

# SARS-COV-2 Infection and Anti-Tuberculosis Immunity: Temporal Association or Real Protective Role?

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## Abstract

**Introduction:** According to the literature consulted to date, there is epidemiological heterogeneity of Covid-19 between countries depending on their vaccination policy, in particular BCG vaccination. These findings have led to several hypotheses, including the protective role of immunity induced by the BCG tuberculosis vaccine against Covid-19 infection. The immunity induced by the BCG vaccine significantly increases the secretion of pro-inflammatory cytokines, in particular IL-1B, which has been shown to play an essential role in antiviral immunity. This cross-immunity, although not specific, if highlighted, is a real providence that must be taken advantage of in the face of this pandemic. The main objective of this study is to rule out or confirm that anti-tuberculosis immunity protects against SARS-COV-2 in our context. **Material and Methods:** Two groups will be compared: cases infected with the virus and controls who have never been infected with the virus. Both case and control groups will undergo a tuberculin skin test: the intra dermal tuberculin reaction (IDR). **Results:** We found that our control group had a high IDR immunity value, with an IDR tuberculin positive percentage of 67.2%. This suggests that immunity to IDR is a protective factor against coronavirus disease. **Conclusion:** The hypothesis of nonspecific anti-tuberculosis protection deserves further verification studies; it would have large positive repercussions for developing countries.

## Keywords

BCG, Nonspecific Anti-Tuberculosis Immunity, Covid-19

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## 1. Introduction

On March 11, 2020, the World Health Organization (WHO) declared severe acute respiratory syndrome caused by the coronavirus epidemic 2 (SARS-CoV-2) to be a global pandemic [1].

According to a general consensus, SARS-CoV-2 originated from bats. There is still no conclusive indication of the transmitting animal host: the virus has somehow adapted to human hosts, spreading rapidly through human-to-human transmission. [2] [3] [4].

COVID-19 is the newest form of respiratory tract infection that can be complicated by severe pneumonia and acute respiratory distress syndrome (ARDS). Most individuals infected with SARS-CoV-2 remain asymptomatic or develop mild to moderate illness. However, a minority of patients can develop severe pneumonia with ARDS, respiratory failure and death, especially older patients [5]. In Morocco, the Ministry of Health reports that the general situation since March 2020 figures 897,000 cumulative cases and 12,749 deaths.

The data available on COVID-19 [6] has revealed that the disease incidence and the mortality vary, even considerably, from country to country. The variability could be caused by different factors including ethnicity, eating habits, climate, social activities, genetic differences and governance structures.

Epidemiological studies have shown a relationship between the BCG vaccination rate and the morbidity and mortality rate due to SARS-Cov-2 [5].

## 2. Materials and Methods

Multicenter case-control study which took place in the region of Tangier, Tetouan, Al Hoceima, region of Rabat Salé Zair and kénitra.

Two groups will be compared:

- The cases: People with Covid 19 confirmed by a viral RT-PCR test in the region of Tangier, Tetouan, Al Hoceima, and the region of Rabat Salé Zair, kénitra.
- Witnesses: People belonging to the same case universe, who have never had a SARS-Cov-2 infection. Each witness will be matched to a case based on age and sex.

Both case and control groups will undergo a tuberculin skin test: intra dermal tuberculin reaction (IDR). The aim is to study the status of cellular immunity against tuberculosis in patients infected with SARS-VOC-2 by comparing them to control cases.

Inclusion criteria: Will be eligible after consent, incident cases;

- Adult
- Informed and consenting
- RT-PCR performed.
- Before administration of treatment with hydroxy chloroquine (or chloroquine) combined with azithromycin following the protocol of the Ministry of Health.

Exclusion criteria: People with at least one of the following criteria:

- Patients already treated for pulmonary or extra-pulmonary tuberculosis;
- history of known allergic reactions to any component of tuberculin [7] during the previous administration.
- a skin condition (eczema, impetigo or others) in the area where tuberculin was injected.
- immunosuppressive treatment, recent corticosteroid therapy (less than 4 weeks), hematologic malignancy, sarcoidosis, HIV infection, recent infection (less than 8 weeks)
- vaccination in the 2 months preceding the IDR test [8] [9].
- Immunomodulatory treatment (Vit D, etc.)

