Tuberculosis (TB) is the leading cause of mortality of infectious origin worldwide, with an estimated 10.6 million new cases each year. In an effort to increase the control of TB globally by 2035, the ANRS MIE and SAMRC are launching a joint call to promote collaboration between researchers based in South Africa and France and accelerate progress towards this goal.

The joint call aims to support research and innovation projects covering the whole spectrum of TB disease, including subclinical and drug-resistant TB. Research proposals may address the following major topics in adults and children:

(I) Epidemiology, pathogenesis, transmission and management of sub-clinical TB;

(II) Identification of biomarkers for disease progression and the development of novel diagnostics based thereon;

(III) Development of rapid diagnostic tools for evaluating drug resistance and precision medicine in the management of TB;

(IV) Development of new vaccine strategies, including new candidates to fill the vaccine development pipeline and strategies for feasibility and implementation of new vaccines that come onto the market;

(V) Evaluation of new drugs or shortened regimens, especially for pediatric populations.

1. **Epidemiology, pathogenesis, transmission and management** **of subclinical TB**

Subclinical TB is described as the stage when TB infected individuals show minimal or no symptoms, yet may still be able to transmit infection to others, making them a reservoir nearly invisible to passive surveillance. Intensive research on subclinical TB seeks to provide primarily a better control of disease transmission by improved understanding, identification and management of such cases. The South African TB Prevalence Survey of 2018 showed that 58% of bacteriologically confirmed TB was asymptomatic or subclinical.

This objective involves expanding research efforts to better understand the epidemiology, pathogenesis, transmission and clinical implications of subclinical TB; as well as improved options for rapid identification and treatment in selected populations. Researchers may explore the epidemiology of subclinical TB, risk factors for progression to active disease, the impact of subclinical TB on TB transmission dynamics, biomarkers and other mechanisms for case finding and treatment options.

1. **Identification of biomarkers for disease progression and novel diagnostics**

This topic includes the identification and/or application of immune or other biomarkers associated with progression of clinical and subclinical TB, which can contribute to better diagnosis, risk stratification, and monitoring of treatment response.

1. **Development of novel, rapid diagnostic tools for evaluating drug resistance and precision medicine in the management of TB**

Whilst there is a plethora of new diagnostic tools using nucleic acid amplification techniques and sequencing, there is currently a shift in the management of mono- and multidrug resistant TB and a rising risk of resistance to new agents. Thus, there is a need for better diagnostics and especially tools for the rapid diagnosis of drug resistance across all classes of drugs especially those positioned for use in the new WHO and South Africa guidelines. Improved diagnostics are also needed for diagnosis in HIV co-infected individuals, paediatric populations and for extra-pulmonary TB.

Current diagnostic methods for TB, such as sputum smear microscopy and culture, have limitations in sensitivity, particularly for detecting latent TB, TB in its early stages, extrapulmonary TB, and resistant TB. There is a need for more sensitive, rapid, and affordable diagnostic tests, especially in resource-limited settings where the price of currently available TB-NAAT tests makes its use in widespread screening limited. These new diagnostics tools need to address current diagnostic gaps, including at various stages of TB disease and in co-infected individuals and other target groups listed above. Preference will be given to proposals that build on already identified markers.

1. **Development of new vaccines strategies**

There is still no highly effective vaccine for preventing adult pulmonary TB, which is the most common form of the disease worldwide. New vaccine generation should focus on controlling and preventing TB infection, including drug-resistant and latent TB. Understanding of immune responses to new vaccines, both in animal models and in different populations and age groups, and identification of correlates of protection as well as development of preventative vaccines and therapeutic vaccines to treat drug resistant TB or shorten treatments are necessary. There is an urgent need for the discovery of new vaccine candidates to fill the vaccine R&D pipeline over the next five years. With only one promising candidate in Phase III vaccine trials in the pipeline, the need for new candidates and strategies is crucial both for adult and adolescent populations, as well as other target populations.

1. **Evaluation of new drugs or shortened regimens, especially for paediatric populations**

Low-cost proposals for the evaluation of new drugs or shortened regimens are invited, especially for pediatric populations, as are proposals on prognostic biomarkers for early treatment cessation.

Overall, this call will foster a better understanding, control and ultimately, elimination of TB through innovative strategies and develop scientific collaboration between researchers from South Africa and France over the long term.