by vaccination. This has raised the question of whether it is possible for a conventional vaccine to confer sterilizing immunity against TB — a gold-standard immune status for vaccines, under which disease is prevented and the pathogen completely eliminated, often before it can even establish a productive infection. On page 95, Darrah *et al.*[1] provide a resounding answer to this question by showing that near-complete protection from TB infection can be conferred using a century-old vaccine, simply by changing its route of administration.

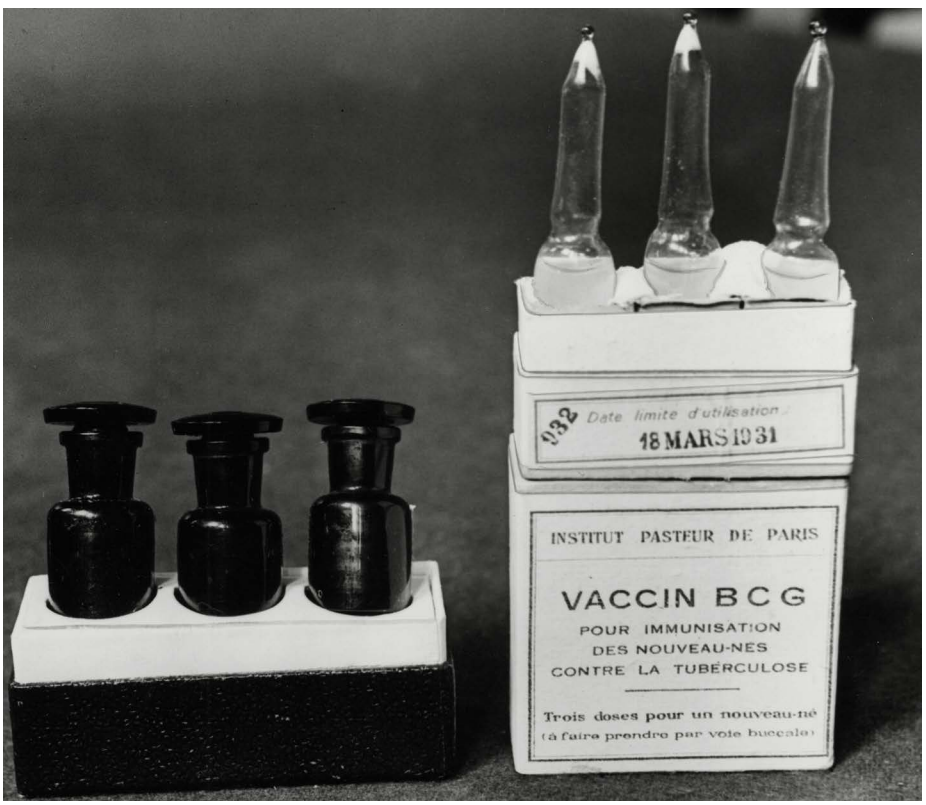
The only currently licensed vaccine against TB is a live strain of the related pathogen *Mycobacterium bovis*, the virulence of which was attenuated in the laboratory between 1908 and 1921. The strain, known as bacille Calmette–Guérin (BCG), has been administered to more than one billion people (go.nature.com/2cxwew6) since then (Fig. 1).

The BCG vaccine is effective against some deadly early-childhood forms of TB. However, its ability to prevent the transmissible pulmonary form, which is the dominant form in adults, has been patchy[2]: it confers protection for some groups of people in some countries, but is generally insufficient to reduce the number of active TB cases in countries where the infection is endemic. Despite these limitations, BCG remains the only TB vaccine to confer protection in large-scale trials[3]. The mechanisms that determine its efficacy are a topic of much interest.

BCG is typically given as an injection into the dermal tissue that lies just beneath the outer layer of the skin. This injection site is convenient and contains specialized cells that stimulate immune responses. However, vaccines that activate immune cells at the site of potential infection can be more effective at destroying invading pathogens. Thus, current immunological thinking suggests that vaccines administered directly into the lung or the upper airways would be better at preventing pulmonary infections, including influenza and TB. Darrah and colleagues therefore investigated whether a different route of BCG administration could improve protection against pulmonary TB.

Darrah *et al.* performed their analysis using rhesus macaques, because TB infection in these monkeys closely mirrors the human disease. They evaluated five vaccination strategies. Animals were given the BCG vaccine in one of the following ways: at the standard dose through the conventional intradermal (i.d.) route; at a higher-than-normal dose intradermally; by means of an aerosol to inoculate the lung; through a combination of the high dose i.d. and inoculation by aerosol; or through an intravenous (i.v.) injection. The authors exposed the macaques to *M. tuberculosis* six months after vaccination, and tracked disease progression to determine how the administration route and dose of the vaccine affected protection against the infection.

Vaccinations given intradermally or by aerosol conferred, at best, modest protection from pulmonary TB. By contrast,



ALFRED EISENSTAEDT/AP/SHUTTERSTOCK

Figure 1 | Ampoules of the BCG vaccine against tuberculosis. This vaccine has been used for almost a century, typically given as an injection just under the skin. Darrah *et al.*[1] now provide evidence in monkeys that the vaccine's efficacy can be greatly improved using intravenous injection.

i.v. vaccination afforded nearly complete protection from the disease. Strikingly, the researchers could not detect any trace of the pathogen in six out of ten animals that received the i.v. vaccination, indicating that the infection had been either prevented or cleared. Three of the other monkeys also showed high levels of protection. Thus, the route of BCG inoculation clearly affects immunity, and the i.v. route confers by far the strongest protection against TB.

