World TB day 2008 – are we closer to a new TB vaccine?

LONDON, UK----27 March 2008----ExpertREACT. March 24th was officially the World Health Organisation TB Day and a good opportunity to review the progress of global efforts to control the disease (Stop TB Strategy). With WHO emphasis on multidrug resistant TB, HIV co-infection and variable progress in reaching certain goals, **VacZine Analytics** reiterates that new TB vaccines; possibly due in 2015 are urgently needed.

World TB day commemorates the day in 1882 when Dr Robert Koch announced that he had discovered the cause of tuberculosis, the TB bacillus *Mycobacterium tuberculosis (M.tb)* Before that time and to the present day TB remains a disease of staggering proportions. It is estimated that one third of the global population is infected with TB with a new person being infected every second. In 2006, an estimated 1.5 million people died from TB (WHO figures, 1) with 9.2 million new cases. Recent reports from the WHO state that while much progress has been made over recent years in controlling TB, progress is too slow. This refers to the objectives of the "Stop TB Strategy" which by 2015 aims to dramatically reduce global disease prevalence and death to 50% of the levels observed in 1990.

Tuberculosis disease has a complex clinical profile. It is important to realise that infection with the causative pathogen (*M.tb*) does not necessarily transform into disease. For example, infected individuals can have what is referred to as "latent TB" i.e. they have no symptoms, are not infectious and so cannot spread the disease. This latent population is estimated to account for 90% of total cases of TB. However, over time latently infected individuals can progress to "active" TB disease where they do show symptoms and can spread the disease. The risk of transition from one form of TB to another is highest in the first 2 years of a new infection and importantly in individuals with Human Immunodeficiency Virus (HIV). About one-third of people with HIV also have TB, which tends to be the leading cause of death in this population, mainly in sub-Saharan Africa.

Both latent and active TB are curable conditions that can be managed with chemotherapeutic antibacterial drugs such as isoniazid (ISN) and rifampin (RIF) within four recommended treatment regimens. The decision to initiate TB drug treatment is based on a number of factors such as clinical, pathological, and radiographic findings; and the results of microscopic examination of acid-fast bacilli (AFB) stained sputum (smears). Patients with active disease normally have to engage in closely supervised or directly observed drug therapy (DOTS), which normally consists of a 2-month initiation phase followed by a 4-7 month continuation phase. Effective treatment also depends heavily on effective diagnosis, which in resource-poor settings can be limited. However, despite this the WHO estimates that in 2004, 183 countries including 22 of the countries with the highest burden (80% of all cases) were implementing DOTS to some extent.

Despite the success of DOTS, many believe that it alone cannot be a long-term strategy. There are many challenges. For example, it is reported that *M.tb* strains with resistance to at least one DOTS drug are present in every TB endemic country (MDR-TB, 0.5 million cases, 2006). Moreover, "super resistant" strains in extensively resistant TB are emerging which have resistance to all drugs used in DOTS (XDR-TB). Both MDR-TB and XDR-TB are considered outcomes of ineffective treatment either due to non-compliance, wrong selection of drugs or inconsistent supply. While many of these issues can be addressed by better resource implementation it is clear that other strategies need to be pursued.

Historically another key strategy in controlling the impact of TB has been preventative vaccination with the BCG vaccine (Bacille Calmette Guerin). BCG, first developed in 1921 was originally a live-attenuated preparation of *Mycobacterium bovis* produced after passaging an original cow isolate 231 times over a period of 13 years. Since 1974, the vaccine has been included in the WHO expanded program for immunization (EPI) and still is probably the most widely distributed vaccine in the world (est 100 million doses per annum). Most developing countries implement BCG vaccination with high coverage rates (~80%) but while the vaccine has many benefits in being one dose, cheap to produce and effective in preventing life threatening forms of TB in infants and young children, it has not controlled rising disease incidence.

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BCG has many weaknesses as a vaccine. Because of question marks around its effectiveness in older individuals, waning immunity and uncertain demand, most Western countries have scaled back BCG vaccination over the last 5-10 years. For example, in the UK, the Joint Committee on Vaccination and Immunization (JCVI) decided in 2005 to stop the school BCG program and reserve vaccination for children of parents from endemic countries, healthcare workers and contacts of known cases. In the US the use of BCG is extremely rare with higher emphasis on "test and treat" policies.

There is a clear need for new more effective TB vaccine that does not only prevent primary disease but is also active in infected individuals. A new vaccine could also be used in combination with drug therapy to improve its outcome. According to a paper from the WHO Strategic plan of the Stop TB Partnership Working Group current research into new vaccines is gaining momentum (2). The authors go as far as to state that a new vaccine will be available by 2015 and if given to everybody would reduce incidence by 20% during the first ten years of use. AERAS, an organization funded by the Bill & Melinda Gates Foundation, also has the same view stating that work is ongoing on six new vaccine candidates, three of which are in early stage trials and three more to enter this year (3). Some of the new strategies focus on "boosting" the primary effect of the BCG vaccine such as Oxford University (MVA Ag85A) currently in Phase II whereas others seek to replace BCG such as the fusion protein Mtb72F being developed by GlaxoSmithKline (GSK).

Developing a new vaccine is an attractive proposition from the perspective of controlling TB but is not without scientific and most of all, commercial challenges. Firstly, new vaccines targetting primary infection are likely to require a different set of antigens to those used in latent infection. Because of latency and the fact *M.tb* is an intracellular pathogen a new vaccine must stimulate complex T-cell responses – a difficult task for vaccinologists. Other issues are avoiding the exacerbations of other underlying disease symptoms. Finally, in terms of funding, many believe there is not a large enough target population in the Western to offset development costs and subsidies to ensure availability of the new vaccine where it is needed most. This challenge is of course not unique to TB.

References:

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(3) Aeras press release. New TB vaccines urgently needed to fight TB. http://www.aeras.org/news/documents/WTBD2008_WHOReportStatement_March152008_Final2.pdf. Accessed March 2008.

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About VacZine Analytics:

VacZine Analytics is a new strategic research agency based in the United Kingdom. Its aim is to provide disease and commercial analysis for the vaccine industry and help build the case for developing new vaccines.