Statistical analysis:

The exploitation of these data allowed us to perform statistical whose results are expressed in forms of charts and tables.

Part of the statistical study was based on calculating the mean, median, mode, standard deviation, minimum, maximum.

Data entry and a first part of the statistical analysis were performed using SPSS 21 software.

A second part was performed using Pearson's chi-square test or Fisher's exact test.

The difference between two observed frequencies was said:

- Not significant, if  $p > 0.05$ ,
- Very significant, if  $p < 0.05$ ,
- Highly significant, if  $p < 0.001$ .

Study approval:

All study protocols were approved by Fes Hospital-University Ethics Committee and all participants provided written informed consent before the blood sample.

### 3. Results

In our study, 120 patients with Covid-19 were included, 74.8% (89) of them are men, and 25.2% (30) are women with the disease. We observed a severe form of the disease in 5 infected patients (4.2%) (**Table 1**).

We observed that men (74.8%) are more affected by coronavirus disease than women (25.2%), the difference was statistically significant ( $p = 0.04$ ) (**Table 1**).

The results show that the clinical forms of coronavirus disease are influenced by the comorbidities of the infected patients. Like, high blood pressure, diabetes, heart disease, kidney failure, and respiratory disease. We observed that 30.3% (36 cases) of cases present with chronic respiratory diseases ( $p = 0.009$ ). 7 cases (5.9%) infected with coronavirus disease present with renal failure ( $p = 0.001$ ) (**Table 2**).

Eight cases (6.7%) had heart disease, 27 cases (22.7%) were diabetic, and 14 cases (11.8%) had high blood pressure ( $p < 0.001$ ) (**Table 2**).

**Table 1.** Demographic and clinical characteristics of the patients.

Characters	Values
Age (years)*	38.92 ± 14.074
Sex <sup>§</sup>	
Male	89 (74.8)
Female	30 (25.2)
Clinical form <sup>§</sup>	
Paucisymptomatic	53 (44.5)
Light	33 (27.7)
Meduim	28 (23.5)
Severe	5 (4.2)

\*: expressed by median and interquartile range, §: expressed by number (percentage).

**Table 2.** Clinical forms according to comorbidities

Characters	Values	P value
P/A*	2.29 ± 7.174	0.4
Chronic respiratory disease <sup>§</sup>		
Yes	36 (30.3)	0.009
No	83 (69.7)	
renal failure <sup>§</sup>		
Yes	7(5.9)	0.001
No	112 (94.1)	
heart disease <sup>§</sup>		
Yes	8 (6.7)	<0.001
No	111 (93.3)	
Diabetes <sup>§</sup>		
Yes	27 (22.7)	<0.001
No	92 (77.3)	
HTA <sup>§</sup>		
Yes	14 (11.8)	<0.001
No	105 (88.2)	

\*: expressed by median and interquartile range, §: expressed by number (percentage).

The results show that the positivity value of IDR is very high in young patients. On the other hand, we have noticed that this value decreases with aging, and that it is low in elderly patients ( $p < 0.001$ ) (**Table 3**).

We found that our control group had a high value of IDR positivity, with a percentage of IDR positivity to tuberculin was higher in non-infected patients (67.2%) than the infected patients, ( $p < 0.001$ ). This suggests that immunity to IDR is a protective factor against coronavirus disease (**Table 4**).

#### 4. Discussion

On the epidemiological level, the observation of a heterogeneity of the geographical distribution with a difference in the number of cases of Covid-19 depending on

**Table 3.** Comparative table of the tuberculin reaction according to: age, sex, clinical forms.

Characters	IDR+	IDR-	P value
Age of infected patients			
≤65	3 (2.5%)	113 (94.2%)	<0.001
>65	0 (0%)	4 (3.3%)	
Age of non-infected patients			
≤65	79 (66%)	37 (31%)	0.8
>65	1 (1%)	2 (2%)	
Sex			
Male	89 (74%)	31 (26%)	0.04
Female	30 (25.2%)	90 (74.8%)	
Clinical forms			
Paucisymptomatic	0 (0%)	53 (44.5%)	0.8
Light	2 (1.6%)	33 (27.7%)	
Medium	1(0.9%)	28 (23.5%)	
Severe	0 (0%)	5 (4.2%)	

