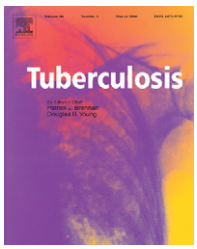
Tuberculosis (2007) **87**, 257–266

Available at www.sciencedirect.com

ScienceDirect

journal homepage: http://intl.elsevierhealth.com/journals/tube



Should a new tuberculosis vaccine be administered intranasally?

Gunilla Källenius[a,b,*], Andrzej Pawlowski[a], Per Brandtzaeg[c], Stefan Svenson[a,d]

[a]*Department of Bacteriology, Swedish Institute for Infectious Disease Control, 17182 Solna, Sweden*
[b]*Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm, Sweden*
[c]*Laboratory for Immunohistochemistry and Immunopathology (LIIPAT), Pathology Clinic, Rikshospitalet-Radiumhospitalet Medical Centre, University of Oslo, N-0027 Oslo, Norway*
[d]*Department of Bacteriology, Swedish University for Agricultural Sciences, Box 583, S-75123 Uppsala, Sweden*

Received 10 October 2006; received in revised form 14 December 2006; accepted 21 December 2006

KEYWORDS
Tuberculosis;
Vaccine;
Nasal;
Mucosal

Summary
Most of the world's population is vaccinated with the only available vaccine against tuberculosis (TB), the Bacillus Calmette-Guérin (BCG) vaccine that was developed almost a century ago. Despite the wide coverage of the BCG vaccine, there are great variations in protective efficacy among different study populations. BCG vaccination protects against childhood forms of TB, but this immunity wanes with age, resulting in none, or insufficient, protection against adult pulmonary TB (PTB). PTB is the major disease manifestation of TB in adults and it causes death at the most productive age, further adding to poverty in already impoverished countries. Therefore, new more effective vaccines and novel immunisation strategies are urgently needed. The most common route of TB is by inhalation of tubercle bacilli leading to the establishment of a primary infection in the lung. Immunising through the nasal mucosal surface should therefore have advantage over other routes, as such vaccine administration elicits protective immune responses also in the lung, i.e. at the site of primary infection. Several new TB-vaccine candidates have been evaluated for their protective efficacy in animal models using the mucosal route of immunisation. In formulating such vaccines, the adjuvants and delivery systems are crucially important.

Introduction

Tuberculosis (TB) is a major health problem, especially in low-income countries, and is currently next to HIV the most important cause of death from an infectious agent. Globally,

*Corresponding author. Department of Bacteriology, Swedish Institute for Infectious Disease Control, 17182, Solna, Sweden. Tel.: +47 8 4572430; fax: +46 8 301797.
E-mail address: gunilla.kallenius@smi.ki.se (G. Källenius).

1472-9792/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tube.2006.12.006

TB causes nearly 2 million human deaths annually and 1/5 of all adult deaths in developing countries. The World Health Organisation (WHO) estimates that one-third of the world's population (i.e., 1.9 billion individuals) is infected with *Mycobacterium tuberculosis* (Mtb).

During the last 20 years, increasing evidence has been presented that TB, especially multi-drug resistant (MDR) TB, is on the rise in many countries. The total number of MDR-TB cases estimated to have occurred worldwide in 2004 is 424,203.[1] If immediate measures are not taken to stop the spread of TB, WHO estimates that within the coming 20 years 70 million people will die from Mtb infections.[2] One important reason for the current rapid increase in TB worldwide is the HIV epidemic, 9% of the 8 million new TB cases worldwide in 2000 and 12% of the deaths being attributed to co-infection with HIV.[3]

The most cost-effective way to combat any infectious disease is the use of effective preventive vaccines. With the increasing number of HIV-positive individuals and the emergence of MDR TB, it is obvious that an efficient TB vaccine is of outmost importance in implementing effective TB control programmes.

