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Is a new tuberculosis vaccine necessary and feasible? A Cuban opinion

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Summary *Mycobacterium tuberculosis* kills more human beings worldwide than any other pathogen. An estimated two billion people are already infected with the bacterium. In 2006, tuberculosis (TB) will kill nearly one million more people than in 1992. In Cuba, TB is not a serious health problem any more and we are striving to eliminate it in the near future.

The most widely applied human vaccine in the world is BCG. It is also a safe vaccine except when it is applied to immunocompromised persons. Its protective efficacy is a controversial topic. In spite of this, more than 80 years of experience with this vaccine has demonstrated that BCG is effective, at least in significantly preventing childhood TB, including the meningeal and disseminated forms of the disease, but does not protect against the predominant pulmonary form of the disease in adults, which means that our best TB vaccine now is inadequate; we therefore need a new vaccine.

The following facts, apart from the experience with BCG, support discussion about the feasibility of a new and better TB vaccine:

Less than 10% of the 2 billion TB infected persons develop active disease. It has been demonstrated that HIV+TB co-infection increases 30 times the risk of contracting active TB and it increases the risk of being killed by the bacterium. Some new vaccine candidates, now under development and evaluation, are showing promising results in preclinical studies, and a few of them have entered clinical trials. There seems to be a consensus that a new TB vaccine will be feasible, but some challenging issues must be positively solved, such as, the lack of universally accepted correlates for protection, improved diagnostics, and final vaccine efficacy evaluation conducted on large phase III clinical trials in underdeveloped countries. The ethical, economical, organizational and scientific questions involved in this global task are enormous, but feasible.
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Tuberculosis: a global threat

According to probably underestimated calculations, *Mycobacterium tuberculosis* kills more persons in the world than any other pathogen. Annual mortality is over 3 million deaths. Every minute more than 10 persons develop tuberculosis (TB), which implies about 8 million new cases per year, and there are more than 2 billion persons infected.[1]

With the appearance and development of the global AIDS epidemic, in addition to adverse socioeconomic factors, a new highly lethal infectious combination was produced: HIV+TB. There are more than 10 million co-infected persons at risk of developing TB, i.e. over 30 times more than those infected by *M. tuberculosis* alone. This combination causes more than half a million deaths per year.[2]

Although, the overwhelming majority of deaths caused by TB take place in poor or developing countries, there is now a clear trend of a rise in the disease in highly developed countries, especially in the least protected population strata.[3] The growing emergence of *M. tuberculosis* strains with multidrug resistance (MDR)[4,5] is a new and important component in this situation that was already recognized by WHO in 1993 as a ''global emergency''.

The existing TB drugs must be taken for a long time and at least three of them are required to prevent the appearance of resistance to those antibiotics. The main antibiotics used in the Directly Observed Therapy Short-course are: isoniazid, rifampin, pyrazinamide, streptomycin and ethambutol (DOTS Program).

It is not easy to comply with this treatment; besides, it is expensive for countries or people with limited resources (10–1000 USD per treatment) and it becomes even more so when TB becomes MDR.

There are now more than 50 million persons infected by MDR strains, which is a practically unsolvable situation under the socioeconomic conditions prevailing in the world for poor countries and for the poor people in rich countries.

TB in Cuba

In Cuba before 1959, TB was one of the main causes of death. In 1959, it was in tenth place. Since then, and together with the development of the Health System during the Revolution, TB showed a significant decrease.

Through the Program for the Control of Tuberculosis that began in Cuba in 1970, TB decreased from 31.2 cases per 100,000 inhabitants in 1970 to 4.8 in 1991. In spite of this, the trend started changing in 1992 and in 1994 the incidence had tripled (14.7 cases/100,000 inhabitants). This negative influence was mainly generated by the crisis known as the 'Special Period', characterized by an intense and generalized economic depression, which negatively affected all areas, including public health.

This re-emergence of TB in the country motivated special attention given by the health authorities that prioritized the establishment of a new, broader and strengthened strategy in the Program for the Control of Tuberculosis, which quickly reverted the situation. At present the incidence is 6.2 cases per 100,000 inhabitants and there is a 5% decrease in the annual number of cases. All cases are treated according to the DOTS strategy with a curing rate of over 90%. Throughout the country there are only 454 cases with a positive bacilloscopy and they are all under medical treatment, controlled and receiving maximum care.[6]

In Cuba, not only the Program for the Control of Tuberculosis receives special attention from the Ministry of Public Health, but also applied and basic research on this disease, and collaboration between numerous scientific and health institutions. This includes projects for obtaining new vaccine candidates, the study of basic immunologic mechanisms for protection against TB, genomic and proteomic studies on vaccine and pathogenic strains and the complete molecular characterization of the strains isolated from clinically confirmed TB cases in the country.

The National Program for Vaccine Research, Development and Production in Cuba and its Experts Committee carry out several projects for obtaining new vaccine candidates, specially from: *M. habana* strains,[7] expression of selected *M. tuberculosis* antigens in BCG strains as live vector, use of alternative live vectors, such as genetically modified *Streptomyces* sp. strains and those based on immunization with DNA.[8,9]

The BCG vaccine and what we have learned from it

Working from 1906 to 1920 in Lille, France, Calmette and Guerin obtained the BCG vaccine. It is based on attenuation by passage in the laboratory of a bovine TB strain, *M. bovis* and prepared as a live attenuated vaccine.

Since its creation, more than 3 billion persons in the world have received this vaccine; this number of vaccinations increases by over 100 million each

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