**Table 4.** Comparison of the reaction of IDR to tuberculin between patients and their matched controls.

	IDR+	IDR-	P value
<b>Infected Patients</b>	3 (2.5%)	117 (97.5%)	<0.001
<b>Non infected patients</b>	80 (67.2%)	40 (33.6%)	

the country as well as the difference in terms of mortality and morbidity to give rise in an interesting way to several publications which suggest the explanatory factors this variability in the incidence and severity of Covid-19.

A set of socio-ecological factors like the low density and mobility of the population, the hot and humid climate have been mentioned as factors involved in the epidemiological pattern observed especially in Africa.

Prognostic factors contain the presence of comorbidity in the literature, cardiovascular disease and hypertension, diabetes and obesity, and chronic respiratory disease, all of which are associated with higher probabilities of hospitalization, admission to intensive care and death. The majority of reviews agree that age is a prognostic factor [10].

Researchers have found genetic abnormalities in some patients with Covid-19 that decrease the production of type I interferons (IFNs). In fact, this decrease in type I interferon secretion has been demonstrated in 3% - 4% of severe forms of Covid-19.

Reduced secretion of type I INF has also been noted in other patients with autoimmune diseases that block the action of type I IFNs (10% - 11% of severe forms). All of these findings would therefore explain 15% of severe forms of Covid-19 [11].

The occurrence of its type I interferon secretion abnormalities in the popula-

tion over 65 years of age partly explains the frequency and severity of Covid-19 in this age group. In our series, the correlation between severe forms and advanced age is consistent with the results of the literature.

In the same reflection aimed at identifying the factors that may intervene to explain the epidemiological characteristics between individuals, the studies have also revealed a relationship between the Bacillus Calmette-Guérin (BCG) vaccination rate and the morbidity and mortality rate in the face of Covid-19.

These observational studies stipulate that countries that adopt the vaccine against tuberculosis (BCG) had a lower death rate among those infected with Covid-19, in comparison with other countries that do not adopt this vaccine in their health policy. In addition, countries using BCG mortality was 5.8 times lower [95% CI 1.8 - 19.0] than in countries not using BCG [12].

Escobar *et al.* showed that each 10% increase in BCG index was associated with a decrease in COVID-19 mortality by 10.4% [13].

At present, it is clear that Morocco, like the majority of African countries, is much less affected than the rest of the world. This contact is consistent with the hypothesis linking BCG vaccination and the low incidence of Covid-19 since BCG vaccination in Morocco is mandatory.

In fact, countries which adopt the vaccine against tuberculosis (BCG) such as Morocco have recorded a lower mortality rate among people infected with SARS-Cov-2 in comparison with other countries which do not adopt this vaccine in their health policy.

BCG vaccination was applied for the first time in Morocco between 1949 and 1951 as part of the international campaign against tuberculosis. [12].

The nonspecific protection of the BCG vaccine against pathogens derives its rationale from several publications which have linked the BCG vaccine to protective immunity against certain viruses.

Shortly after its introduction to the vaccination program, epidemiological studies reported that BCG vaccination greatly reduced infant mortality, which could not be explained by a reduction in tuberculosis alone.

Later, similar studies in other localities, including randomized controlled trials have shown a reduction of up to 50% of the mortality induced by BCG in young infants [14]. This reduction in infant mortality from BCG can be caused by the protection against unrelated infectious agents and in particular respiratory tract infections and neonatal sepsis.

It is well known that viral pathogens are the main cause of respiratory tract infections in children. This hypothesis was reinforced by a study showing that BCG decreased the incidence of infection by respiratory syncytial virus [1]. The same protective effect of BCG on respiratory tract infections has been found in elderly people in Indonesia [2], and a clinical trial in Japan has shown protection against pneumonia in elderly people negative for tuberculin [3].

Finally, a recent study among adolescents in South Africa also reported a 70% reduction in respiratory tract infections thanks to BCG vaccination [4].