What makes i.v. BCG vaccination so effective? Clear immunological correlates of protection (characteristics indicative of immunity against a disease) proved difficult to identify in the current study, because only one of the ten animals that received i.v. BCG was not protected against the infection, making it hard to properly compare protected and unprotected animals. To gain an understanding of the potential underlying mechanism, Darrah and colleagues therefore compared the immune responses of animals vaccinated by the different routes.

Compared with i.d. and aerosol vaccination, i.v. BCG led to a massive influx of immune cells called T cells into the lungs. The increased number of T cells was still apparent six months later, when the animals were exposed to *M. tuberculosis*. It is likely that this expansion occurs because i.v. injection leads to the delivery of a high dose of BCG to the lung — a hypothesis consistent with a recent study[4] showing that direct intrabronchial inoculation of BCG can also protect against *M. tuberculosis*.

The authors next showed that the T cells recognized protein fragments called antigens produced by BCG. Because BCG and *M. tuberculosis* are closely related bacteria, these T cells also recognize *M. tuberculosis* antigens. The T cells that were recruited to the lung were classified as differentiated 'memory' T cells on the basis of their gene-expression profiles, the proteins on their surfaces and their function. These T cells survive long after vaccination, and, because they recognize the antigens produced by *M. tuberculosis*, they can be rapidly activated on infection, producing many 'effector' T cells, which combat the invading pathogen.

Although this circumstantial evidence implicates T cells in immunity against *M. tuberculosis*, the surprising efficacy of i.v. BCG relative to the other vaccine routes (which also elicit T-cell responses) suggests that other mechanisms of immunity are also involved. As Darrah *et al.* propose, these might involve: antibody responses against *M. tuberculosis*; innate immune cells, which are activated indirectly by infection (and do not require specific recognition of *M. tuberculosis* antigens); or innate training, a process by which immune cells such as macrophages gain an enhanced ability to protect, often nonspecifically, against microbes.

Darrah and co-workers' findings raise the obvious possibility of controlling TB by giving people BCG by i.v. injection. In support of this idea, the intervention proved to be safe in the small cohort of rhesus macaques studied. But there is currently a drive to simplify vaccine deployment by eliminating the need for vaccines to be kept cold or for experts to administer them[5] — both of which are crucial for i.v. injection.

Whether or not i.v. BCG is developed for clinical use, research that builds on Darrah and colleagues' work could lead to an improved understanding of what protection against TB looks like — that is, to define correlates of protection. In addition, future work must delineate the mechanisms that lead to sterilizing immunity after i.v. BCG. If successful, it might be possible to develop a vaccine designed to activate the same protective immune mechanisms as those triggered by i.v. BCG, but that could be administered in a way that is safe and adaptable to mass vaccination programmes.

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Microbiology

Food for thought about manipulating gut bacteria

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Knowing how dietary fibre nourishes gut microorganisms might suggest ways to boost health-promoting bacteria. A method developed to pinpoint bacteria that consume particular types of dietary fibre could advance such efforts.

Certain gut microorganisms can boost human health, but it is unclear how diet could be harnessed to easily manipulate the composition of gut microbes to boost the levels of desired bacteria. Writing in *Cell*, Patnode *et al.*[1] present a useful approach for assessing interactions between human gut microbes and the dietary fibre that sustains their existence.

Dietary fibre is promoted as part of a healthy diet worldwide. Many people, however, do not achieve their recommended fibre intake because they consume insufficient fruit, vegetables and cereals. Inadequate fibre intake is associated with common conditions including obesity, diabetes and cancer[2]. Yet understanding the mechanisms that link fibre-rich food to good health is challenging. Dietary fibre encompasses a wide range of complex molecules, most of which are present in plant cells; among them are carbohydrate molecules called glycans, which are resistant to digestion by human enzymes. As a consequence, some ingested fibre is excreted unchanged in faeces, whereas most is metabolized by gut microbes.

These microbes have a diverse and extremely complex metabolic capacity. Bacteria that express different enzymes for metabolizing fibre can survive and grow using a range of foods. Some bacterial species might compete with each other for the same food source, which could lower the abundance of species that compete less successfully. How might gut microbes be manipulated through human dietary intervention? For example, the concept of using prebiotics — compounds that affect gut microbes, thereby benefiting the human host — has been proposed. One such idea is to use particular fibre sources that provide food for the desired gut microbes[3,4]. However, determining whether dietary fibre can promote health in this way requires a sophisticated understanding of the interactions that occur when the complex community of gut microbes encounters a source of fibre.

Previous work[5] had indicated that transferring the gut microbes of human twins who have contrasting body masses (obese and lean) into mice induced a corresponding difference in the animals' body masses. However, when some of the obese mice were housed with the lean mice, they had less adipose fat than did obese animals that were not co-housed with lean mice — and this weight-loss effect correlated with the transfer of *Bacteroides* bacterial species from the lean mice to the obese mice[5]. High consumption of fibre-rich plant foods was required for this adipose-fat reduction to occur[5]. However, the types of fibre responsible for this effect, and how these interact with specific gut microorganisms, was