The Bacillus Calmette-Guérin (BCG) vaccine

The live attenuated BCG vaccine has been used for almost a century. The first report of such successful vaccination in 1921 led to the distribution of BCG cultures to laboratories all over the world for further propagation.[4] Since 1923, BCG vaccines have been used in most countries, being the most widely used vaccines available through the WHO Expanded Programme for Immunisation.[5] Since its introduction, over 3 billion doses of the vaccine have been given, and 100 million newborn children are still immunised with BCG every year.

One important observation shared by most efficacy studies, is that the BCG vaccine protects against childhood TB[6] but that this immunity wanes with age, resulting in insufficient protection against adult pulmonary TB (PTB). Because PTB is the most contagious form of TB, this means that the BCG vaccine is not efficient in controlling the disease. Hence, the development of a new, more efficient TB vaccine(s) is one of the top priorities in TB research. The most important reason why BCG vaccines are still widely used is the good protective effect seen against disseminated TB disease in childhood[6] together with the reported cross-protective effect against leprosy.[7]

Reasons for the failure of BCG vaccines

The reasons for the waning protection of BCG vaccines remain unclear. Recent deletion analyses of the genome of different strains of BCG by microarray technology have shown that the various BCG strains have lost some genes now thought to be important for establishment of protective immunity. The loss of some of these genes might have occurred during the original attenuation process from the parental strain and/or during further propagation, before the lyophilisation of seed lots was introduced in the 1960s.[4] Major antigenic proteins were found to be present in the parental strain but either absent or not expressed in several BCG vaccines.[8] There is still a need of elucidating to what extent these strain variations can account for the observed variability in the vaccine efficacy.[9]

It has also been proposed that the low protective efficacy of BCG vaccination, seen in adults in the tropical regions of the world, could at least in part be due to sensitisation by environmental mycobacteria prior to BCG vaccination. As some atypical mycobacteria are abundant in certain geographic areas, the early exposure to such microorganisms could induce immunity that would either mask the responses to ensuing BCG vaccination, or even inhibit the BCG-induced immunity by interfering with persistence of the vaccine strain in the host.[5,10–12] Also, persistent helminth infestation can interfere with the establishment of protective anti-TB responses. Helminths shift the immune response towards a Th2 type, thereby significantly reducing the protective efficacy of BCG.[13,14] This is well in line with earlier observations that de-worming of helminth-exposed BCG-vaccinated individuals improves purified protein derivative (PPD)-specific responses.[15]

Another important reason contributing to the inability of the current live BCG vaccine to protect against adult PTB, could be that the parenteral route of immunisation normally used for vaccination does not elicit optimal immune responses in the lung. Thus, to achieve protection of the lung and the upper airways, which are the port of entry of Mtb, a vaccine should preferably, in addition to a systemic immune response, also elicit local immunity along the whole respiratory tract.

New TB vaccines

The search for new vaccine candidates is concentrated not only on developing vaccines to protect naïve, healthy individuals, but also to protect the large proportion (80%) of the world's population that has already been BCG-vaccinated in childhood and is in need of a booster vaccine to avoid adult PTB.[16] Today, nearly 200 new ''laboratory bench'' vaccine candidates have been developed by different research groups.[17] They include live attenuated vaccines, recombinant virus- and bacteria-vectored vaccines (including BCG vector), DNA vaccines, subunit vaccines including fusion proteins and carbohydrate–protein conjugate vaccines, as well as killed BCG and *Mycobacterium bovis*, combined with novel adjuvants and delivery systems.

Advantages of mucosal vaccination

There are several logistic and immunological advantages of mucosal vaccination. One obvious but very important asset of mucosal vaccines is that they can be administered without needles and syringes. Hence, the mucosal approach makes immunisation practice more acceptable, safer and better suited for mass administration. However, so far few vaccines approved for human use are administered mucosally, including the live attenuated oral polio vaccine, oral rotavirus vaccines, various oral cholera vaccines (killed whole-cell/cholera toxin (CT) B subunit or live-attenuated), nasal influenza vaccine and oral typhoid vaccine (live attenuated).

The best example of the practical success of mucosal vaccination is the polio eradication campaign. Based on the oral route, millions of people were immunised with polio vaccine in a single day.[18] Such mass vaccination efforts are only