In general, the BCG vaccine generates a very strong immune stimulation which goes beyond the installation of immunity against tuberculosis. This effect is related to stimulation of the cells of the innate immune system (macrophages, neutrophils, etc.) (“trained immunity”) [15] [16] [17] [18].

The nonspecific defense mechanism of BCG relies on the induction of innate immunity memory. It was long believed that only B and T lymphocytes were capable of acquiring immune memory. There is now data showing that the functional program of cells involved in innate immunity can be altered after certain infections or vaccinations such as NK cells, monocytes and macrophages [15] [16] [17] [18].

The literature review suggests that even SARS-Cov2 infection is among the viral infections that could be influenced by BCG.

The possible defense mechanism of BCG against Covid-19 is based on a functional reprogramming of cells involved in natural immunity, which results in an enhanced response upon further stimulation.

- This reprogramming uses epigenetic and metabolic mechanisms without modification of the genome. Cell lines involved in trained immunity include bone marrow stem cells that transform into monocytes and macrophages that are found in the circulation and tissues, as well as natural killer cells. Many metabolites are involved in defense processes, including cytokines and interferon (IFN $\gamma$ ).
- Some epithelial cells and fibroblasts can also be reprogrammed to participate in the trained immunity. The duration of this reprogramming seems to decrease over time, but some have suggested long-term, even transgenerational, reprogramming [19].
- BCG can generate T lymphocytes against SARS-CoV-2 by nonspecific cross reaction because BCG has been shown to contain 9 amino acid sequences similar to SARS-CoV-2, and these closely related peptides have affinity moderate to high binding to common HLA class I molecules [20].
- BCG may modulate anti-inflammatory cytokine and chemokine responses, preventing hospitalization and leading to milder cases of COVID-19. This could be attributed to the suggestion that the modulation of the innate immune system could be caused by the BCG vaccine. The most severe forms of COVID-19, and in particular the pulmonary forms, appear to be associated with a “cytokine storm” as seen in systemic reactions after the use of CAR-T cells or in hemophagocytic syndrome [6].

Several clinical studies are underway to confirm the protective effect of BCG vaccination against Covid-19, however, additional studies will be necessary to better understand the different axes of nonspecific anti-tuberculosis immune protection against Covid-19.

Indeed, several questions remain in abeyance in the absence of sufficient evidence between BCG vaccination and protection against Covid-19.

The possibility that a single exposure to an attenuated pathogen during infan-

cy could result in lifelong improvement in immune surveillance is difficult to prove and results from randomized clinical trials.

Our study investigated an axis of nonspecific anti-tuberculosis cellular immunity explored *in vivo* by the intradermal reaction to tuberculin in patients with covid-19 in order to look for a delayed hypersensitivity reaction to tuberculin that may occur following infection with a tubercle bacillus or as a marker of acquired immunity after the BCG vaccine.

The objective of our study is to explore anti-tuberculosis immunity *in vivo* in a population infected with Covid-19 by comparing it with the population not infected with SARS-Coc2.

We used as a means to explore nonspecific anti-tuberculosis immunity against Covid-19 which is the tuberculin skin test, or Mantoux test. It is a skin test exploring the delayed type hypersensitivity induced *in vivo* by the injection of tuberculin into the dermis on the anterior aspect of the forearm. Tuberculin contains a mixture of many different mycobacterial peptides (“purified protein derivatives”, PPD) most of which are shared between *M. tuberculosis* and the BCG vaccine of bovine origin and, to a lesser extent, with several species of atypical environmental mycobacteria. A subject vaccinated with BCG may therefore show a positive reaction to IDR in the absence of an encounter with *M. tuberculosis*.

The injection of tuberculin causes a local influx of innate immune cells. These cells, if the subject has already been in contact with antigens contained in tuberculin, recruit, at the site of the injection, CD4 + memory T lymphocytes which differentiate towards a Th1 profile mainly secreting IFN gamma, which recruits in turn locally activated macrophages.

Several writings have characterized the innate cellular response against infection with SARS-CoV-2.

Indeed, recent data seem to show that a defect in cell recruitment and therefore in IFN response has also been observed in infections by SARS-CoV-1 and MERS-CoV [21].

Similarly, other data have indicated that the IFN response is deficient after infection with SARS-CoV-2 [19], even though the production of chemokines (CCL2, CCL8) and proinflammatory cytokines (IL6, IL1RA) remains normal or even exaggerated.

Interestingly, it could also be shown that the cellular receptor for SARS-CoV-2, ACE2, itself being a protein of the ISG (Interferon Stimulated Gene) family and therefore inducible by IFN, allowed the virus to divert the cellular response and promote its own multiplication [22].

In our work, the choice of IDR for tuberculin is based on the fact that it explores post-vaccination cellular immunity but also anti-tuberculosis cellular immunity which can be the result of latent infection.

By using the tuberculin test was shown in our study that *in vivo* immunity in patients with Covid-19 is low compared with subjects contact of same age and sex as evidenced by comparing the diameter of induration 72 hours the tubercu-



lin test with a statistically significant difference.

The skin induration directly reflects the cellular infiltrate with influx of polymorphonuclear cells, monocytes and lymphocytes to the site of the injection.

The result obtained in our series is consistent with recent data suggesting the role of trained immunity. Such immunity may be related to BCG or related to latent tuberculosis infection.

In fact, tuberculosis infection can remain dormant for years thanks to the body's defense system which manages to control the pathogen CD4 + T lymphocytes and 3 cytokines and/or interleukins: Tumor Necrosis Factor  $\alpha$  (TNF $\alpha$ ), Interferon  $\gamma$  (IFN $\gamma$ ) and interleukin 12 (IL12) are major players in this control.

T lymphocytes specific for Mycobacterium Tuberculosis (MT) antigens recruited by the initial inflammatory reaction, will recruit a second wave of inflammatory polynuclear cells but especially monocytes thanks to chemotactic cytokines. These cytokines will also activate monocytes and polymorphonuclear cells, stimulate the pro-coagulant activity of macrophages as well as local fibrin deposits explaining the indurated and delayed nature of the reaction.

In highly endemic tuberculosis areas such as Morocco, the positivity of the IDR reflected contact with the tuberculosis bacillus. In our study, considering the epidemiological situation and the BCG vaccination policy in Morocco and according to Berket [23] a positivity limit of 5 mm gives the best sensitivity and specificity and a good negative predictive value, on the other hand, the limit of positivity of 15 mm gives the best positive predictive value.

In Morocco, it is estimated that 8.3 million Moroccans are carriers of a latent tuberculosis infection, and therefore represent potential reservoirs.

The relationship between anti-tuberculosis cellular immunity and Covid-19 by means of the tuberculin test deserves molecular exploration by in vitro tests with assay of anti-tuberculosis gamma interferon.

In our study, we were also able to objectify the variation in the value of the IDR for tuberculin with age, so its value decreases over time and can become negative after variable delays. Reactivity to tuberculin decreases with age; over 65 to 70 years of age, a negative IDR can be observed in 30 to 40% of cases of tuberculosis infection [24].

The duration of hypersensitivity is variable. It persists as long as the Koch's Bacillus (BK) continues to live in the body and behaves like a living antigen, often a very long time after a significant infection with BK (as evidenced by a significant tuberculin reaction), on average about ten days, years after BCG in the absence of tuberculosis contact or revaccination [25].

The answer seems to depend on the intervention of a genetic control probably carried by chromosome 1 [26]. Moreover, according to our study, there is no relationship between sex and the size of induration, tuberculin reactivity is not physiologically dependent on sex as pointed out by several authors [16].

## 5. Conclusions

The implication of innate nonspecific anti-tuberculosis immune memory for

protection against Covid-19 will greatly improve our understanding of the mechanisms underlying the epidemiological and prognostic differences between different countries. However, a full understanding of the molecular mechanisms underlying this phenomenon is relevant to achieve.

If the hypothesis of nonspecific anti-tuberculosis protection holds true, it would have large positive repercussions for developing countries, as BCG vaccination coverage could play a key role in reducing the severity of COVID-19. In addition, certain mobility restrictions or even containment measures adopted by countries will be exceeded, which will allow their economies to revive, and could lead to a response to new pandemics.

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## Conflicts of Interest

The authors declare no conflict of interest.

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